Disease, Darwin, and Medicine in the Third Epidemiological Transition

Why We Get Sick: The New Science of Darwinian Medicine

By Randolph M. Nesse and George C. Williams (1994). New York: Random House. 291 pp. $24.00 (cloth). ISBN 0-8129-2224-7. Also published in 1996 as a Vintage Book. Also published in the United Kingdom in 1996 as Evolution and Healing: The New Science of Darwinian Medicine. Orion Press.

Evolutionary Medicine: Rethinking the Origins of Disease

By Marc Lappé. San Francisco: Sierra Club Books. 1994. 255 pp. ISBN 0-87156-519-6. $30.00. (cloth).

Evolution of Infectious Disease

By Paul W. Ewald. Oxford and New York: Oxford University Press. 1994. 298 pp.$35.00 ISBN 0-19-506058-X.

Man and Microbes: Diseases and Plagues in History and Modern Times

By Arno Karlen. 1995. New York: G. P. Putnam's Sons. $24.95 0-87477-7593. Also published as a Touchstone Book, Simon and Schuster. $13.00 (paper). ISBN 0-684-82270-9.

Disease has played a significant role in the evolution of human populations. The competition between hominids and bacteria would seem a mismatch. A bacterium may weigh as little as 0.00000000001 gm, whereas the average human weighs about 33,000 grams.[10] However, when you consider that there is only a single species of humans compared to between .3 million and 1 million species of bacteria and 5,000 viruses,[10] (p. 175) it becomes a contest. Consider the difference in generation time (20 minutes for the pathogen compared to 20 years for humans) and the race is on.

As humans evolved bioculturally, they underwent changes that altered their relationship with pathogens and other insults (for example, toxins, trauma, and ultraviolet radiation), and thus created new disease patterns.[11] In the technological process of extracting energy from the environment and in the course of their daily social activity, humans frequently encounter pathogens and other insults that cause disease. The adaptive changes that altered the human-pathogen interaction can be described as a series of epidemiological transitions.[12–14]

According to Armelagos and Barnes,[14] the first epidemiological transition appeared with the shift to primary food production (agriculture) and resulted in the emergence of many infectious diseases. Diseases emerged at an increasing rate as humans transformed their habitats into urban and then industrial settings,[15,16] establishing a pattern in human evolution that continues to this day.

Within the last century, the second epidemiological transition (the original epidemiological transition described by Omran[17]) emerged with the decline in the occurrence of infectious disease in some populations. With the decline in the prevalence of infectious disease, there was a rise in chronic and degenerative conditions.[18] The reason for the decline in infectious disease was thought to be the application of the germ theory to medical practices. However, McKeown[19,20] has argued persuasively that public health measures and improved nutrition were the reasons for the decline in mortality and the rise of the so-called modern population. The debate has been rekindled with the work of Riley[21–24] and Johansson.[25,26]

Human populations are currently entering their third epidemiological transition[13] and are experiencing the rapid emergence of a vast array of diseases. Twenty-nine new diseases, among them Ebola, Lyme disease, and HIV, have emerged in the last two decades. In addition there has been a reemergence of diseases such as tuberculosis, once thought to be under control.[27] Many of these reemerging diseases have evolved multiple antibiotic resistance so that the current historical period can be described as the twilight of the antibiotic era. Within our lifetime, the challenge of pathogens that are resistant to all known antibiotics is a reality. In the third epidemiological transition, diseases are now a global threat because effective transportation systems[28] create a "virtual viral highway" through which disease can circumnavigate the earth in a matter of hours. The public, encouraged by films such as *Outbreak*, often believe that emerging diseases are the result of a mutation that increases the virulence of a pathogen. However, the biomedical community has been clear in their understanding that although changes in microbes do occur, anthropogenic factors are the real basis of the problem. The indiscriminate use of antibiotics, the deterioration of the environment,[29,30] global warming,[31] forced migration of millions of refugees, and the collapse of the infrastructure in many of the Third World nations is creating this crisis, in other words, the third epidemiological transition.

In 1995, 17 million of the 52 million deaths through out the World were the result of infectious disease according to the 1996 World Health Report. It is estimated that there are 20 million adults with HIV and 500 million people are infected with malaria and half of all humankind is at risk for endemic diseases.[34] It is not surprising that given the threat of disease to human population, there will be many assessments of how we became mired in this predicament and how we can extricate ourselves from it.

Randolph M. Nesse and George C. Williams' *Why We Get Sick*, Marc Lappé in *Evolutionary Medicine*, Paul Ewald's *Evolution of Infectious Disease* and Arno Karlen in *Man and Microbes* chronicle human disease history and the contemporary crisis. All but Karlen are committed to an evolutionary perspective using natural selection (Darwinian Medicine) to interpret the disease process. *Why We Get Sick* and *Evolutionary Medicine* provide a more comprehensive assessment of disease, while Ewald and Karlen limit their discussion to infectious disease. Ewald frames his argument from a model that sees modes of transmission affecting the virulence of the pathogen. Karlen believes that there is a symbiotic evolution of pathogens and humans, but he presents a discussion of the history of disease without a theoretical perspective.

From an anthropological point of view, I am starting with Karlen be-

cause he covers the diachronic changes from the Paleolithic to the present. *Man and Microbes* provides the most comprehensive discussion of disease in human evolution. Karlen, who is the author of *Napoleon's Glands and Other Ventures in Biohistory*, writes in the tradition of natural history. While he provides a panoramic view of diseases in human history from australopithecines to the emergence of HIV in modern *Homo sapiens*, he lacks a theoretical perspective in which to frame the story. Even though he accepts what has been considered the "common wisdom" that pathogens and humans evolve to a state of mutualism or commensalism, that concept plays little role in his analysis. He states, "Disease is not just biological thuggery, in which one species molests another. Rather, infection is an ancient event, basic to life, and tends to lead toward peaceful coexistence (p.16)." This coexistence, according to Karlen, occurs in three stages: Diseases begin as epidemics, become endemic, and finally reach a symbiotic state. This perspective has historical perspective in the work of Burnet,[35] Burnet and White,[36] Dubos,[37] and McNeill.[7,38] While Karlen is aware that some researchers believe that the mode of transmission has some role in evolution of virulence, he dismisses it as not "the majority scientific view" (Ewald, who is the proponent of this position, is cited in the bibliography but not in the text). The breakout of virulent forms of malaria and tuberculosis speaks against commensalism as a universal outcome.

Karlen provides a good introduction for those who have little knowledge of the impact of disease on human populations throughout history. I found many fascinating facts in his book, but some of his analysis tends to be superficial. For example, he characterizes the origin of the hominids (described as "the first shock") as our ancestors coming "down from the trees and into the meat." Descriptions such as this, and instances of imprecise analysis, detract from his discussion of the disease potential during the Paleolithic. The agricultural revolution is viewed as "both a triumph and a disaster." His discussion of the Neolithic disease patterns is interspersed with examples of disease from contemporary settings. Having been a part of the research team[39] that helped to establish the biocultural impact of the Neolithic, it is surprising to hear it described as a "disaster" or the "worst mistake in the history of the human race."[40] The first epidemiological transition had biological costs, including increases in nutritional and infectious diseases, but without the development of agriculture we could hardly have this discussion.

It is this first epidemiological transition that sets the stage for the subsequent pattern of emerging disease that has continued to the present. Emerging diseases require three conditions for transmission. There must be a preexisting focus of infection, social disruption or unusual population density that increases contact with the pathogen, and the opportunity for secondary spread of the disease (Lappé, p. 18). Neolithic technology creates changes in the ecology and provides a localized population with the critical density. As post-Neolithic technology expanded to incorporate larger and larger areas and disrupted the ecology to a greater extent, and as populations grew exponentially, the emergence of diseases accelerated.

Karlen provides a standard discussion of the changes in disease patterns since the Neolithic, showing that pathogen threats transmitted by air, water, human contact, and insects are exacerbated with urbanization. He discusses plague, leprosy, tuberculosis, and smallpox in detail. He explores the intriguing possibility that the rise of tuberculosis and the disappearance of leprosy are linked to the cross reactivity of *Mycobacterium leprae* and *Mycobacterium tuberculosis* and differences in their transmission. As urban population centers grew, *M. tuberculosis* has such a distinct advantage that it outcompeted *M. leprae*. Manchester[41] has effectively used this model to explain the decline of leprosy in Great Britain.

Without a theoretical perspective, Karlen creates a fact-filled discussion that often lacks direction. For example, while he discounts the New World origin of syphilis,[42] he does not provide a consistent discussion of the issues. He accepts Hudson's[43] unitarian hypothesis that the various forms of treponemal infections (yaws, bejel, pinta, non-venereal treponemal infection and syphilis) are caused by the same pathogen, and that their modes of transmission create different symptomologies. In a single paragraph (p. 125) Karlen says that syphilis existed in Europe before 1492 but was lumped with leprosy, became visible only after the Black Death, represents a mutation that produced a new strain of the treponeme and that it may be of African origin. The paleopathological and documentary evidence for these statements is not fully discussed.

Karlen considers the decimation of Native Americans after European contact within the context of the introduction of new diseases. He implies that the Native Americans had immune systems that were "naïve" to the European diseases. It is not clear if he means to imply a genetic difference in the response to disease, since a discussion of this issue is missing. For example, Francis L. Black[44,45] argues that there is evidence that Native American populations may have had a susceptibility to European diseases but subsequently evolved specific genetic response to these diseases. C. Svanborg-Eden and B. R. Levin,[46] however, find this evidence problematic. While there are clear examples of disease-mediated cellular polymorphisms such as the sickle cell trait (in the Old World), the specific genetic response is not likely to occur within existing human variation.

The last half of *Men and Microbes* covers the historical impact of epidemics such as cholera, polio, influenza, and a host of diseases that have emerged during the last quarter of the century. The polio epidemic of the 1950s was unusual in that the outbreak occurred in more affluent middle and upper class communities. The inhabitants of the economic ghettos were immune to the debilitating effects of polio because they lived in an environment that exposed them to the virus early in their development causing little biological damage and providing them with a lifetime of immunity.

Karlen presents an extensive discussion of transmissible spongiform encephalopathies (TSE) which cause

mad cow disease in cattle, kuru and Cruetzfeldt-Jakob disease (CJD) in humans, and scrapie in sheep. These diseases are thought to have a common origin in an infective agent that is a protein, a prion that appears to lack DNA or RNA. Recent research[47] on the prion has shown that differences in the folding of the protein can cause different expressions of the disease. However, Lasmezas and coworkers[48] report the transmission of TSE without evidence of prions. Still, the occurence of TSE infections in disparate species living in geographically separate regions demonstrates the inter-connectedness that occurs in nature. Pathogenically, it is indeed a small world.

Karlen does provide an extensive discussion of the anthropogenic factors that feed the third epidemiological transition. These include the breakdown of public health measures, economic development and land use, international travel and trade, technology and industry, human demographics and behavior, microbial genetic change and adaptation. Karlen's history of disease narrative is best for diseases with plentiful historical documentation. However, the method he uses for citation limits the book's usefulness. There are no references in the text, and the bibliography is not keyed to pages in the book. If you are familiar with the literature, you may have some sense of who is the source of the material. Thus, McNeill[7] remains the more authoritative and readable history of human disease. McNeill's discussion of the role of disease in molding world history provides a framework that allows one to evaluate his position; it is difficult to do the same with Karlen's history.

While Karlen shows that disease plagued ancient and modern populations, the next three books attempt to apply Darwinian Medicine to this finding. Marc Lappé provides a clear assessment of the cause of the present emerging disease dilemma and interesting speculation on how to apply evolutionary principles to problems. Lappé, the prolific author of such books as *Chemical Deception, Genetic Politics and Germs That Won't Die,* tackles the explosion of the AIDS epidemic, the emergence of antibiotic resistant pathogens and autoimmune disorders. Throughout the book, he attempts to demonstrate that these problems have common evolutionary roots. He writes (p. 10)

> …medicine can not be limited to blind ministrations to the ever-changing panoply of human ills and disorders but must understand the evolutionary consequence of such acts.

and our medical woes are

> …the result of a special blindness to the natural forces that have shaped human disease and the consequences of adding powerful medical forces to the very organisms they are intended to control. All human diseases have evolutionary origins.

Lappé effectively demonstrates how ecological disruption of the ecosystem creates the conditions that set the stage for diseases to emerge. He illustrates the process with examples from Lyme disease, plague and dengue fever in diverse global locales. In all of these cases, the coincidence of three factors provide the focus of infection: disruption, exposure and secondary spread.

Lappé links clonal cellular selection to the aging process, the decline of the immune system with age and the development of cancer with age. He suggests that recent research on aging in drosophila indicates that earlier notions of the inevitability of cellular death proposed by L. Hayflick and others needs to be reevaluated. Although his perspective is not novel, he attempts to suggest "evolutionary strategies" that can be used to solve medical problems associated with these processes. His attempts to explicate these "strategies" are interesting, but they are not always convincing. For example, he suggests that changing the selective forces rapidly and radically during therapy can create a kind of "evolutionary whiplash" that can catch tumor cells off guard in an evolutionary sense (p. 65). He says that this can be accomplished using an array of treatment modalities such as hormones, retinoids, cytokines, growth-factor antagonist, as well as traditional radiation therapy applied at critical stages of tumor development. However, Lappé's proposals are so general that I doubt they will have much impact on cancer researchers.

Evolutionary medicine should have its greatest impact in the arena of infectious disease. Alexander Fleming, the discoverer of penicillin, suggested as early as the 1940s that antibiotic resistance would be a problem. The culture of Medicine in the antibiotic era, has consistently assumed that another antibiotic would be available if a pathogen became resistant. It is not the fault of the pathogen, but the failure of the medical community to understand evolutionary principles that made antibiotic resistance inevitable. The indiscriminate use of antibiotics produces rapid selection in the pathogen. Presently, 40,000,000 pounds of antibiotics are manufactured yearly in the United States; this is 80-fold more than the 500,000 pounds produced in 1954.[49] Antibiotic resistance in pathogens was inevitable given the intense selective pressures produced by the onslaught of antibiotic use.

Lappé's discussion of infectious disease transmission accepts the theoretical underpinnings of Ewald's model in which differential modes of transmission affect virulence, but they are not a critical feature of his analysis. Lappé's research spans many levels of analysis. Early in his career he investigated RNA infections that impair the immune function, and more recently he completed a program in bioethics. He speaks as a biologist who has an understanding of the political and economic implications of the issues he raises. He applies these evolutionary strategies to AIDS, tuberculosis and malaria and often discusses the social implications of their treatment.

Even though Lappé's evolutionary strategies are speculative, they can be tested. For example, he suggests intentionally substituting more benign HIV viral agents along the chain of contagion as a means of altering the outcome of infection. This is not a very convincing strategy, but he nevertheless is well aware that any long term solution to the HIV epidemic will require behavioral changes that reduce human contact with the virus.

The progression of HIV infection sets the stage for Lappé's discussion of autoimmune disease. As he notes, "The paramount lesson of AIDS—that without an immune system, we succumb rapidly to opportunistic infec-

tions—also provides a way of looking at the evolution of the immune system itself (p.135)." The capacity that gives the immune system its edge for "zeroing" in on a deviant cell may have "too sharp a tooth" and attacks its own self. He uses allergy to show the overreaction of the immune system to benign substances.

Lappé concludes his book by suggesting that our "evolutionary neglect" can be remedied by what he calls the "apotheosis of evolution." The knowledge of how humans and pathogens co-evolve, the application of immunization programs, and the Human Genome Program will be the keys to moving us beyond the present situation. For my part, I doubt that the Human Genome Project will have a great impact on our knowledge of disease because so little epidemiologic information is being collected.

Ewald's early contribution[50] on the evolutionary function of symptoms was seminal in the development of Darwinian medicine. He demonstrated that many of the symptoms of diseases are actually advantageous to the host. This contribution, updated in chapter 2 of *Evolution of Infectious Diseases*, reviews the adaptive aspects of fever, symptoms of the common cold and of diarrheal disease.

Evolution of Infectious Disease is having a profound impact on how disease is portrayed in human populations. It represents one of the most thoroughly researched books on infectious disease. Ewald provides a detailed analysis of the role of disease in evolutionary theory. He recognizes that his contribution incorporates evolutionary epidemiology into Darwinian Medicine and that his perspective will push the narrow world view of health science. It will extend "…beyond medical settings to encompass parasitism in nature and agriculture involving both plants and animals (p. 8)."

Nesse and Williams describe infectious disease as "an arms race without end" (p. 52). The human response to pathogen is governed by the "Red Queen Principle" (Red Queen tells Alice that she will need to run as fast as she can just to stay in place). In this predator-prey model, humans are at a distinct disadvantage in their adaptive strategies. Ewald's model[51] of virulence provides a pathogen's view of this process.

The key contribution of evolutionary epidemiology is an understanding of virulence (which he defines as the negative effect of the pathogen on the host) with respect to modes of transmission. Specifically, Ewald argues that pathogens spread by biting insects will have higher virulence than those transmitted by personal contact. For example, the *Plasmodium falciparum* that causes malaria will be benign in the anopheles mosquito that carries it, but virulent in humans who are its final host. Those pathogens spread by cultural vectors, which are defined as cultural practices that allow transmission of a pathogen from an immobilized host to a susceptible one, are more virulent than others. For example, human activities that pollute waters with human wastes will result in the transmission of highly virulent pathogens. As sanitation is improved, the virulence will decrease because the pathogens require a more mobile host to spread the disease. Pathogens spread from person to person, for example by respiratory secretions, will be less virulent since mobility is essential for disease transmission. Ewald's use of "cultural vectors" is puzzling in that cultural practices are at the foundation of diseases that are spread by insect and cultural vectors. For example, in West Africa, it was a cultural practice (slash and burn agriculture) that disrupted the ecological setting, displacing the non-human primates that were sources of meals for the mosquitoes, creating a new environment for the mosquitoes to breed, and providing the human population as a new food source.

Ewald uses two case studies, the 1918 influenza epidemic and the HIV epidemic, to test his theoretical perspective. The presentation of both cases is disappointing. His advocacy is so strong, his evidence so one-sided, and his dismissal of those that disagree with him so cursory, that the serious reader quickly becomes frustrated in what he has to say. He dismisses a consideration of plague in his model because it not only has an insect vector but can be transmitted by humans. It seems, however, that the plague would be precisely the example that would be most effective in testing his model. The 1918 influenza pandemic claimed 20,000,000 lives (twice the number that died during World War I). Ewald states (chapter 7, War and Virulence) that these deaths were "caused evolutionarily by the war rather than coincidentally with the war (p. 115)." Trench warfare immobilized the infected soldiers, creating a more virulent form of the pathogen (the virus was easily spread to those lacking immunity). The virus became less virulent following the war as the populace dispersed and became more mobile.

Almost a third of Ewald's book (chapters 8 and 9) is devoted to the HIV/AIDS epidemic. He clearly sees the origin of HIV as a zoonotic disease that evolved from a simian virus. However, readers should not expect a balanced treatment of the epidemic since Ewald uses it to push his theoretical position. For example, he states that HIV-2, found in West Africa, is less virulent than HIV-1 because individuals in these populations have fewer sex partners. This is in line with his belief that we should invest in interventions[52] that reduce the frequency of sexual and needle-borne transmissions of HIV. This, he contends, will provide a long term solution to the AIDS epidemic by causing the evolutionary transformation of HIV into a more benign pathogen.[53] While Massad[54] offers support for this assertion, Lipsitch and co-workers[55,56] show that he commits errors that invalidates this conclusion. According to Ewald, we are now in a position to get "evolution to work *for* us instead of *against* us" (p.214).

> ....I have advocated social intervention to find out whether certain cultural changes can reduce virulence. I suggest that we ought to invest regionally in mosquito-proof housing to determine whether this intervention would make vector borne pathogens like *Plasmodium falciparum* and dengue evolve towards lower levels of virulence.

He states that "We shall, in a sense, domesticate them so that they can live with us in a less damaging way than they have throughout our history" (p. 215). While it is one thing to develop

an attenuated pathogen in the laboratory and use it to develop a vaccine, it is quite another to assume that we can do this in nature. Ewald's position is one of evolutionary arrogance, in which he assumes that we can manipulate the evolution of pathogens in nature as we wish. Does this position differ much from the physicians who assumed that there would always be a "magic antibiotic bullet" that would be ready for the next epidemic of a drug resistant pathogen, or a public that believes we can "genetically engineer" ourselves out of the multi-drug resistant pathogen dilemma, or the malariologist who thought they could exterminate the mosquito as the means to eradicate malaria? I have assumed that interventions that save lives should be worthy goals in and of themselves. Instituting public health practices that isolate humans from pathogens will save lives. However, I find the suggestion that this will also provide a test for a theory in evolutionary epidemiology (Ewald's long term solutions) somewhat self-serving. I also expect that this is not likely to promote what Ewald calls "short term benefits" of the public health measures.

What is missing from Ewald's work is a serious testing of his hypotheses by the use of epidemiological models. There are a number of studies that model the evolution of virulence and test Ewald's pronouncements. Recently, M. Lipsitch and coworkers[57] question simple models of virulence-avirulence that follow only the horizontal and vertical transmission continuum. They examine the evolution of virulence in pathogens that incorporate both horizontal and vertical transmission and conclude that Ewald's simple model does not reflect reality.[56] Bull[58] demonstrates a variety of factors that effect virulence beyond the mode of transmission. Levin and Bull[59] show that within host selection for more virulent forms of HIV, poliomyelitis, and bacterial meningitis is a distinct possibility. Others[60–63] demonstrate the limitations of Ewald's simple model and provide methods for testing their validity.

Finally, theoretical discussion about the evolution of disease loses sight of one of the ultimate causes of disease. Nearly 150 years ago one, Virchow,[64] a prominent scientist of the day, predicted that,

> Once medicine is established as anthropology, and once the interest of the privileged no longer determine the course of public events, the physiologist and the practitioner will be counted among the elder statesmen who support the social structure. Medicine is a social science in its very bone and marrow.

The 1995 WHO World Health Report[65] echoes Virchow's observation,

> The World's biggest killer and greatest cause of ill-health and suffering across the globe is listed almost at the end of the International Classification of Diseases. It is given in code Z59.5—extreme poverty.

Paul Farmer[66] shows how global social inequalities are at the center of many emerging diseases. Americans are not immune to the impact of poverty. Adults in New York City's Harlem have a greater age specific mortality than do adults in Bangladesh.[67] Infectious disease in Harlem is the greatest factor in these deaths.

If Darwinian medicine is going to have an impact on our intellectual life, it will have to encompass more than the study of infectious disease. Randolph Nesse, an influential psychiatrist at the University of Michigan who founded the program in Evolution and Human Behavior, and the eminent evolutionary theorist George Williams provides a clearly stated theoretical perspective in which evolutionary principles are the basis for understanding an array of disease processes. *Why We Get Sick* is an extension of their influential article "The Dawn of Darwinian Medicine"[68] in which they argue that an understanding of natural selection would profoundly affect medical practices. The lack of attention by the medical community is, they said,

> … unfortunate, because new applications of evolutionary principles to medical problems show that advances would be even more rapid if medical professionals were as attuned to Darwin as they are to Pasteur (p. 2).[68]

Concern with diagnosis, symptomology, and comforting the sick focuses on the individual as the carrier of disease and certainly limits physicians' perspective. Darwinian Medicine seeks evolutionary explanations for the vulnerabilities to disease by applying the adaptationist program. This adaptationist program involves the evolutionary origins and functional significance of "unsuspected facets of human biology"[68] (p. 1) as illustrated by the adaptive value of fever.

Evolutionary explanations of disease can include categories such as body defenses, infections, novel environments, genes, design compromises, and evolutionary legacies. For example, the body defends itself against respiratory pathogens by coughing. The use of cough "medicine" increases an individual's chances of extending an infection since the suppressant will inhibit expelling the pathogen by coughing. Like other mammals, humans have an immune system that may effectively control pathogens, but it may also be so responsive that it reacts to its own body, causing autoimmune disease. We walk upright which creates design compromises that increase the risk of complications at birth and predispose us to lower back problems. These and similar examples are grist for the Darwinian Medicine mill. Evolutionary medicine is not intended just to "spark" doctor's chat at cocktail parties, Nesse and Williams expect it to spawn a field of study that will transform medical theory and practice.

Nesse and Williams believe that "the dawn of Darwinian Medicine" will affect the way we view disease, and therefore will change medical education, influence clinical practice, inspire public policy, alter personal behavior, and inform philosophic thought. They expect that Darwinian medical thinking will lead to changes in the practical aspects of every day life by teaching people to avoid pathogens, reject fever reducing medication (unless the fevers are life threatening), and eliminate iron supplementation when chronic infection is present. Diarrhea will be allowed to run its course (Lappé suggests that Pepto-Bismol, in which the active ingredient is bismuth subsalicylate, can be taken prophylactically since it does not affect trans-

port, and that drugs such as Lomotil should be avoided because they do).

Adaptation by natural selection is at the heart of Darwinian Medicine. According to Nesse and Williams, adaptation is not confined to the human response to disease, but also concerns the adaptations of pathogens to host, the maladaptative cost of host adaptations, and the mismatches between our adaptation and the environment. While medicine focuses on the proximate causes of disease, Darwinian Medicine seeks the ultimate cause of disease (p. 6). By understanding the evolutionary origin and adaptation of disease, medicine will be able to effectively achieve its goals.

Nesse and Williams' approach is sociobiological and incorporates a functional analysis that is amenable to evolutionary hypothesis testing (p. 20). Specifically, their research strategy is to search out plausible hypotheses that are not so obviously right or wrong and then test them. They do not champion specific hypotheses like Ewald does but instead develop a framework for investigating them.

Because health declined during the Neolithic, there are those who describe the Paleolithic as an idyllic time in which well-nourished populations lived in a disease free environment. Nesse and Williams move beyond this "Club Med" perception of the Paleolithic. However, they are inconsistent in their view of the "Stone Age." They claim that "(h)uman biology is designed for Stone Age conditions."[68] They see a balance between mortality and fertility so that Paleolithic populations were stable for much of the period because maximum fertility was balanced by very high mortality rates. They also argue that infectious disease increased during the Neolithic period. If this contention were true, however, it would have been difficult for the human population explosion following the Neolithic. Alternative scenarios[69] suggest that fertility was not at its maximum during the Paleolithic and that humans were able to respond reproductively to meet the Neolithic demand to have more children when they experienced increasing mortality due to nutritional deficiencies and infectious disease.[39]

A key to Darwinian Medicine is the postulation of an incongruity or discordance between genetic make-up and the environment in which we live. We have a genetic system that evolved to the African savanna, but now live in canyons of skyscrapers. In this scenario, diseases of civilization result from a human genetic system that adapted to a Paleolithic environment and has not had a chance to evolve or to adjust to our modern industrial setting ("Stone age genes in the fast lane" is how Eaton and colleagues[70] describe it). The human craving for sugar and fats, myopia, cancer, allergies, food aversions, and diabetes are examples of the incongruity of our genetic adaptation. Some of these conditions are the result of hyper-efficient metabolic diseases grounded in adaptations to Paleolithic periods of food scarcity which become problematic when there is an abundance of food. On the other hand, some of these conditions are design defects that reflect legacies of our evolutionary history. In a sense, these legacies are "scars of evolution"; they include, for example, adaptations that represent compromises to upright posture. The arthritic degeneration of the vertebra column, inguinal hernia, and sacroiliac degeneration that plague many contemporary humans are additional scars of evolution.

While Nesse and Williams discuss trade-offs in evolution, they frequently revert to a position that implies perfection in natural selection. They jokingly suggest that many of the problems of our biological systems make it seem as if our bodies were designed by a "prankster." How else can we explain the occurrence of allergy and asthma? Ten million Americans are affected by allergy, and about 4,500 asthma deaths occur each year at an estimated annual cost of 4 billion dollars.[71,72] In Western society, the incidence of asthma has doubled in the last 20 years.[73] Tongue-in-cheek, Nesse and Williams say that the

> IgE antibody seems to do almost nothing, at least in modern industrial countries, except cause allergy. It would appear that we evolved this special IgE machinery for no better reasons than to punish random individuals for eating cranberries or wearing wool or inhaling during August (p.160).

However, with the power of Darwinian Medicine this puzzle is solved:

> We can be sure that the capacity for an allergic reaction is a defense against some kind of danger, or else the underlying mechanism, the immunoglobulin-E (IgE) part of the immune system, would not exist. It is perhaps conceivable that our IgE system is a remnant of a system that was useful for other species, but this is unlikely because systems of this complexity degenerate quickly if they are not maintained by natural selection and even more quickly if they cause any harm. It is much more likely that the IgE system is somehow useful (p. 159).

Three of these books, those by Lappé, Ewald and Nesse, and Williams, use Profet's[72] interpretation that allergy is an adaptation that expels toxins from the body. Given the choice of considering allergy as an immunological mistake or as a defense against parasites such as helminths, Profet opts for a functional explanation. She argues that the "evolutionary persistence of allergic capability, despite its physiological costs, implies the existence of an adaptive benefit... that outweighs the cost..."[74] (p. 24–25). She suggests that there is an inverse relationship between allergy and cancer and that the function of allergy[74] is analogous to that of morning sickness and menstruation.[77] Profet[75,76,78] has proposed that the nausea of morning sickness is an evolutionary defense against the toxins ingested by a pregnant woman. Nausea causes the mother-to-be to "throw-up" any toxins she has ingested and to avoid foods containing them. Accordingly, Nesse and Williams state that pregnant women should "respect their nausea" and maintain that children who steadfastly refuse to eat their vegetables are showing evolutionary wisdom. They support Profet's argument that menstruation functions as a defense against pathogens that enter the vaginal tract attached to sperm during sexual intercourse. Strassmann,[79] however, criticizes this hypothesis and shows the

replacement of the endometrium following the failure of implantation is an energetically cost-effective adaptation.

To Nesse and Williams, allergy is like a "smoke detector" that sets-off a false alarm now and then (in cases of allergic reaction to benign substances), but is not disarmed because it will "be there" when there is a real threat from inhaled or ingested carcinogenic toxins. An allergic response occurs when a protein substance such as pollen or a food stimulates the IgE antibody to produce a cascade of reactions, including watering eyes, sneezing, itching, and a rash. In more severe reactions, asthma occurs when there are bronchial spasms that create a respiratory crisis that can lead to death.

Lappé uses a "gatekeeper" analogy to explain allergies in general and asthma in particular. He argues that asthma is an adaptation that is tied to the domestication of grains 14,000 years ago. The risks of inhaling moist grain contaminated by products such as molds (*Aspergillus*) and fungal spores (p. 205) was the selective force in the development of asthma. Asthma originated as a means of shutting down the respiratory system enough to inhibit inhaling molds or fungi. He argues that the present allergy crisis is an overreaction caused by an environment packed with industrial pollutants and by the fact that people live in contemporary houses so tightly built that they lack proper ventilation and are loaded with allergens (p. 208).

What is missing from Darwinian Medicine's interpretation of allergy is a truly evolutionary interpretation of the disease. Allergy is on the list of diseases that arose following the second epidemiological transition. Prior to this transition, helminthic infestations were controlled by the elevation of the IgE antibody. Nesse and Williams mention the relationship of IgE and helminthic infection but dismiss it since the schistosomes are no longer present in the United States and because production of IgE should be selected against. Hypersensitivity to helminths is blocked by the production of IgG which is specific for the parasite but not other allergens. With helminthic infestation controlled, humans maintain an elevated titer of IgE and thus a hypersensitivity to substances in the environment.[72] Barnes and co-workers[72] see the inverse relationship between allergy and cancer as a circumstantial benefit. The "allergic" responses developed long before hominoids attained life expectancy sufficient for cancer to have been a significant selective force. Recently, Shigrakawa and coworkers,[80] have demonstrated that in Japan asthma decreases with tuberculin response. They suggest that *M. tuberculosis* may have modified the immune system in such a way that inhibits atopic disorder. Others[73] have suggested that there has been a decline in other infectious diseases that must be considered. Cultural changes that lead to the decrease in exposure to the parasites usually increase exposure to allergens. For example, homes are built so "air-tight" that they increase breeding sites for cockroaches, a major source of allergens. Synthetic material in modern homes are also very allergenic.

In reality, all three of these Darwinian Medicine volumes (Ewald, Lappé, and Nesse and Williams) fail to delve back into an evolutionary time depth that is worthy of the name. Ewald's evolutionary "glimpse backwards" (chapter 10) is a short case study of Mesopotamian and Egyptian notions of parasites and disease. His retrospective is limited and short sighted. Researchers using an evolutionary lens should not "quit early," because it may be necessary to go back to the origins of the hominids or to the age of mammals to understand the basis of human adaptation to disease. When Ewald restricts himself to the ancient period, he owes it to the reader to provide a more thorough discussion of the diseases of the period. For example, his discussion of Egypt fails to consider therapeutic practices[81] such as the ancient use of antibiotics in Egypt and the Sudan[82] although this certainly is relevant to disease evolution[83] and the human response. Lappé's and Nesse and Williams' discussion of allergy is similarly time-limited.

There is a facile aspect to the presentation of Darwinian Medicine. To say that teenagers are showing evolutionary wisdom in their dislike of vegetables or to suggest that "instinctive diversification" minimizes the damage of dietary toxins misses important evolutionary aspects of food choice.[84] The diversification of human food choice has roots in our mammalian ancestors in what Paul Rozin[85] calls the "omnivore's dilemma." Cultural aspects of food choice are subverted for biological explanations. The biological basis of our "sweet tooth" or "fat tooth" is not a sufficient explanation of our excessive consumption of these foods. Mintz in *Sweetness and Power*[86] explains how this biological propensity for "sweetness" in foods is exploited by an economic system. In some sense, the original paper ("The Dawn of Darwinian Medicine") offers a more satisfying analysis than do these books. Even though it can be subjected to the same criticism that I am making with regard to the books, the original paper provides the evidence that the authors believe supports their examples of adaptations that support evolutionary medicine. Presenting the case for Darwinian Medicine to a wider audience requires that a balanced case for their arguments be made.

Darwinian Medicine underplays the extension of longevity and its impact on diseases such as cancer. Although human biology is designed for the "Stone Age," it seems equally effective in adapting to the modern industrial state. More people in contemporary society live longer than their predecessors, but this improvement has biological costs. For example, osteoporosis (not mentioned by Nesse and Williams) is obviously related to our increase in longevity. Ancient populations show a similar pattern of bone loss between the ages of 20 and 55 years. However, in ancient populations only a small percentage (5% in ancient Nubia) live to their 80th year, whereas in 1993 in the United States 65% reached this plateau. To use a phrase such as "Stone Ager genes" suggests that modern humans are restricted in their ability to respond to today's environment. Sapolosky[87] demonstrates that contemporary human responses to stress are quite different from those of our ancestors. While this can present problems in how we react to stressors, there are also positive behavioral changes that can mediate stress and minimize its deleterious effects.

Darwinian Medicine has to clarify the concept of adaptation to one that includes the idea of imperfect adaptation. While discussing the trade-offs that occur in evolutionary adaptation, these authors seem to assume that a perfect adjustment is the ultimate outcome of the process. Their interpretation of allergy exemplifies this notion of perfect adaptation. An evolutionary perspective on health and disease should consider adaptation as a temporal process that often involves trade-offs that may not represent a perfect adjustment to the insult. If the selective pressure for a specific adaptive feature is reduced, natural selection will not necessarily lead to a quick degeneration of the system. Adaptations are built upon existing systems that do not always respond to challenges in a perfect manner. Furthermore, once there is a reduction in the selection for a particular trait, it may be maintained because of the inertia that exists in a cascade of complex features that are part of the adaptive system. I am not sure that Darwinian Medicine as it is now conceived and as it is represented in these books is effectively studying evolutionary change. Lappé, Nesse and Williams, and Ewald present narrowly defined examples that represent a hyperadaptationlist perspective within a contemporary time frame. In a sense, their conception of adaptation is less evolutionary than it is an asynchronic functional analysis.

Darwinian Medicine provides a number of compelling examples of diseases of civilization. The occurrence of reproductive cancers are related to changes in the reproductive histories of contemporary women who have fewer pregnancies and therefore have three times the number of menstrual cycles than their ancestors did. Modern women's breast tissue is therefore more frequently exposed to estrogen, and this results in an increased risk of cancer. Scholars of Darwinian Medicine suggest that it may be possible to artificially produce a hormone that will mimic the effects of pregnancy.

Sleep disorders are also amenable to an evolutionary interpretation. Modern medicine assumes that if you can not get your eight hours of sleep between 11 p.m. and 7 a.m. you have a sleep disorder. This sleep schedule was imposed by an industrial society and is a recent pattern in human evolution. Similarly, Mckenna suggests that for mothers and infants to sleep independently is also a recent pattern in human history and one that has many health implications.[88]

As the world enters the third epidemiological transition, there will be unprecedented threats to the health of vast segments of human populations. This crisis requires a re-evaluation of the paradigms that framed our understanding of how this came to be. The proponents of Darwinian medicine whose work I have reviewed here are proposing public health policy based on hypotheses that, in many cases, have not been tested. Evolutionary principles applied to issues of health and disease is a profound intellectual development that illuminates many of the issues raised by this most recent disease transition. For this reason, Darwinian Medicine should have a strong foundation that will withstand the scrutiny of a skeptical medical community. As it now stands, the foundation of Darwinian Medicine needs to be reinforced. Darwinian Medicine built on a sound theoretical foundation and tested empirically will become an essential tool for evolutionary anthropologists seeking to understand the basis for healthy adaptations to complex environments.

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George Armelagos
Department of Anthropology
Emory University
Atlanta GA 30322
antga@anthro.emory.edu

Epidemiologic transition, the process by which the pattern of mortality and disease in a population is transformed from one of high mortality among infants and children and episodic famine and epidemics affecting all age groups to one of degenerative and human-made diseases affecting principally the elderly.Â Thank you for your feedback. Our editors will review what youâ€™ve submitted and determine whether to revise the article. Join Britannica's Publishing Partner Program and our community of experts to gain a global audience for your work! Share. SHARE. Facebook Twitter. Epidemiologic transition. sociology. WRITTEN BY.