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## Essay Review

## Empirical evolutionary medicine

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**Evolution and Medicine, Robert L. Perlman. Oxford University Press, Oxford (2013). 176 pp., Price 44.95\$ Paperback, ISBN: 978019966172-5**

Medicine and evolutionary biology have crossed path several times since the publication of *On the Origins of Species* but the “new science of Darwinian medicine” dates back only to the early 1990s (Nesse & Williams, 1994). For psychiatrist Randolph Nesse and evolutionary biologist George C. Williams, the founders of Darwinian medicine, “there is no branch of medicine that cannot benefit substantially from an evolutionary approach in its research and, sometimes, its current clinical practice” (Nesse & Williams, 1997, p. 664). Though evolution did not have the profound transformative effect on medical research and practice envisaged at the outset by Nesse and Williams, there is a growing interest for evolutionary explanations of health and disease among biomedical researchers (Gluckman, Beedle, & Hanson, 2009).

Robert L. Perlman's *Evolution and Medicine* builds on this interest and offers a series of examples that beautifully illustrates the relevance of evolutionary thinking in medicine. After describing how an evolutionary perspective currently informs our understanding of genetic diseases, senescence, and cancer, the bulk of the book is devoted to understanding the dynamics of infectious diseases and host–pathogen coevolution—two of the most successful loci of interaction between evolutionary and medical concerns—and closes with a chapter on gene and culture coevolution and another on man-made pathologies.

Throughout eleven engaging chapters, Perlman carefully treads between evolutionary biology and medicine and successfully brings out the connections between the two fields that often go unnoticed. The prime aim of the book, however, is not to demonstrate that medicine—as a whole—needs to be embedded into an evolutionary framework. Indeed, one of the lessons of the book is that evolutionary medicine should be empirical. That is, one should first look at cases where evolution is likely to inform medicine

rather than rigidly applying evolutionary principles to all dimension of the biomedical sciences from above, and hope good results will turn up. Consequently, Perlman doesn't indulge in speculation about the evolutionary significance of health and disease. Instead he concentrates on the details of well-chosen examples to demonstrate how evolution, acting on genetic and phenotypic variation, can illuminate a number of related aspects of biomedical research and sometimes practice. With this short book Perlman has possibly achieved more in showing how evolution and medicine can be brought closer to one another than many other contributions. Let us follow Perlman through the book.

In Chapter 1 Perlman explores the ways in which the “different subject matters of medicine and evolutionary biology” have led their practitioners to develop “different intellectual styles” (p. 8). As he points out, whereas medicine has traditionally focused on individual patients, the Darwinian theory of evolution has always been—and still remains—a population-based science. Also, while physicians concentrate on the inner dysfunctions of organisms, evolutionary biologists consider organisms as deeply embedded in a web of ecological relationships. Consequently, Perlman argues, medicine and evolutionary biology have historically been concerned with “different biological problems” and “have developed as separate, unrelated disciplines” (p. 10).

These and similar other conceptual differences cannot be ignored when thinking about the relationship between the two fields, but are they decisive epistemological obstacles to the rise of evolutionary medicine to the extent Perlman seems to think? Take the concept of individual in medicine, for example. What is an individual? According to a long-standing view, an individual in biology and medicine is the developmental result of a monogenetic lineage (Dupré, 2011). Recent advances in symbiosis, medical microbiology, developmental biology, and epigenetics, however, are now providing a different view, namely that the medical individual is itself the result of several interacting and constantly evolving lineages (Dupré, 2011, p. 122, 123). The point is that the individual patient—the classical locus of medical intervention—can itself be regarded as an evolving population. Taking a proper view

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on what an individual is could help to overcome some of the obstacles identified by Perlman, and brings medicine and evolution closer to one another.

The relations between the human species and its parasites throughout evolutionary time, as well as the emergence of “new” diseases, are examined in Chapter 2. Perlman pays attention to the rise of agriculture and how it facilitated the transmission of diseases from domesticated animals to man. This chapter also introduces the concept of a “demographic transition,” which usually accompanied a decline in birth rates. In countries where this transition came together with an increase in wealth, evolutionary biologists expected to see birth rates skyrocketing. The truth, however, contradicted these predictions, which raises the question as to why we would voluntarily decrease our fertility and our fitness as a species? “Because of our evolutionary history”, Perlman argues, “we may well have evolved psychological predispositions to pursue socioeconomic success and to invest heavily in our children, even if that means limiting reproduction” (p. 25). Though the chapter is generally convincing, the appeal to evolutionary theory doesn't seem as illuminating here as in other places in the book. Surely there are significant non-biological reasons why people decided to limit their fertility, and such explanations do not require postulating predispositions to balance parental investment with reproduction in ways that would have presumably optimized the fitness of our ancestors. For instance, and as Perlman briefly mentions, such social changes, as career opportunities for women and education, are critical factors in explaining this phenomenon that puzzles evolutionary biologists (p. 25).

Chapter 3 is a primer on evolutionary genetics that provides the conceptual and empirical background for the chapter that follows, which addresses the nature and causes of cystic fibrosis. This chapter offers a succinct but informed panorama of the theoretical reasons for the persistence of deleterious alleles in human populations, and discusses in detail how processes such as natural selection, drift, and migration determine the fate of new mutations. Perlman uses the theories and concepts introduced earlier to explain why cystic fibrosis is a complex disease. The disruption of the myriad biological activities of the cystic fibrosis transmembrane conductance regulator (CFTR) is the proximate cause of cystic fibrosis. This protein (CFTR) plays different roles in cells and is expressed at several levels in the body, including in sweat glands, intestine, pancreas, lungs, and kidneys, all areas of the body affected by CF. More than 1900 CFTR alleles have been identified, the most common being a variant called the  $\Delta F508$  mutation. This genetic variation correlates with phenotypic variation; indeed, manifestations of the disease are also diverse and affect organs differently at different times during an individual's life. Even patients with the same CFTR genotype can show differences in phenotype as cystic fibrosis depends on the action of other genes and on environmental inputs such as respiratory pathogens and secondary smoke.

But what explains the spread of  $\Delta F508$  mutation among human populations? The geographical and evolutionary origins of the  $\Delta F508$  allele, Perlman says, remain “uncertain” (p. 48). The preservation of gene diversity appears to be the most plausible explanation of its spread throughout human populations. Yet, the exact nature of this evolutionary advantage—ranging from resistance to various pathogens to reduced risks of asthma and increased fertility—remains unclear. The hypothesis according to which the  $\Delta F508$  allele spread in European populations because it increased resistance to *Mycobacterium tuberculosis*, the agent of tuberculosis, is currently the “most attractive.” But as Perlman remarks, “we may never know the reasons for the spread of the  $\Delta F508$  allele” (p. 48).

The fundamental questions of “how and why do we age?” from the perspective of life history theory and evolutionary biology is

addressed in Chapter 5. Drawing on the works of G. C. Williams (1957) the argument advanced in this chapter is that natural selection cannot prevent ageing or death, and that most diseases of old age are the result of the action of such genes that provide benefits during the lifetime of an individual, in particular, those genes that increase reproductive fitness. Organisms, it turns out, do not age and die to make room for new ones and there are, in principle, no good physical reasons of why we age at all. Apparently some invertebrate species just don't age in nature! (p. 54). Individuals “don't have genes ‘for’ aging” (p. 58), Perlman reminds us; rather, individuals have sets of genes whose role is to allocate and regulate available energy, either for tissue repair or other biological functions related to fitness. There will thus inevitably be tradeoff between those competing demands such as survival and fertility. Drawing on the “disposable soma” hypothesis and on the concept of “physiological capital” Perlman's view is that “natural selection has optimized our ability to transmit our genes to our children and grandchildren, but once we have completed that task, our bodies are disposable and are recycled” (p. 58).

Chapter 6 addresses the problem of cancer as a disease of ageing from an evolutionary standpoint. Whereas oncologists have long tried to explain “the hallmarks of cancer” in evolutionary terms, Perlman notes that cancers are best regarded as a family of diverse diseases characterized by abnormal somatic cell growth and characterizes the dynamics of cancer as “a process of variation and selection” (p. 69). Cancer cells thus progress in the body following a process of competition for space and nutrients among cancerous cell lineages, cells being selected for traits such as “increased replication, decreased apoptosis, avoidance of host defences, ability to spread locally and to metastasize to distant sites, and resistance to therapy” (p. 71). Often called “tumor archaeology” phylogenetic studies of cancer provide the evolutionary pattern of genetic changes through time among cells for a given patient.

Adopting an environmental perspective on the development of cancer, Perlman suggests looking at cancers as “evolving ecosystems” (p. 73). Cancer cells, for Perlman, evolve in a changing environment that affects their differential replication and where their fitness and growth “are constrained by the ecological interactions between these cells and the tissues that surround them” (p. 76). When looking ecologically and evolutionarily at cancer cells, Perlman has a clear eye on the therapeutic implications of cancer management. For, while chemotherapy successfully eliminates a cancerous cell lineage, there is a risk it also selects for the growth of other lineages by opening-up new space for growth and replication in which they will thrive (p. 76).

Perlman's main concern in Chapter 7 lies with the dynamics of pathogens' transmission and how several interrelated variables influence the evolution of virulence. For pathogens “we are like islands” (p. 78), in that disease transmission from infected to uninfected people is similar to the colonization of islands by animals and plants. From a tradeoff perspective, hosts evolve in ways that minimize the fitness cost of pathogens, and pathogens evolve in ways that optimize their fitness. In light of the tradeoff model we can understand why emerging diseases such as Ebola did not cause massive epidemics: the pathogens killed their hosts too fast to be transmitted and thus, their population died out. Perlman also discusses the cases of the myxoma rabbits in Australia, which strikingly exposes how “new infectious diseases arise from a combination of ecological and evolutionary changes” (p. 85).

Ending this chapter, Perlman examines the way in which pathogens have evolved higher levels of virulence in response to cultural practices. In that respect, if the development of antibiotics was a “triumph of modern medicine,” then the rapid evolution of antibiotic resistance was a “perverse triumph of natural selection” (p. 87). A nuanced and detailed discussion of the ways in which

*Staphylococcus aureus*—a commensal microorganism of humans' microbiome that may protect us from being colonized by other pathogens—has rapidly evolved resistance against both penicillin and methicillin is offered. A last aspect of this fascinating chapter concerns community acquired strains, and particularly methicillin-resistant strains (MRSA) that are found outside the hospital. Perlman notes that their spreading out of the hospital is puzzling from a tradeoff point of view, and poses a serious public health threat, which requires an evolutionary understanding.

"Given that sexual reproduction may have evolved as a defense against pathogens", Perlman writes in Chapter 8, "it is ironic that it opened up a new route of pathogen transmission" (p. 91). The ubiquity of both sex and sexually transmitted diseases, and their relationship with one another, sets the stage for this chapter devoted to understanding the coevolution of transmitted pathogens and sexual reproduction as widespread phenomena in nature. Here, Perlman begins with a discussion of the epidemiology of sexually transmitted diseases and the evolutionary responses of the host before moving on to the natural histories and evolution of syphilis and HIV/AIDS.

How do aspects of STDs look like when viewed from an evolutionary perspective? According to Perlman, we can understand asymptomatic periods of STDs as a sign of the "evolution of the pathogens to decreased virulence." Why? "Because infected people might have or raise children and so contribute to their reproductive fitness during that time" (p. 92). The author hastens to add, however, that such diseases still have devastating consequences from the human point of view, even if such consequences are sometimes delayed.

Another way of inquiring into the relevance of an evolutionary approach to understand STDs is to look at the ways in which hosts have historically responded to sexually transmitted pathogens. Humans and other mammals have evolved ways to protect internal fertilization processes. This way, the sexual activity of the hosts led to adaptive changes in their behaviour, physiology, and immunological defences. Likely, the existence of bodily defences against sexually transmitted pathogens, such as those present in the female reproductive tract, are evidence of the influence of those pathogens, acting as selective factors, as well as the coevolution of those pathogens with mammals throughout the whole of mammalian evolution (p. 94).

In Chapter 9, Perlman applies the theoretical principles discussed previously to the evolution of malarial disease, which "most clearly illustrates the principles of human-pathogens coevolution" (p. 103). The chapter is not just about sickle cell haemoglobin and its selective advantages. Substantial space is devoted as well to the life history of *Plasmodium falciparum* and the natural history of malaria infections and their intriguing ecological, physiological, and evolutionary connections. Perlman goes into details about these complex biological processes and the readers learn a great deal about the life cycle of the pathogen, its mode of infection, and its consequences for infected individuals. As Perlman notes, the natural history of malaria infections is replete with evolutionary considerations. Here, one may think of the fever caused by *P. falciparum*, which "is evidently a manipulation of our physiology by the parasite" that "is likely to enhance parasite transmission" (p. 106). *P. falciparum* infection is one central area of biomedical research where Perlman strongly urges scientists to consider evolutionary processes when devising public health measures (p. 114).

Chapter 10 examines the process of the coevolution of genes and culture and concentrates on the example of lactase persistence in human populations. One underlying assumption in this shorter chapter is that we humans have become "unprecedented 'niche constructors'" (p. 116), and that this process goes both ways.

Altering the environment, as humans did when they went from a nomadic to a settled lifestyle, profoundly modified the selection pressures as well as the fitness of our ancestors and their descendants. Conversely, the genetic constitution of human populations played a role in the development and transmission of cultural practices (p. 116). Perlman brings together a variety of evidence coming from anthropological, cultural, metabolic, and biochemical research on milk consumption, which he links to a larger body of evolutionary considerations, the domestication of animals, and the practice of dairy farming.

Perlman suggests that the ability to consume milk likely increased the fitness of the individuals who retained this capacity after the weaning period, particularly in an environment shaped by new cultural practices where fresh milk became available under different forms. Yet those benefits related to milk consumption may be more difficult to determine, not to mention diverse, than we usually imagine: lactose and calcium could provide post-weaning sources of food; lactose itself could help absorb calcium better and confer protection against solar radiations during migrations; and finally, milk could be a source of uncontaminated fluid, possibly of central importance in arid environments. As Perlman nicely sums up, "not only did lactase persistence arise independently in different populations, it may have enhanced fitness for different reasons in different environments" (p. 123). Finally, this chapter considers how the gene-culture hypothesis clarifies the meaning of the concept of "genetic disease": in societies where milk consumption is common, lactase deficiency is better seen as a genetic disease. In contrast, cultures that do not rely on milk consumption tend to ascribe the inability to drink milk to the environment (p. 125).

The concept of "environment of evolutionary adaptedness" (EEA) (p. 127), often discussed in evolutionary medicine, is critically examined in Chapter 11. Perlman warns against swift interpretation of the concept but considers that "we now live in an environment that differs in many respects from the environments in which our evolutionary ancestors lived and to which they became adapted" (p. 127). Thanks to the effects of the epidemiological transition, there is a "mismatch between our culturally constructed environment and our genetic inheritance" (p. 128). This chapter offers a balanced discussion of the still controversial "hygiene hypothesis", and the ways it supports his argument about the alleged mismatch between our biology and current environments. According to the hygiene hypothesis, the lack of exposures to a number of pathogens leaves people at greater risk of being more reactive to them in case of an unexpected encounter. Asthma and various autoimmune diseases are thus likely to be the result of this lack of early exposure to helminths' infections and also of our "cultural obsession with avoidance of 'germs'" (p. 137). Perlman is cautious when making those claims, however, and he notes that the burden of these new diseases is largely outweighed by the benefits of modern hygiene. In fact, the central message of this chapter is not the significance of the mismatch but rather the urgent need to understand how microorganisms are shaping our immune system. Instead of ending with a conclusion that pulls the different strands of the arguments together, the book closes with a thoughtful reference to late epidemiologist Geoffrey Rose (1985), which is a plea for greater attention to the value of population-based intervention such as vaccination, as these are likely to showcase the relevance of evolutionary theory to medicine.

## 1. Evolution, medicine, and eugenics: some historical remarks

In the opening of *Evolution and Medicine*, Perlman considered medicine and evolution as two different styles of thinking, which

could account for the existing gap between them, apparent even today. Yet could it be rather that because evolution and medicine interacted *too closely* they did not integrate properly with one another, thus postponing the emergence of Darwinian medicine to the mid-1990s? Let me illustrate the plausibility of this hypothesis with the example of eugenics.

Although the word eugenics itself does not come up often in the book (see p. 3), I would argue it was a major force in shaping the relations between the medical sciences and evolutionary biology from the late 1860s to the 1940s and beyond. Eugenics, the idea of artificially selecting for (or against) specific traits among human populations, acquired a new applicability following Darwin's works on evolution and heredity, and became entangled with a popular understanding of evolution characterized as the process of the "survival of the fittest". The then-perceived consequences for society of tampering with the law of natural selection were regularly addressed from a medical point of view. In an essay "On the Failure of Natural Selection in the Case of Man" (1868), William R. Greg raised the possibility that natural selection has ceased to operate in human societies and warned about possible degradation of health following medical progress: "medical science is mitigating suffering, and achieving some success in its warfare against disease; but at the same time it enables the diseased to live" (Greg, 1868, p. 362). One year later, Lawson Tait, a prominent surgeon from Birmingham, asked whether "the law of natural selection by survival of the fittest failed in the case of man" (1869). Tait was primarily concerned with the apparent tension that "medical science enables the diseased to live, those whom it saves from dying prematurely it preserves to propagate dismal and imperfect lives" (cited in Shepherd, 1982, p. 1386).

Though Charles Darwin expressed similar concerns about the effects of a prolonged relaxation of natural selection—partly made possible thanks to medical advances, e.g. small-pox vaccination—for the march of societies toward progress (1871, p. 168), he noted that the sympathy instincts that lead us to give protection to the "imbecile, the maimed, and the sick" are themselves the product of evolution by natural selection. Suppressing those instincts, for Darwin, would have been impossible "without deterioration in the noblest part of our nature" (1871, p. 168, 169). In 1869, Francis Galton, Darwin's cousin, published *The Hereditary Genius*. Separating the realms of nature and culture, this treatise stressed the "unity of type" over individual variations. Faithful to his eugenic utopic vision, Galton saw the use of artificial selection as the easiest and quickest way to achieve what natural selection would eventually realize (Gayon, *in press*). Reacting to the apparent failure of the positive effect of natural selection in the case of human societies, Galton sought to impose constraints on human reproduction. In 1912, the biometrician and then-director of the Francis Galton Eugenics Laboratory in London, Karl Pearson, gave a Cavendish lecture at the West London Medico-Chirurgical Society titled "Darwinism, Medical Progress, and Eugenics". In his address, Pearson also argued that evolutionary theory as formulated by Darwin and medical progress are radically "opposed forces", and that the tension between them could indeed only be resolved through the implementation of strict eugenics policies of birth control (1912, p. 27).

With the rediscovery of Mendel's laws of inheritance, and the beginning of genetics, Pearson's project of birth control became to a large extent a social and political reality for countless individuals. When the association of Nazi crimes during the Second World War with a number of eugenics movements was brought to light, the application of Darwinian concepts to "medical" questions became

for a time morally untenable at a political level. Though publically dismissed, eugenicist concerns with degeneration continued to be promulgated by prominent scientists and medical geneticists until the late 1960s in United States, Britain, and Germany (Paul, 1984). As the founders of Darwinian medicine Randolph Nesse and George Williams recognized: "whenever evolution and medicine are mentioned together, the spectre of eugenics arises" (Nesse & Williams, 1998, p. 32). More than any intellectual difference, *this* is certainly one of the main causes of the discernible "oblivion" of evolutionary approaches to medicine in the 20th century (see Zampieri, 2009, p. 24).

## 2. Conclusion: is evolutionary medicine a field?

In *Evolution and Medicine*, Perlman convincingly shows us how the two disciplines could benefit from a stronger dialogue and how evolutionary medicine could provide us with a "richer understanding of health and disease" (p. 10). But is "evolutionary medicine" now an independent field? Historians have described three important steps in building up a new field (Bensaude-Vincent, 2013). First, the discipline coalesces around the names of prestigious individuals and their personal trajectories; second, the emergent field becomes stabilized through "community-making devices" such as the creation of academic journals, scholarly societies, textbooks, annual conferences, etc.; and third, throughout this process, the field shapes its identity in relation to the novel perspective it brings while making constant reference to central historical moments, and at the same time developing agendas for the future (Bensaude-Vincent, 2013, p. 123).

The early works of Nesse and Williams in the 1990s were widely read and discussed even if their conclusions were not always endorsed. Williams was a respected figure and he brought credits to a project that was otherwise, often characterized as ideological. He is rightly depicted as one of the founders of the modern perspective of Darwinian medicine, notably because of his pioneering works on aging theory (Williams, 1957). Nesse played a crucial role in promoting the need for an evolutionary perspective in medicine, particularly in psychiatry.

After an initial phase of marketing by these two men, the field was more or less stabilized with the publication of central Darwinian (or evolutionary) medicine questions and topics, textbooks (Gluckman et al., 2009), and the organization of international conferences. In 2012 the *Journal of Evolutionary Medicine* was launched and in 2013, *Evolution, Medicine, and Public Health* released its first issue. Research institutes are steadily appearing, such as the Centre for Evolutionary Medicine at the University of Zurich and the Centre for Evolutionary Medicine and Informatics at Arizona State University.

What about the third step? In a sense, evolutionary medicine cannot avoid confronting the eugenicist past that has characterized much of the earlier relations between evolutionary thought and medical sciences. Because of this problematic history, however, evolutionary medicine can hardly reach back in time to firmly ground itself in a series of epochal-making events or influential intellectual figures—Darwin himself, indeed, was not tremendously interested in the medical consequences of his theories. Another internal conflict concerns the future of evolutionary medicine, which brings us to the question of whether evolutionary medicine is a unified discipline or a collection of loosely related research programmes (Méthot, 2011).

Forced to admit that they did not create a new field, evolutionary medicine's advocates now argue that evolutionary medicine "consists of all areas in which evolutionary thought



productively informs medical and epidemiological issues” (Stearns, 2012, p. 4305). But what, then, is the added value of labelling research “evolutionary medicine” instead of evolutionary ecology, nutrition, or medical anthropology? Giving a narrower definition of a field provides clear-cut boundaries of what works are seen as part of the evolutionary medicine paradigm and what aren’t. However, this more specific approach runs the risk of marginalizing areas of research that could support the goals of understanding health and disease evolutionarily. But if defined too generally (e.g. “all areas...”) evolutionary medicine becomes not much more than a label added on top of existing bodies of research. Faced with these issues, we should recognize that the third step in the discipline building process is not yet completed: the vision of evolutionary medicine is hampered because of its problematic connections to a historical past and of an uncertain future, either as a discipline or a guiding concept. Perlman’s book can usefully help us appreciate that evolutionary medicine, at the moment, is perhaps best conceived as a series of empirical case studies rather than as a field as such.

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