

Darwinian Medicine and Public Health

Sara Abdollahian and Ruth Magtanong

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I. Introduction:

Darwinian medicine is a new field of study integrating evolutionary biology with medicine. Essentially, Darwinian medicine, also known as evolutionary medicine, is the application of evolutionary theory to medicine. Evolution by natural selection is central to understanding human susceptibility to diseases. Darwinian medicine seeks to answer two types of explanations for the existence of diseases: proximate explanations, answering the “what” and “how” questions pertaining to disease rates and transmission patterns, and ultimate explanations, answering the “why” question regarding origins and functions of disease. Both perspectives are needed to fully comprehend why humans get sick especially in terms of how biological mechanisms and evolutionary history are integrated processes in the creation of disease.

In this chapter of the MPHP 439 online textbook, we seek to explain why an evolutionary perspective on human susceptibility to disease is both needed and useful in public health. By using examples, we hope to show how Darwinian medicine has already been applied within a public health context in order to suggest how principles of evolutionary biology can be utilized in future interventions. This new and controversially argued field of study seeks to explain more popularly accepted disease models in the terms of natural selection and evolution. This evolution-based approach has also been used to explain variation in human behavior (e.g. evolutionary psychology or psychiatry) as causes for the development of pathology in some mental disorders but evolutionary hypotheses with a focus on the relationship between human social behavior and its association to individual reproductive fitness will not be addressed here. Instead, this chapter focuses on evolutionary models that have a basis in the regulation of biological and physiological mechanisms as potential sources of disease pathology. “Darwinism gives no moral guidelines about how we should live or how doctors should practice medicine. A Darwinian perspective on medicine can, however, help us understand the evolutionary origins of disease, and this knowledge will profoundly be useful in achieving the legitimate goals of medicine.”¹

The Evolutionary Perspective:

Past models of disease etiology have highlighted the importance of an integrated approach. The epidemiological wheel and ecologically based models have attempted to explain how the complex interactions between pathogen and host within social, physical, and biological environments result in producing disease states. However, an evolutionary perspective is often

¹ Nesse & Williams 1994. Pp. 12.

missing in past models of disease etiology. Evolution is the process of change in genetic frequency in a given population of distinct species that affect survival and reproduction. In a process of natural selection, traits are under selective pressure in changing environmental contexts to maximize an individual's ability to survive and reproduce. Evolution is important because it gives a historical basis on which to interpret why we are the way we are in relation to adapting pathogens and the changing environment. Evolutionary arguments have the ability to contextualize our ancestral adaptations according to their selective pressures in comparison to the way we are now. Using this model, we can look at how the pathogen or condition has evolved, or how the host, us, has evolved—either way, an evolutionary argument looks for why we are the way we are and experiencing the types of ailments that we are. As much as we look for how we have evolved, we must also look for how we have not evolved, in order to investigate the dynamic changing relationships between environment, genetics, and the pressures they create in changing living organisms.

In contrast to the biomedical metaphor of the human body as a machine and disease is viewed as a system malfunction, an evolutionary perspective of human susceptibility to disease views the human body as a “bunch of evolutionary compromises.”² Diseases are vulnerabilities that have origins in the human evolutionary history. The human body is the result of adaptations developed in an ancestral environment. Pathology ensues when biological mechanisms are activated in our current environment, an environment producing lifestyle changes and cultural practices different from the one in which the human body was adapted for. “An evolutionary view of medicine sees the body as a product of natural selection, extraordinary in many ways but also flawed for evolutionary reasons.”³

Darwinian medicine has created its own classification system for explaining the existence of diseases in human populations using evolutionary principles. Diseases are classified by the following six categories: 1] diseases are viewed as defenses e.g. fever fights off pathogens by encouraging the host to recuperate in order to recover; 2] diseases are infections e.g. HIV; 3] diseases are a result of introduction into novel environments; because there are no selective pressures to eliminate the foreign pathogen, the new environment is ideal for efficient proliferation. For example, think of the zebra mussel, brought to the Great Lakes on the sides of shipping barges. Once these organisms were introduced into their new environment, without any predators to eat them or pressures of the natural food chain to eliminate them, they efficiently spread and overrun the entire ecosystem. Much like a zebra mussel in the Great Lakes, diseases too can benefit from a new environment without selective pressures to either eliminate them or keep them from causing harm. 4] Diseases are consequences of changes in the genes; the most commonly referenced of which is cancer. Cancer is characterized by the uncontrolled proliferation of cells due to DNA damage that results in mutations to genes that code for the proteins controlling cell division. 5] Diseases are the result of design compromises e.g. how the evolution of bipedalism has resulted in low back pain for many humans and 6] diseases are evolutionary legacies; our ancestors adapted to the condition, or somehow benefited from it in the past whereas now it may not be so e.g. peptic ulcers, which evolutionary medicine believes were once beneficial to our ancestors due to the co-existence of the *Helicobacter pylori* within the stomach for maintaining of stomach acidity balance.

The Adaptationist program is utilized as a method of inquiry to explore explanations of disease etiology. Biological mechanisms and human traits are hypothesized to be adaptations in

² Nesse & Williams 1994. Pp. 4.

³ Nesse, RM. 2001. Culture and Medicine: How is Darwinian Medicine Useful? *WJM* 174: 358-360.

response to selective pressures in the environment. Questions to ask when creating an evolutionary hypothesis are:

- Why does this trait exist?
- What is the function of a given structure or organ?
- How does the trait contribute to the reproductive success? What is the evolutionary history of the feature?
- Is the trait part of some other adaptive machinery?

Not all of these questions will necessarily be answered for each subject; however, it is important to ask why you cannot answer them or what other ways you can ask the question that fits the subject. A word of caution when using the Adaptationist Program is in making the naturalistic fallacy, the assumption that all adaptations are good. Also known as the Panglossian paradigm, the naturalistic fallacy “assumed that any trait had to have a good use to explain its presence, even if none was obvious.”⁴ The current function of the trait may not explain why the trait evolved. The trait may perhaps just be a consequence of development carried over from evolutionary processes but not considered an adaptation. In using the Adaptationist Program, it is important to demonstrate “what kind of evidence is necessary to support the hypothesis that a trait is an adaptation formed by natural selection and what evidence could point towards some other cause of the current state of the trait in question.”⁵ In addition, as stated previously, an evolutionary perspective seeks two different kinds of explanations: proximate explanations that address the biological mechanism involved for a disease and ultimate explanations, the evolutionary basis for the disease. Both explanations are necessary in order to completely gain a better understanding of disease etiology especially in terms of how the ultimate and proximate causes work together in producing the disease.

One important thing to keep in mind when addressing any topic concerning evolution is that idea of race. Race is a cultural construction, and it is important to realize that within the same racial classifications there are often more genetic differences than found between individuals from what are classified as different races. Specific theories based in evolutionary fundamentals usually explain differences between societies, by positing different societies at stages of development. The entire notion of “race” has no biological reality, thus no disease or condition can be “racially specific.”⁶ Racial classifications can be a problem in regards to Darwinian medicine if physicians and health care providers use racial classifications as a means of administering genetic based treatment options. Darwinian medicine supports the idea that human susceptibility to diseases is not as result of differences in race, but occurs as result of natural selection applying selective pressures on human populations living in specific locations, under specific environmental contexts.⁷

There are several specific human populations that are particularly susceptible to certain diseases. For example, Tay Sachs disease has a higher prevalence in Eastern European Jewish populations where 1/3,600 births are diagnosed with the condition.⁸ Tay-Sachs is a fatal

⁴ Pigliucci, M. and Kaplan, J. 2000. The fall and rise of Dr. Pangloss: Adaptationism and the Spandrels paper 20 years later. *TREE* 15(2): 66-70.

⁵ Pigliucci & Kaplan 2000. Pp. 66.

⁶ Gaines, Atwood D. 2005 Race: Local Biology and Culture in Mind. In *Companion to Psychological Anthropology: Modernity and Psychocultural Change*. Conerly Casey and Robert B. Edgerton, Editors. Oxford: Blackwell. Pp. 255-278.

⁷ Diamond, J. 1991. Curse and blessing of the ghetto. *Discover* (March): 60 – 65.

⁸ Diamond 1991.

homozygous recessive genetic disorder in which biochemical abnormalities cause excessive accumulation of a fatty substance called G_{M2} ganglioside in nerve cells due to a missing enzyme hexosaminidase A that generally breaks it down.⁹ However, there is a selective advantage in this type of fat accumulation, because those who are heterozygote for the Tay-Sachs trait are protected against Tuberculosis. Because Eastern European Jews were forced to live in crowded ghettos where TB thrived, they may have disproportionately evolved to acquire this trait in their population towards selection to evolve genetic resistance to TB. There are many genetic diseases such as Tay-Sachs and sickle cell anemia that may persist as both “blessings and curses.”¹⁰ On the one hand they may kill or impair individuals who inherit two copies of the faulty gene; however, those who receive only one gene may benefit by acquiring its protection against other diseases. Although further research is needed in order to find the biochemical mechanism by which fat accumulation might confer resistance against TB, for such ailments, specific health interventions may be tailored based on genetic markers associated with the disease. This example further expresses the importance of an evolutionary perspective in order to capture the evolutionary history depicting the interplay between population genetics and the environment in which certain traits or conditions produce distinct results. However, when administering treatments to these groups that are more greatly affected by these conditions due to the evolutionary pressures put on them by their environment, health care professionals must keep in mind racial classifications are not definitive biological realities, but social constructs. Inferring racial classifications can lead to misdiagnoses and potentially harmful treatments that are not evidence based. By solely looking at genetics, one disregards evolutionary histories, and their account for human populations under natural selection.

Case study: Acute Phase Response

A classic application of Darwinian medicine is in explaining why when humans get sick; the body experiences a range of nonspecific symptoms, one of them being fever. Darwinian medicine argues that fever, instead of being a manifestation of the disease and seen as a “defect” that needs to be fixed, is actually one of the body’s defenses against infection. Fever is a regulated response to infection.¹¹ Method of treatment and disease outcome is influenced when perception of fever is thought of either as a defect or a defense. If fever is a defect, then any intervention aimed at correcting the fever would be a good thing. On the other hand, if fever is part of the body’s natural defense system, as part of the acute phase response, then any intervention attempting to block or eliminate fever can perhaps impede one’s body from repairing itself in the natural way it has been evolved to do so.

II. Public Health Application: Virulence Management

What is virulence management? Virulence management has three major functions in managing infectious diseases: 1] it actively selects for mild strains over the more virulent forms of the pathogen; 2] it minimizes the severity of damage caused by the pathogen by implementing direct and indirect strategies of disease management and 3] it anticipates the consequences of human interventions in regards to treatment and prevention of disease by taking into account the past trends of the disease, and attempting to foresee the future trends. The objectives of virulence

⁹ Diamond, 1991.

¹⁰ Diamond 1991.

¹¹ Kluger, MJ., Kozak, W., Conn, CA., Leon, LR., and Soszynski, D. 1997. The adaptive value of fever. *Fever: Basic Mechanisms and Management* 255-266.

management are the use of evolutionary principles to minimize pathogen virulence in infectious diseases and to predict how other types of interventions might affect virulence.

Methods in virulence management are interventions that directly target virulence (e.g. vaccines). There are also indirect selections against virulence via social interventions such as targeting pathogen's mode of transmission. Using this framework, we will investigate HIV/AIDS and TB as examples in which virulence management has potential in enhancing the effectiveness of the development of medical interventions (e.g. vaccines and antibiotics) and in combination with the implementation of social intervention programs, to reduce infection. "Understanding the epidemiology of infectious diseases from an evolutionary point of view permits many assessments – including why virulence evolved in the past, what is currently maintaining it, how it may evolve in the future and, most important, how human activities can influence this evolution."¹²

Adaptations and Counter-adaptations:

Existence of infectious diseases is accounted for by Darwinian medicine as result of pathogen-host interactions in generating adaptations and counter-adaptations. The pathogen-host interaction has been compared to an "arms race" in which pathogens counteract host defenses and hosts generate adaptations in response.

The Evolution of Virulence:

A past assumption of parasite-host interactions is that the relationship between parasite and host evolve to a benign coexistence. A parasite's reproductive success is greater when the host is kept alive. However, evolutionary biologists have a different perspective. Evolution through natural selection acts on pathogens in two ways: 1] contest of the pathogen within the host favors competitors that most effectively use host resources for replication and 2] competition among variant pathogen species in the transmission to new, uninfected hosts.

Changes in virulence is a highly evolvable trait that depends on any one or a combination of four factors: 1] mode of dispersal, 2] ability to live outside the host, 3] location within the host and 4] ability to deal with host's immune system. Each of these factors incurs or reduces costs on the pathogen affecting its evolution.

The evolution of virulence is explained by the trade-off model; virulence is a consequence of the trade-off between reproduction and transmission in pathogen-host interaction. A more virulent (i.e. increased ability to replicate) pathogen cannot rely on host mobility for transmission. A pathogen that relies on its host for mobility cannot be as virulent as those that do not rely on a host for transmission because the ability of the host to move is compromised. In this regard, diseases that do not rely on host mobility and are instead, transmitted via vectors such as animals, insects, and water, are predicted to evolve into more virulent forms. In other words, the easier and less dependent the pathogen is on host mobility for the transmission, the greater evolution towards greater virulence.

Human behavior can also affect changes in virulence. Cultural vectors, "pathogen transporters" created by human behaviors (e.g. dams, medical equipment, etc.) and humans themselves (e.g. medical personnel in hospitals) can aid in the spread of infections. Antibiotic resistance in hospitals and the HIV/AIDS epidemic are examples in which human behavior has influenced the extent and spread of disease.¹³ In order to prevent the spread of many diseases,

¹² Nesse & Williams, 1994, pp. 92-93.

¹³ Ewald, PE. 1993. The evolution of virulence. *Scientific American* 86-93.

interventions that address human behavior aspects should be taken into account alongside those that are biologically focused.

There are many challenges to virulence management. Evidence for the trade-off model underlying virulence management can be obtained from two sources, experiments carried out under artificial conditions e.g. laboratories and animal models, and experiments under natural conditions. Differences between natural and artificial conditions can alter the interpretation of the data produced or provide the necessary strength in arguing that a trade-off actually occurs.¹⁴ In addition, the complexity of the interplay between pathogen and host provide many confounding factors that may be impossible to control and hold constant in experiments, thus influencing the reliability of the data. Another experimental challenge is the lack of data demonstrating that a change in transmission results in the selection of milder strains of the pathogen and as a result, the disease inflicted in human populations is less harmful. Experiments that may provide the data needed to provide evidence for this hypothesis are expensive, time-consuming and labor intensive.¹⁵ The data used to support virulence is based on “unnatural conditions;” there are challenges to applying theoretical models to real-life situations.¹⁶ In laboratory experiments, the differences seen in altering transmission is slight, unlike the data evidenced from observations in real-life situations.

These challenges perhaps give evolutionary biologists looking for more evidence for virulence no other option but to observe “natural experiments.”¹⁷ In addition, the current biological information is insufficient to test theory or for application. Often, the cause of virulence for a pathogen is unknown, and thus, direct selection by developing vaccines that target virulence directly is not possible. More empirical studies of pathogens must be done to address these challenges and provide more data to support the theory of virulence.¹⁸

Direct selection of virulence: Vaccines

Virulence management in developing ways to directly select against virulent forms of the pathogen has been successful in many cases (e.g. vaccines). Vaccines have aided many countries in reducing prevalence rates of rubella, polio, measles, mumps, and typhoid, and eliminating small pox. Vaccines may be living, weakened strains of a viruses or bacteria, killed or inactivated organisms, or purified products derived from them administered to a potential host in order to establish immunity in the host against future exposure to the pathogen. Vaccines do not necessarily provide complete protection from a disease because even after a vaccination, there is still a possibility that an individual may get the disease. Direct selection (e.g. vaccines) targets virulence and applies selective pressure by increasing the costs of infecting new hosts, thus driving the selection towards milder forms. One of the ways in which vaccines increase the cost for pathogens to infect humans is by making entry into human cells more challenging. Pathogens infect hosts to use host resources for reproduction. If entry is blocked, the pathogen cannot reproduce and transmit to other hosts. Some vaccines are developed to block cell entry by altering specific receptor sites. Other vaccines target the production of toxin that the more virulent form of the pathogen produces. One example is diphtheria. Diphtheria has two forms: a

¹⁴ Zimmer, C. 2003. Taming pathogens: An elegant idea, but does it work? *Science* 300: 1362-1364.

¹⁵ Zimmer, C. 2003. Pp. 1364.

¹⁶ Ebert, D. and Bull, JJ. 2003. Challenging the trade-off model for the evolution of virulence: is virulence management feasible? *TRENDS in Microbiology* 11(1): 15-20.

¹⁷ Zimmer 2003.

¹⁸ Gandon, S. and Day, T. 2003. Understanding and managing pathogen evolution: a way forward. *TRENDS in Microbiology* 11(5): 206-207.

benign form and a virulent form that produces toxin. The toxin in the more virulent form of Diphtheria enables the bacteria to reproduce faster and triggers cough in the host in order to implement an air mode of transmission.¹⁹ In areas where vaccination programs are not well-managed; virulent forms have increased prevalence due to the inconsistent utilization of vaccines.²⁰ In situations of poor management and lack of adequate resources to effectively implement vaccination programs, the use of vaccines could have the ability to alter pathogen virulence by selecting for more virulence strains or providing ways for strains to acquire resistance through genetic exchange. Direct selection of virulence management by tailoring vaccines to favor more benign strains within species competition requires an in-depth understanding of biological mechanisms underlying the pathogenesis of infectious agents.²¹ Therefore, the most effective implementation of vaccination programs is in areas where the benign form of the pathogen is selected for and becomes the more dominant strain.

Indirect selection of virulence: Social Interventions

One of the ways in which virulence management has been proposed to be utilized is in targeting transmission. According to the trade-off model, the easier the transmission, the more virulent forms will dominate. Altering transmission will tip the balance in favor of more benign strains. For example, in malaria control, barrier methods such as mosquito nets and screens disrupt the mode of transmission. In addition, the use of barrier methods to isolate individuals with severe symptoms of malaria may serve to contain the virulent forms and shift the selection towards milder strains. Another example is cholera, a water-borne disease. In areas of poor sanitation (e.g. lack of toilet facilities, uncovered water sources, etc.), cholera is prevalent and contributes to high mortality rates especially among the most vulnerable in the population, children under five years of age. In the case of cholera, poor sanitation has contributed to higher virulence in providing more opportunities to infect large numbers of people. With protected water supplies, the mode of transmission is cut off.²² Just by implementing these small, generally inexpensive means of transmission control, the evolution of disease to more virulent strains can be minimized.

Case Study: HIV/AIDS and Human Behavior

The human immune-deficiency virus (HIV) is sexually transmitted. Distribution and prevalence of HIV in human populations is directly influenced by changes in human behavioral patterns, culture, migration, economy, etc. The prevalence of HIV worldwide, especially increased incidence rates of infection result from a shift in behavioral patterns: increased sexual activity with frequent changing partners. An evolutionary explanation correlates differences in HIV virulence between HIV-1 and HIV-2 to differences in socio-cultural context in which the two viruses evolved.²³ HIV-1 is predominately found in Central and East Africa. HIV-1 is more lethal and has a more rapid progression to AIDS. HIV-2 is localized in West Africa and has a slower onset of AIDS. Differences in transmission rates reflect differences in social patterns. East and Central Africa experienced an economic crisis in the 1960s and 1970s that led to

¹⁹ Zimmer 2003.

²⁰ Zimmer 2003.

²¹ Ebert & Bull 2002.

²² Ewald, PE. 1991. Waterborne transmission and the evolution of virulence among gastrointestinal bacteria. *Epidemiology and Infection* 106(1): 83-119.

²³ Ewald 1993.

increased migration to urban centers. Men left rural villages to find employment in the cities. Sexual patterns altered in cities to increased sexual contact with various partners. A potential contributor to facilitating transmission for the virus is sex commerce. In contrast, countries in West Africa did not experience a similar migration pattern. However, in areas where a noticeable shift in human behaviors resulting from lifestyle changes from rural to urban was observed, HIV-2 strains were found to be more virulent although not as virulent as HIV-1.²⁴ The use of condoms may apply selective pressure among HIV variant strains, allowing for mild strains to proliferate as a result of reduced opportunities for transmission. “It is conceivable that in the absence of a vaccine or antiviral drugs, the human population will evolve and ultimately adapt to HIV infection, in much the same way that HIV is evolving and adapting to selective pressures within its host.”²⁵

Case Study: TB and Antibiotic Resistance

Tuberculosis (TB) is caused by mycobacterium tuberculosis. This bacterium is considered to be the “most successful human pathogen” because of its global epidemic status. In 2004, the WHO estimates of multi-resistant TB (MDR-TB) were at half a million cases.²⁶ MDR-TB is defined as resistance to at least two of the first line of TB drugs, isoniazid and rifampicin. Extensively drug-resistant TB (XDR-TB) is TB resistant to fluoroquinolone and one of the second line drugs.²⁷ In a rural area of KwaZulu, South Africa, multi-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) were identified. Out of 1539 hospital patients tested for TB, 221 had MDR-TB and 53 had XDR-TB. 52 of the 53 patients with XDR-TB died; 44 of these patients were immune-compromised and co-infected with HIV.²⁸ Prevalence of XDR-TB authors believe is the result of transmission of XDR strains between individuals especially in hospital settings. MDR-TB and XDR-TB arise from challenges of infection control in places with limited resources and high HIV infection rates; TB is most common opportunistic infection and HIV patients are most vulnerable²⁹.

Antibiotics are drugs used to fight infection caused by bacteria by disrupting bacterial growth and survival through different ways. Antibiotics can inhibit the assembly of bacterial cell growth, e.g. penicillin, vancomycin. They inhibit bacterial protein synthesis by disrupting mRNA and rRNA, e.g. erythromycin. They can also inhibit DNA replication and repair, e.g. ciprofloxacin.³⁰

Pathogens may acquire antibiotic resistance through adaptations to the host that result in the pathogen’s ability to resist effects of an antibiotic. Essentially antibiotic resistance is a consequence of evolution via natural selection. As the pathogen is exposed to the environmental pressures within the host, those who are able to best adapt will pass their superior traits to their

²⁴ Ewald 1993.

²⁵ Heeney, JL., Dalgleish, AG., and Weiss, RA. 2006. Origins of HIV and the evolution of resistance to AIDS. *Science* 313: 462-466. [p. 463]

²⁶ <http://www.who.int/tb/xdr/faqs/en/index.html> [Accessed 2007 April 25]

²⁷ <http://www.who.int/tb/xdr/faqs/en/index.html> [Accessed 2007 April 25]

²⁸ Gandhi, NR., Moll, A., Sturm, AW., Govender, T., Lalloo, U., Zeller, K., Andrews, J., and Friedland, G. 2006. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *The Lancet* 368: 1575-1580.

²⁹ Gandhi et al. 2006.

³⁰ Normark, BH., and Normark, S. 2002. Evolution and spread of antibiotic resistance. *Journal of Internal Medicine* 252: 91-106.

offspring in order to develop a fully resistant generation of pathogen to the host's defenses.³¹ Antibiotic resistance is achieved through mechanisms of efflux, destruction, and mutation. Efflux is the process of rapidly pumping out the antibiotic and keeping the concentration levels low. Bacteria can destroy antibiotics by neutralizing their effects by inactivating enzymes. The third mechanism is mutation in which bacteria changes the structure of the antibiotic attack site.³²

Human behavior can also contribute to the rise of antibiotic resistance. One example is in the misuse of antibiotics worldwide to kill infections whether or not the pathogen has been determined to be bacterial or viral. Antibiotics only work on bacterial infections, but a common assumption prevalent in some health beliefs is "when in doubt and infected, treat with antibiotics." Although antibiotics are designed to kill all strains of bacterial infections, over time and with excessive utilization of antibiotics, more resistant forms of the pathogen will be difficult to kill as these forms have undergone selective pressure from natural selection to acquire resistance to survive and reproduce. The use of antibiotics acts as a selective agent in increasing pathogen virulence. An evolutionary perspective highlighting the "arms race," the metaphor used in the continuous struggle between pathogen and host to acquire adaptations and counter-adaptations to survive, provides insights into the selection for virulent forms of disease. By taking into account selective pressures that actively favor more virulent forms of the pathogen to survive, perhaps interventions and behavioral practices that knowingly select for milder strains may assist in combating disease prevalence.

III. Public Health Application: Health Promotion

Medical interventions can be costly. Procedures and medications used in the treatment of diseases in the United States are expensive and often, such health services are only accessed by those who can afford health insurance or those who can pay out of pocket expenditures. However, these endeavors are important to increasing the health of the population because "health promotion is the process of enabling people to increase control over, and to improve their health."³³ Chronic care in America is estimated to be twice as high as in other countries of comparative wealth. In 1995, the American health care system spent \$470 billion in providing quality of care to people suffering from chronic diseases.³⁴ Often, patients with chronic care are more likely to undergo expensive medical interventions to treat the disease. For example, severely obese individuals, those at high risk for complications and death, have the option to undergo Bariatric surgery to reduce risk. Bariatric surgery, a surgical procedure that temporarily or permanently alters stomach size, is an invasive and expensive medical procedure. The price of Bariatric surgery is estimated at \$20,000-\$50,000. In addition, serious complications may result such as pulmonary embolism, internal bleeding, and gastrointestinal leaking.³⁵ To further add to the expense of treating chronic diseases, are the additional costs of prescribed medications and medical supplies essential in maintaining the disease. In 1996, the U.S. health care system spent \$2,136,738,660, and the pharmaceutical companies gained a net profit of \$12.26 billion.³⁶

³¹ Baquero, F., and Blazquez, J. 1997. Evolution of antibiotic resistance. *TREE* 12(12): 482-487.

³² Normark & Normark 2002; Baquero & Blazquez 1997.

³³ Nutbeam 1998, p. 351

³⁴ The Institute for Health & Aging, University of California, San Francisco. (November 1996). Chronic Care in America: A 21st Century Challenge. *The Robert Wood Johnson Foundation*. Retrieved April 24, 2007 from www.rwjf.org/files/publications/other/ChronicCareinAmerica.pdf

³⁵ Steinbrook, R. 2004. Surgery for severe obesity. *N Engl J Med* 350(11): 1075-1079.

³⁶ Public Citizen. Report on the International Comparison of Prices of Antidepressant and Antipsychotic Drugs. <http://www.citizen.org/publications/release.cfm?ID=6642>. [Accessed 2007 Apr 25]

Despite the high expenditures generated by the U.S. health care system, not all Americans have access to such services. In 2005, there were approximately 46.6 million people uninsured and 37 million Americans living in poverty.³⁷ What about in developing countries? Developing countries are widely recognized to have multiple health challenges. Some of these challenges are access to health services, specialized treatment facilities, advanced medical interventions, medications, and medical supplies. In situations where inadequate access to treatment and medication, what options do people have? What programs can be offered to address these issues of treating diseases? Programs addressing the problems of health services delivery and access are needed. Complimentary actions to treatment programs based on medical interventions are disease prevention and health promotion initiatives.

In 1986, the first international conference on health promotion met in Ottawa and brought to the global agenda of healthcare the importance of health promotion and application of practical strategies to the conceptualization of health defined as “a state of complete physical, social, and mental well-being, and not merely the absence of disease;”³⁸ the definition developed from the Alma Ata conference in 1978. At this time a distinction was made between disease and health. Since then, organizations such as the World Health Organization (WHO) have been central in promoting the concept of Health for All, “the attainment by all the people of the world of a level of health that will permit them to lead a socially and economically productive life”³⁹ as a more effective strategy for reducing disease rates worldwide. Health for ALL defined future health initiatives to incorporate a more holistic approach.

Since “disease prevention covers measures not only to prevent the occurrence of disease, such as risk factor reduction, but also to arrest its progress and reduce its consequences once established,”⁴⁰ recent trends in preventative medicine and public health have highlighted a movement towards “healthy living,” and an increased awareness for a comprehensive approach to understanding the prevalence of diseases in humans. These recent trends result from the increasing body of evidence of the rise of chronic diseases and its link to changes in living practices worldwide. As one example, the WHO jumpstarted a movement towards the promotion of healthy living through such programs as the “Healthy Cities” initiatives aimed at decreasing incidence rates of chronic diseases appearing on a global scale.

In contrast to infectious diseases where there is a direct causal link between pathology and infectious agent, chronic disease etiology is more complicated. In addition, infectious diseases such as HIV have altered the single agent, single disease model explaining the etiology of infectious diseases to a more exacerbated condition involving the influence of human social behaviors in the spread of disease. Past health initiatives have been based on the concept of disease as caused by a single agent. Treatment and prevention efforts have centered on the elimination of the agent. In developing countries, a “double burden of disease” has emerged in which rates of infectious diseases have remained high, in addition to increasing rates of chronic diseases. Public health has attempted to address these challenges by developing health initiatives targeting health behavior change. In targeting health behavior change as a strategy for reducing infectious and chronic diseases, public health has further demarcated the distinction

³⁷ The Census Bureau. 2006. Income, poverty, and health insurance coverage in the United States: 2005. Retrieved April 24, 2007 from <http://www.census.gov/>.

³⁸ Primary health care: Report of the International Conference on Primary Health Care, Alma Ata, USSR (1978). WHO Geneva.

³⁹ Nutbeam, D. 1998, Health promotion glossary. *Health Promotion International* 13(4): 349-364, p.352

⁴⁰ Nutbeam 1998, p. 353

between the different strategies utilized by various health providers in treating diseases or preventing diseases to promote health. “One issue is that public health defines itself as responsible for promoting health, while its practices are organized around disease concepts. Another is that its practices tend not to consider the distance between the concept of disease (a mental construct) and falling ill (a lived experience), thus substituting one for the other. Concepts of disease shape specific forms of intervention.”⁴¹ Differences in concepts of disease and health influence the development of effective health programs.

Health promotion needs a conceptual framework and evolutionary biologists may have the answer. Evolutionary medicine can perhaps provide health promotion with the conceptual framework it needs to be a more effective tool in disease prevention.⁴² What is evolutionary health promotion? Evolutionary health promotion is based on the following three premises: 1] there is a disassociation between the lifestyle the human genome was selected for in past environments and the current lifestyle of today; 2] cultural behaviors and practices have evolved more rapidly than genetic changes to the human genome; and 3] this disassociation has resulted in a mismatch between our biology and lifestyle promoting the development of chronic degenerative diseases.⁴³ “The discourse of prevention is based on modern epidemiological knowledge. It aims to control the transmission of infectious diseases and reduce the risk of degenerative diseases or other specific ailments. Health prevention and education projects are structured by circulation of scientific knowledge and normative recommendations to change habits.”⁴⁴

For evolutionary health promotion to be applicable to the prevention and promotion of diseases in existence in our current environment, a few assumptions need to be clarified in arguing the validity of an evolutionary perspective in preventative medicine. Evolutionary health promotion assumes the following: 1] increases in life expectancy has contributed to the prevalence of chronic diseases; 2] little genetic variation has occurred between our ancestors and us in the last 10,000 years; 3] there are marked differences between the ancestral environment and the current environment and 4] humans are highly adaptable species.⁴⁵ Life expectancy has increased in recent decades due to improved medical technology and better sanitation practices. At least in America, chronic diseases have been shown to be age-related. In using an evolutionary-based model to account for the rise in chronic degenerative diseases, an assumption is made that humans who have lived longer are more vulnerable to disease; our ancestors did not live long enough for chronic conditions to manifest.⁴⁶ In making this assumption of an association between life expectancy and chronic diseases, one questions whether this phenomenon is really age related or more of differences in changes to lifestyle, cultural practices, increased medical developments, and shifting environmental conditions. Differences in past and current life patterns may highlight ways to promote better health. In order to effectively maintain

⁴¹ Czeresnia, D. 1999. The concept of health and the difference between prevention and promotion. *Cad. Saude Publica* 15(4): 701-709, p.702

⁴² Eaton, SB., Strassman, BI., Nesse, RM., Neel, JV., Ewald, PW., Williams, GC., Weder, AB., Eaton, SB., Lindeberg, S., Konner, MJ., Mysterud, I., and Cordain, L. 2002. Review: Evolutionary health promotion. *Preventative Medicine* 34: 109-118.

⁴³ Eaton et al. 2002.

⁴⁴ Czeresnia 1999, p. 705

⁴⁵ Eaton, SB., Cordain, L., and Lindeberg, S. 2002. Evolutionary health promotion: A consideration of arguments and counter arguments. *Preventative Medicine* 34: 119-123.

⁴⁶ Eaton et al. 2002.

healthy behaviors, health programs must be culturally sensitive, and able to be adapted into daily life and norms.

The advantage provided by using a conceptual framework based on evolutionary principles for promoting health and preventing is in reducing risk factors. Disease models that utilize the concept of the body not as a machine that breaks down occasionally in the presence of disease, but as a body shaped by natural selection as a consequence of adapting to specific environmental conditions that insured the survival of the individuals living in these environments, can result in new ideas for treatment. The following health promotion case studies are on the topics of obesity and depression.

Diseases of Civilization: Case Study Obesity

Many researchers that implement the Darwinian model examine what they call “diseases of civilization.” On the basis of this topic the term civilization describes a complex society in which many people live together in a concentrated area, dependent on agriculture for food. The classification of civilization is meant to contrast that to a hunter-gatherer way of life. Rather than living day by day in small societies searching for game and foraging for food, more modern societies function in cities with specialized labor, depending on others to bring food to centers of commerce and trade. Diseases of civilization are diseases and conditions that have increased in both incidence and prevalence during the recent evolutionary history of humans, and occur as result of modern differences in comparison to our ancestors in diet, exercise, and consumption of substances such as alcohol, drugs, and smoking. When seeking to ask why this is, one can look at how our daily life tasks and dietary trends have changed from our ancestral modes. In order to model the evolutionary history of diet, Darwinian researchers study both modern hunter-gatherers and archaeological records to notice patterns and make realistic generalizations. Because chronic diseases are nearly nonexistent in modern-day hunter-gatherer societies, a logical correlation to our ancestors can often be made.⁴⁷ Since these aspects of lifestyle were not present in our ancestors, many researchers hypothesize that conditions such as cancer, diabetes, and obesity are result of the changed behaviors of humans due to the advent of civilization in modern societies. Evolutionary changes and adaptations to the environment of city living take place very slowly; “natural selection has produced only minor alterations during the past 10,000 years so we can remain nearly identical to our late Paleolithic ancestors.”⁴⁸ This section of the chapter will focus on the topic of obesity and two of its evolutionary models, The Thrifty Gene Hypothesis, and The Fetal Origins Hypothesis, to contextualize how Darwinian medicine can help make Public Health recommendations to solve this epidemic.

Proximate Mechanism #1: Genetics

The complex genes of importance for common forms of human obesity have yet to be identified; however, a strong genetic component for obesity is established in numerous studies in twins and relatives.⁴⁹ Since approximately 95% of human biology and some behaviors were selected during late Paleolithic era, it has been suggested that if there have been significant

⁴⁷ Roberts, Christian K., Barnard, James. “Effects of exercise and diet on chronic disease.” *Journal of Applied Physiology* 2005; 98: 3-30.

⁴⁸ Eaton, Boyd, Eaton, Stanley. “An Evolutionary Perspective on Human Physical Activity: Implications for Health.” *Comparative Biochemistry and Physiology* 2003; 136: 153-159.

⁴⁹ Arner, Peter. “Obesity- a genetic disease of adipose tissue?” *British Journal of Nutrition* 2000; 83 (1): S9-S16.

changes produced by civilization, there should be systematic genetic differences between peoples who, like ancestral humans, lived as hunter-gatherers until the last few centuries.⁵⁰ However, this does not seem to be the case and there have been few genetic deviations from our ancestors. “Genetic evolution has been wholly unable to match the rapidity of cultural change and our genes remain adapted for conditions that existed during their selection by Darwinian mechanisms.”⁵¹

In general, research on the genetic contributors to disease use animal models to identify genetic mechanisms in order to direct human studies.⁵² Investigators first determined which DNA markers were inherited along with the obese phenotype in over 1,600 mice crossbred from obese and non-obese strains.⁵³ Of six genes thus isolated, one was found to be expressed exclusively in adipose tissue in normal mice rendering it a likely candidate for the obesity gene.⁵⁴ Results from genomic scans suggest that major obesity genes are located on chromosomes 2, 10, 11, and 20.⁵⁵ Some of these genes may promote obesity by gene-gene interactions or gene-environment interactions such as diet and exercise, as well as smoking and drinking. These behavioral patterns largely affect the genetic contributors to disease outcomes; both genes and environmental effects should be taken into consideration on the topic of obesity.⁵⁶ Since obesity has a significant genetic component, the identification of the genes involved in the expression of the disease would likely assist in the development of prevention and treatment strategies.

Proximate Mechanism #2: Imbalance in Energy Consumption and Expenditure

It is a commonly accepted fact that the decline in daily physical activity levels is a major factor contributing to the current obesity epidemic. Physical activity is no longer necessary for our daily survival. Our ancestors’ survival was dependent on the procurement of food which was in turn dependant on physical activity. However, the food supply was never consistent and there were cycles of feast and famine punctuated with periods of physical activity and rest. Therefore, gene selection in our ancestors was influenced by daily periods of activity and rest meant to obtain food. In modern societies, we no longer have to expend such energy in order to obtain food, therefore, many Darwinian medicine models build upon the idea that our modern diet is “environmentally mismatched” with our ancestor’s. An environmental mismatch from our previous environment, diet, and activity has resulted in the onset of chronic degenerative diseases such as obesity.

Thus, our bodies have evolved to endure different types of food, consumed sporadically over different amounts of time, and punctuated with exercise. The *Thrifty Gene Hypothesis* was developed in 1962 in order to describe the idea that metabolically thrifty genes permit more efficient food use through fat deposition in time of food abundance. A key point is that the

⁵⁰ Chakravarthy, Manu V., Booth, Frank W. “Eating, exercise, and “thrifty” genotypes: connecting the dots toward an evolutionary understanding of modern chronic disease.” *Journal of Applied Physiology* 2004; 96: 3-10.

⁵¹ Eaton et al. 2003.

⁵² West, David B., Goudey-Lefever, Jo, York, Barbara, and Truett, Gary. “Dietary Obesity Linked to Genetic Loci on Chromosomes 9 and 15 in Polygenic Mouse Model.” *Journal of Clinical Investigation* 1994; 94: 1410-1416.

⁵³ Lindpaintner, Klaus. “Clinical Implications of Basic Research: Finding an Obesity Gene- a Tale of Mice and Man.” *The New England Journal of Medicine* 1995; 332 (10); 679-680.

⁵⁴ Lindpaintner 1995.

⁵⁵ Arner 2000.

⁵⁶ Roberts & James 2005.

cycling by feast-famine and physical activity-rest triggers cycling of the storage levels of glycogen and triglycerides. By storing energy in fat, our ancestors could survive longer periods of time without food. This storage in turn triggers cycling of other metabolic pathways with the duration of the cycling being less important.⁵⁷ Essentially the thrifty genotype is efficient in the intake and/or utilization of food, thus inferring an evolutionary advantage on anyone who possessed it.⁵⁸ It is hypothesized that most individuals in the modern populations have this type of gene; however, since we can obtain food without experiencing periods of famine in between meals, possessing the gene may no longer be necessary or advantageous.

In terms of diet, the Paleolithic diet consisted of a higher proportion of calories from meats than in current United States populations which directly influenced the increased proportion of iron in their diet. The Paleolithic diet consisted of mostly wild game and gathered plants available in the areas. In modern societies our diets consist of many more carbohydrates, fats, and sugars and there is little emphasis on consumption of meats in comparison to our ancestral diet. Because it is rare in a mobile society to obtain grains grown in an agricultural setting, our ancestor's diet consisted of a variety of different carbohydrates than in comparison to the modern diet; however, their diet was still substantially higher in fiber than ours today. Despite the fact that the absolute caloric intake of modern humans is lower compared with hunters-gatherers, the increase in sedentary lifestyle outweighs this and greatly contributes to obesity.⁵⁹ In addition, hunter-gatherer populations ate more fruit and vegetables (except in areas where these were scarce due to environment), and consumed more of a different type of fat found in game meat and oily nuts. Also, in modern societies we consume about 128 lbs of sugar per person per year—far more than the ancestral diet contained due to scarcity of that resource. Our contemporary food pyramid guide provides diet recommendations based on the historical needs of our ancestors. This means we are advised to eat less fat, more meat, more fruits and vegetables, more fiber, and fewer grains. Overall, the estimated caloric intake relative to body size was 2.5 times that of ours, the estimated total daily caloric intake was 2,900 calories, in comparison to the 2,000 we are recommended to consume.

The type of diet consumed by hunter-gatherers is meant to support their body type and activity levels. Overall, ancestral populations had a higher proportion of bone and muscle in order to compose a more robust skeleton, with a lower proportion of fat. Therefore, this supported the “Paleolithic physical exertion patterns [which] likely resembled cross-training, not the more focused regimens of pure runners or weight-lifters.”⁶⁰ Today, 70% of the US population undertakes less than 30 minutes per day of moderate intensity physical activity.⁶¹ Men were estimated to have hunted one to four non consecutive days per week, and women were estimated to have gathered food every one to three days, amounting to a lot more exercise on a more regular basis than typical modern humans.⁶² This has resulted in the fact that humans living today inherited a genome that was programmed for more daily physical activity.⁶³ The alleles that evolved are now exposed to sedentary lifestyle, fat rich, fiber poor and calorically

⁵⁷ Chakravarthy & Booth 2004.

⁵⁸ Chakravarthy & Booth 2004.

⁵⁹ Chakravarthy & Booth 2004.

⁶⁰ Eaton et al. 2003.

⁶¹ Chakravarthy & Booth 2004.

⁶² Chakravarthy & Booth 2004.

⁶³ Roberts & James 2005.

imbalanced diets; this with an extended lifespan is a selective disadvantage with respect to chronic health conditions.⁶⁴

A second hypothesis that addresses an environmental mismatch focuses more on the mismatch between one's fetal environment and adult environment. This model is called the Fetal Origins Hypothesis and is based on David Barker's observations depicting that low birth weight babies are more likely to have CHD as adults⁶⁵; this has been replicated for many populations and many different chronic diseases. Birth weight indicates caloric intake and nutrition, so if one has a low birth weight they may be more adapted to a poor environment as an adult, as long as their environment remains the same. In the same sense, if a baby is born with a high birth weight, they may be adapted to good environments, but only if both environments in and out of the uterus resemble one another.

Between these two evolutionary models, The Thrifty Gene Hypothesis is more widely accepted; however, both provide insight as to how people, public health professionals and physicians may think about solutions to our obesity epidemic.

Public Health Prevention: Obesity

"Recent data estimate that physical inactivity and poor diet caused 400,000 deaths in 2000, ranking second only to tobacco and that it is likely that inactivity and diet will soon rank as the leading cause of death in the United States.⁶⁶ In order to come up with a successful public health approach to chronic disease prevention, we cannot rely on pharmaceuticals or an individual's ambition to exercise. Long term sustainable behaviors must be implemented that encourage healthy lifestyles. Based on the evolutionary model, many suggestions can be made in order to improve the population's poor health outcomes due to consequences of obesity.

Due to the genetic component of obesity, completing the identification of the genes involved in the expression of the disease would likely assist in the development of prevention and treatment strategies. Genome scan of common obesity genes have been surprisingly reproducible despite differences in ethnicity and environmental factors.⁶⁷ Therefore, once the genetic components of obesity are identified, perhaps these individuals can prevent weight gain through tailored exercise and diet programs for their conditions. Also, physicians would have the ability to monitor their patients for the other genetic-based outcomes associated with specific genotypes such as diabetes and cardiovascular diseases.

However, beyond the genetic contribution to obesity, the environmental factors of our modern lifestyles must also be addressed. Since there is a mismatch between exercise and diet between our modern society and our hunting and gathering ancestors, perhaps programs that focus on obtaining patterns of exercise and diet that more closely resemble those of hunter-gatherer lifestyles should be encouraged. For example, an urban transportation infrastructure system would encourage walking and jogging between work and school. Physical activity itself can be used as a prescription for disease prevention! To address diet, the new revamped food pyramid encourages more consumption of fruits, vegetables, carbohydrates, and meats in combination with exercise, reflecting the lifestyle which we were selected to life by. Visit <http://www.mypyramid.gov/>, in order to obtain more details on these new suggestions and track

⁶⁴ Chakravarthy, Manu V.

⁶⁵ Barker, DJP. 1994. Mothers, babies and disease in later life. London: BMJ Publishing Group.

⁶⁶ Roberts & James 2005.

⁶⁷ Boutin, Phillipe, Froguel, Phillipe. "Genetics of Human Obesity." *Best Practice & Research Clinical Endocrinology and Metabolism* 2001; 15(3): 391-404.

your own diet and exercise to see how well you compare to your hunting and gathering ancestors!

Case Study: Depression

Depression, or major depressive disorder, is a mental disorder resulting from exposure to chronic stress when using an evolutionary perspective in explaining the existence of depression in human populations. Symptoms of depression include loss of interest or pleasure, feelings of guilt, feelings of low self-worth, disturbed sleep or appetite (e.g. changes in weight), low energy and poor concentration. Thoughts of death may occur and in the most severe cases, depression can result in suicide.

Depression is the leading cause of disability in America and the 4th contributing to the global burden of disease. Depression has been estimated to affect approximately 121 million people worldwide.⁶⁸ In America, depression has been found to be more prevalent among women.⁶⁹ Risk factors for depression are many. Some risk factors include previous episodes of depression, other diagnoses of mental disorders, family members with depression, low socioeconomic status, exposure to stressful events early in life, exposure to trauma, and suffering from chronic diseases, just to name a few.⁷⁰

Current treatments for major depression combine prescription medications and counseling. Adverse side effects are common in the treatment of depression using prescription medications (i.e. antidepressants). Depression is hypothesized to be attributed to a chemical imbalance in the brain. Antidepressants alter chemical imbalances in the brain by increasing levels of serotonin, dopamine or norepinephrine reduced during depressive episodes. Different antidepressants cause different side effects, some of which include anxiety, diarrhea, dry mouth, fatigue, increased heart rate, insomnia, muscle twitching, hand tremors, nausea, sexual dysfunction, vomiting, bladder problems, and blurred vision. Some studies have provided evidence for efficacy and effectiveness of treatment for depression with the use of antidepressants. Guidelines for recommended doses and duration of treatment have been carefully obtained through clinical drug trials. However, due to differences in individual responsiveness to an antidepressant, psychiatrists must adjust the guidelines through trial and error with each patient they treat in order to find the dose that best matches an individual's chemical reactivity to the antidepressant. This experimentation process subjects patients to potential harm in attempts to find a cure.

A possible explanation for the existence of depression may be linked to stress. Increased exposure to stressful life events and trauma has been shown to produce depression in some individuals. Some sources of stress are disease, social status, losing a loved one, failure in achieving important goals, relationship conflicts, stressful living environments, and lack of social support. Potentially, differences in individuals' perceptions of stress-causing factors highlight the complexity of depression and the challenges of finding ways to cure this mental illness. Anthropological studies have questioned the validity of diagnosing depression using standard

⁶⁸ WHO 2000.

⁶⁹ Blazer, DG., Kessler, RC., McGonagle, KA., and Swartz, MS. 1994. The prevalence and distribution of Major Depression in a national community sample: the National Comorbidity Survey. *The American Journal of Psychiatry* 151(7): 979-986.

⁷⁰ Blazer et al. 1994.

measures of assessment such as the DSM-IV in cross-cultural settings.⁷¹ Physical and behavioral manifestations similar to depressive symptoms have been observed, and yet, symptomatology may be the result of appropriate cultural responses to specific life events rather than an expression of pathology.⁷²

Distinctions made between illness and disease, resulting from differences in perspective between the perceived experience of the patient and physicians' concept of disease states as resulting from pathology further challenge diagnoses of mental disorders in varying context. Similar physical expressions, but differences in variation of potential sources of causation have possible implications for the treatment of diagnosed cases in different cultures. Although some studies have provided evidence for the efficacy of the use of antidepressants in developing countries, treatments involving the use of prescribed medications are a challenge in countries with inadequate access to medical resources.⁷³ At least in the treatment of mental disorders, some studies have highlighted differences in treatment outcomes between developed and developing countries. Possible explanations of better treatment outcomes for mental illness in developing countries have been cited as differences in perceptions of the etiology of mental illness (e.g. acute vs. chronic) and individuals involved in the decision-making process for treatment.⁷⁴ Depressive mechanisms explained through evolutionary models involving ways the human body responds to stress may highlight ways individuals can be assisted in negotiating complex social problems without adverse side effects.

Evolutionary Models of Depression

The dysregulation model, as one of the evolutionary models explaining the existence of depression in human populations, categorizes depression as an “environmental mismatch.” Environmental mismatch is one of the categories explaining disease etiology for evolutionary medicine. Diseases in this category result from a “mismatch” of the human body designed in an ancestral environment and currently functioning in an environment different from the one in which the body had been adapted for. Depression has been hypothesized to be a consequence of evolutionary processes; in our current environment, human stress mechanisms adapted during the ancestral environment have become maladaptive.⁷⁵

The acute stress response, also known as the “fight or flight response,” regulates mechanisms responsible for how the human body responds to stressors.⁷⁶ In our ancestral environment, the stress response was activated in the presence of danger from the physical environment. The acute stress response has been adaptive in the ancestral environment by minimizing the damage caused by physical injury. The acute stress response is critical to the body's normal defenses to physical injury and is responsible for maintaining allostasis within the

⁷¹ Kleinman, A. 1988. Chapter 2: Do psychiatric disorders differ in different context? The methodological questions. In: *Rethinking Psychiatry: From Cultural Category to Personal Experience*. New York: The Free Press, pp. 18-33.

⁷² Gaines, AD. And Farmer, PE. 1986. Visible saints. *Culture, Medicine and Psychiatry* 10: 295-330.

⁷³ Patel, V., Chisholm, D., Rabe-Hesketh, S., Dias-Saxena, F., Andrew, G., and Mann, A. 2003. Efficacy and cost-effectiveness of drug and psychological treatments for common mental disorders in general health care in Goa: a randomized, controlled trial. *The Lancet* 361: 33-39.

⁷⁴ Waxler, N. 1979. Is outcome for schizophrenia better in non-industrial societies? The case of Sri Lanka. *Journal of Nervous and Mental Health* 167: 124-134.

⁷⁵ Nettle, D. 2003. Evolutionary origins of depression: a review and reformulation. *Journal of Affective Disorders* xx:1-12.D

⁷⁶ McEwen, BS. 2005. Stressed or stressed out: What is the difference? *J Psychiatry Neurosci* 30(5): 315-318.

body. Allostasis refers to systems in charge of maintaining homeostasis in the human body and “provide[s] how the essential protective and adaptive effects of physiologic mediators that maintain homeostasis are also involved in the cumulative effects of daily life when they are mismanaged or overused.”⁷⁷

Over time, exposure to stress and the consistent activation of stress responses leads to alterations in the brain, specifically hormonal levels and the atrophy of memory cells. With stress hormones, an increase in glucocorticoids (cortisol in humans) and decrease in norepinephrine (adrenalin) result in loss of concentration and energy. There is a decrease in dopamine, the hormone responsible for feelings of euphoria and serotonin levels, altering the mechanisms regulating mood and sleep cycles.⁷⁸

Different stressors may activate the acute stress response. Stressors from the social environment impact the human body in the same way stressors experienced from the physical environment. One type of stressor produced from the social environment is psychological stress in which “perceived distress/threat” activates the acute stress response. Psychological stress has the following characteristics: lack of predictability, lack of control, lack of outlets for frustration and lack of social support.⁷⁹ The degree to which an individual experiences psychological stress with any or all of the characteristics makes an impact on increasing or minimizing the stress response. For example, stress is reduced when the individual regains a sense of control.

Specifically in the case of depression, psychological stress is adaptive. However, in our current environment of prolonged exposure to multiple stressors, the stress response becomes as harmful as the actual stressors. Mental health disorders result from the excessive and continuous activation of the stress responses in the absence of ways to minimize or stop the reactivation of stress pathways. In the dysregulation model for depression, stressors as well as the mechanisms responsible for regulating stress cause damage; the body is unable to maintain allostasis leading to symptoms of depression.

Another evolutionary model for depression is the Fetal Origins Hypothesis. As mentioned in the case study for obesity, stressors affecting pregnant mothers during critical fetal development periods produce changes in the uterine environment influencing fetal growth and development.⁸⁰ Observation studies have linked the effects of nutritional stress to birth outcomes particularly birth weight. Low birth weight is used as a proximate indicator for the presence of nutritional stress experienced by the mother and its significant impact on the fetus. One study often cited as evidence for the impact of nutritional stress on fetal development is the Dutch famine project. Studies that have traced the impact of the reduced caloric intake among pregnant women during the German embargo of food supplies in 1945 of the Netherlands found low birth weights outcomes associated with nutritional stress at critical periods of fetal development. In addition, low birth weight babies who had undergone nutritional stress in the second trimester were found to be at increased risk for depression in later life stages.⁸¹

Public Health Prevention: Postpartum Depression

⁷⁷ McEwen 2005. p. 316.

⁷⁸ Sapolsky, RM. 2003. Taming Stress. *Scientific American* 87-95.

⁷⁹ Sapolsky, RM. 2004. Social status and health in humans and other animals. *Annu Rev Anthropol* 33: 393-418

⁸⁰ Ellison, PT. 2005. Evolutionary perspectives on the Fetal Origins Hypothesis. *American Journal of Human Biology* 117: 113-118.

⁸¹ Lumey, LH. 1998. Reproductive outcomes in women prenatally exposed to under nutrition: a review of findings from the Dutch famine birth cohort. *Proceedings of the Nutrition Society* 57: 129-135.

Statistics from the CDC's Pregnancy Risk Assessment Monitoring System (PRAMS) on self-reported postpartum depression in seven states, 32,176 (7.1%) out of 453,186 women reported severe depression after delivery and 233,844 women reported having low to moderate depression.⁸² Women self-reported to experience depression were more likely to be exposed to multiple stressors.⁸³ Maternal depression has been shown to directly affect relationships, particularly mother-infant bonding.⁸⁴

Maternal and infant vulnerability is increased during pregnancy and post birth. Public health recommendations for postpartum depression based on evolutionary hypotheses would incorporate ways to minimize stress during pregnancy, specifically at times of critical periods of fetal development and after birth and target vulnerable populations most at risk for exposure to multiple stressors. Interventions that can accurately find women most at risk for postpartum depression and provide treatments based on minimizing exposure to stressors may be more cost-effective in reducing incidence rates of postpartum depression without resorting to more expensive options. One example of a public health intervention program is the development of the Women, Infants, and Children (WIC) Nutrition Program that targets women and children at high risk for nutritional stress. WIC is a supplementary feeding and education program providing ways to prevent inadequate caloric and nutritional intake for women and children at risk e.g. low income or anemia. Other programs highlight the importance of providing social support by providing new mothers with a community that understands the needs and demands of motherhood. Such programs provide support groups, resources, and education for additional information on child rearing practices and perhaps the assistance of other caregivers in taking care of the child.

IV. Conclusion: Darwinian Medicine and Public Health

Although evolutionary biology has provided a foundation for studies of antibiotic resistance and population genetics, there are many more areas of medicine in which applications of this theory may be appropriately applied. This chapter of the MPHP 439 online text book has sought to provide examples that can help both physicians and those in public health in order to convince them to embrace evolution as a means of exploring treatment and prevention options. It is important to keep in mind that evolution is not concerned to maximize the health or well-being of organisms; rather, its focus is on successful genetic reproduction, and "what serves this purpose is only contingently related to the health and well-being of the organism serving as the temporary vehicle for the genes."⁸⁵ Although there are many journal articles and suggestions within research topics for the validity of this field, evolutionary hypotheses about human physiology are hard to investigate due to long human life-spans and ethical issues concerning genetic testing scenarios; however, the observations provided by the Darwinian model suggest that treatments should not cause further stress to the body.⁸⁶ Without appreciating evolutionary dynamics of both health and disease, one cannot understand the origin, persistence, and options for treating the human body.

⁸² CDC. 2004. Postpartum Fact Sheet. [www.cdc.org]

⁸³ Deal, LW. 1998. Young maternal age and depressive symptoms: results from the 1988 National Maternal and Infant Health Survey. *American Journal of Public Health* 88(2): 266-270.

⁸⁴ Murray, L., Fiori-Crowley, A., Hooper, R., and Cooper, P. 1996. The impact of postnatal depression and associated adversity on early mother-infant relationships and later infant outcome. *Child Dev* 67(5): 2512-2516.

⁸⁵ <http://myweb.lmu.edu/tshanahan/DarMed.html>

⁸⁶ <http://myweb.lmu.edu/tshanahan/DarMed.html>

MORE TO EXPLORE:

The following internet sites provide useful general information on evolution:

- Evolution resources: www.nationalacademies.org/evolution
- Understanding Evolution: <http://evolution.berkeley.edu/>
- National Center for Science Education: <http://www.ncseweb.org/>
- Evolution and Medicine Network: <http://evolutionandmedicine.org/>
- Darwinian Medicine: <http://darwinianmedicine.org/>

Books on Darwinian Medicine:

Nesse, R. M. and Williams, G. C. 1994. Why We Get Sick: The New Science of Darwinian Medicine. New York: Vintage Books.

Trevathan, W. R. 1999. Evolutionary Medicine. Oxford: Oxford University Press.

Sapolsky, R. M. 1998. Why Zebras Don't Get Ulcers. New York: W.H. Freeman.

Further reading on Darwinian Medicine from ANTH 302/402 Syllabus⁸⁷:

Abbott, A. (2005). "Medics braced for fresh super bug." Nature (London) **436** (7052): 758.

Allen, N.B., & Baddock, P.B. (2006). "Darwinian models of depression: a review of evolutionary accounts of mood and mood disorders." *Progress in Neuro Psychopharmacology and Biological Psychiatry*, 30(5), 815.

Barr, R.G. (1999). "Infant Crying Behavior and Colic: an interpretation in evolutionary perspective." In W.R. Trevathan, E.O. Smith & J.M. McKenna (Eds.), *Evolutionary Medicine* (pp.27-52). New York: Oxford University Press.

Brett, J. & Niermeyer, S. (1999). "Is Neonatal Jaundice a Disease or an Adaptive Process?" In W.R. Trevathan, E.O. Smith & J.M. McKenna (Eds.), *Evolutionary Medicine* (pp. 7-26). New York: Oxford University Press.

Blaser, M.J. (2005). "An Endangered Species in the Stomach." Scientific American (February): 38-45.

Bower, B. (1999). "Slumber's Unexplored Landscape. People in Traditional Societies sleep in eye-opening ways." Science News **156** (September 25): 205-207.

Check, E., 2006. "Human evolution: how Africa learned to love the cow." *Nature* 444, 994-996.

Christensen, D. (2001). "Fighting Herself." Science News **160** (July 28): 58-60.

Deutsch, J.A. (1994). "Pregnancy sickness as an adaptation to concealed ovulation." Rivista di Biologia **87** (2/3): 277-287.

⁸⁷ Case Western Reserve University, Spring Semester 2007, Dr. Cynthia Beall

- Diamond, J. (2003). "The double puzzle of diabetes." Nature **423** (6940): 599-602.
- Dryna, D. (2005). "Founder Mutations." Scientific American (October): 78-85.
- Eaton, S.L. Cordain, et al. (2002). "Evolutionary health promotion: a consideration of common counterarguments." Preventive Medicine: An International Journal Devoted to Practice and Theory **34** (2): 119.
- Eaton, S.B., Pike MC, Short RV, Lee NC, Trussell, J., Hatcher RA, Wood JW, Worthman CM, Jones NG, Jonner MJ, et.al. 1994. "Women's reproductive cancers in evolutionary context." Q Rev Biol **69**, 353-367.
- Eaton, S. 3rd, E.S., Konner, M. 1997. "Paleolithic nutrition revisited: a twelve-year retrospective on its nature and implications." Eur J Clin Nutr. **51**, 207-216.
- Ebert, D. and J.J. Bull (2003). "Challenging the trade-off model for the evolution of virulence: is virulence management feasible?" Trends in Microbiology **11**(1): 15.
- Elliot, S.L. (2003). "Evolutionary perspectives on the fetal origin hypothesis." American Journal of human biology: the official journal of the human biology council. **17** (1): 113.
- Ewald, P.W., (1993). "The Evolution of Virulence." Scientific American.
- Ewald, P. W. (1996) *Evolution of Infectious Disease*. Oxford University Press, Oxford.
- Ferber, D. (2003). "Microbiology. Triple-treat microbe gained powers from another bug." American Association for the Advancement of Science. Science **302** (5650): 1488.
- Galvani, A.P. and R.M. May (2005). "Epidemiology: dimensions of super spreading." Nature (London) **438** (7066): 293.
- Gandon, S. and T. day (2003). "Understanding and managing pathogen evolution: a way forward." Trends in Microbiology **11** (5): 206.
- Gosnell, M., 2007. "Killer Fat." Discover February, 28-53.
- Heeney, J.L., Dagleish, A.G. & Weiss, R.A. (2006). "Origins of HIV and the evolution of resistance to AIDS." American Association for the Advancement of Science. Science, **313**(5786), 462.
- Holland, T.D., O'Brien, M.J., 2003. "On Morning Sickness and the Neolithic Revolution." Current Anthropology **44**, 707-711.
- Holmes, K.V. (2005). "Structural Biology. Adaptation of SARS coronavirus to humans." American Association for the Advancement of Science. Science. **309** (5742): 1822.

- Huxley, R.R. (2000). "Nausea and vomiting in early pregnancy: its role in placental development." Obstetrics & Gynecology **95** (5): 779.
- Jablonski, N. and Chapin (2003). "Skin Deep." Scientific American, May.
- Kluger, M.J., W. Kozak, et al. (1997). "The Adaptive Value of Fever." Fever: Basic Mechanisms and Management. P.A. Mackowiak. Philadelphia, Lippincott-Raven: 255-265.
- Krogman, W.M. (1951). "The scars of human evolution." Scientific American (December):54-57.
- Kwiatkowski, D.P. (2005). "How Malaria has affected the human genome and what human genetics can teach us about malaria." *American Journal of Human Genetics*, **77**(2), 171.
- Landry, D.W., and J.A. Oliver (2004). "Insights into Shock." Scientific American (February): 37-41.
- Lee, P.Y. Yun, A.J., & Bazar, K.A. (2004). "acute coronary syndromes and heart failure may reflect maladaptation of trauma physiology that was shaped during pre-modern evolution." *Medical Hypotheses*, **62**(6), 861.
- Leffell, D.J. and D.E. Brash (1996). "Sunlight and Skin Cancer." Scientific American (July): 52-59.
- Leonard, W. (2003). "Food for thought. Dietary change was a driving force in Human evolution." *Scientific American*, **287**(6), 106-115.
- Lev-Ran, A. & Porta, M. (2005). "Salt and hypertension: a phylogenetic perspective." *Diabetes/Metabolism Research and Reviews*, **21**(2): 118.
- Libby, P., (2002). "Atherosclerosis: The New View." Scientific American (May): 47-55.
- Maziak, W. (2005). "The Asthma epidemic and our artificial habitats." *BMC Pulmonary Medicine* **5**, 1-7.
- McEwen, B.S., (2005). "Stressed or stressed out: what is the difference?" *Journal of Psychiatry & Neuroscience*, **30**(5), 315.
- McKenna, J.J., and T. McDade (2005). "Why babies should never sleep alone: a review of the co-sleeping controversy in relation to SIDS, bed sharing and breast feeding." Pediatric Respiratory Reviews **6**(2):134.
- Murray, M.J., A. Murray et. Al. (1980). "The Salutary effect of milk on amoebiasis and its reversal by iron." British Medical Journal **280** (6228): 1351-2.
- NIAIDNetNews "The Immune System." <http://www.niaid.nih.gov/final/immun/immun.htm>. last

[updated September 25](#), 2003.

- Nesse, R.M., Stears, S.C. & Omenn, G.S. (2006). "Medicine Needs Evolution." *Science* 311: 171.
- Nestler, E.J. Makenka, R.C. 2004. "The Brain on Marijuana." *Scientific American* November.
- Pigliucci, M. & Kaplan, J. (2000). "The fall and rise of Dr. Pangloss: adaptation and the Spandrels paper 20 years later." *Trends in Ecology & Evolution*, **15**(2): 66-69.
- Ridley, M. (2000). "Asthma, Environment, and the Genome." *Natural History* (March): 55-64.
- Rose, M. (2004). "Will Human aging be postponed?" *Scientific American* June.
- Sherman, P.W. and S.M. Flaxman (2001). "Protecting Ourselves from Food." *American Scientist* **89**(March-April): 142-151.
- Sinclair, D.A., Guarente, L. (2006). "Unlocking the Secrets of Longevity Genes." *Scientific American*, February.
- Siegel, J.M. (2003). "Why do we sleep?" *Scientific American* **289**(May): 92-97.
- Slev, P.R. and W.K. Potts (2002). "Disease consequences of Pathogen adaptation." *Current Opinion in Immunology* **14** (5):609.
- Trevathan, W.R. (1996). "The Evolution of Bipedalism and Assisted Birth." *Medical Anthropology Quarterly*, **10**(2): 287-298.
- Ward, R. (1999). "The Puzzle of Hypertension in African-Americans." *Scientific American*, February.
- Way, W. Gibbs, X. (2003). "Untangling the Roots of Cancer." *Scientific American*, June.
- Williams, G. C. & Nesse, R. M. (1991). "The Dawn of Darwinian Medicine." *Quarterly Review of Biology*, **66**, 1-22.
- Wheelwright, J. (2005a). "Native America's Alleles." *Discover*, **26**(5).
- Wheelwright, J. (2005b). "Finland's Fascinating Genes." *Discover*, **26** (4).
- Wick, G, P. Berger, et al. (2003). "A Darwinian-evolutionary concept of age-related diseases." *Exp Gerontol* **38**(1-2): 13-25.
- Zimmer, C. (2001). "Do Chronic Diseases Have an Infectious Root?" *Science* **293**(September 14): 1974-1977.

Zimmer, C. (2003). "Infectious diseases. Taming pathogens: an elegant idea, but does it work?" *Science* **300**(5624): 1362.

Zimmer, C. (2007). "Evolved for Cancer?" *Scientific American* (January): 68-75.

Zouali, M. (2005). "Taming Lupus." *Scientific American* (March), 2005.

Further reading on Evolutionary Based Obesity topics:

Curtis, Michael. "The Obesity Epidemic in the Pacific Islands." *Journal of Development and Social Transformation* 37-42.

There are many societies, such as those located in the Pacific Islands that have only come into contact with Western cultures only recently in history. These societies are specific case-studies of the thrifty gene hypothesis. By looking at them, we may see how our modern society's food and exercise habits have conferred extreme health problems as result of obesity. This article describes the cultural implications of obesity, and how these populations have extreme health problems.

Isganaitis, Elvira, Lustig, Robert H. "Fast Food, Central Nervous System Insulin Resistance, and Obesity." *Arterioscler Thromb Case Biol* 2005; 2451 (25): 2451-2462.

This article looked at the epidemiology of fast food consumption, obesity and insulin resistance in relation to the central nervous system based on the "mismatch" proximate cause of obesity. By analyzing the characteristics of fast food, these researchers investigated the development of CNS insulin resistance and obesity.

Lawrence, Regina G. "Framing Obesity: The Evolution of News Discourse on a Public Health Issue." *Press/Politics* Summer 2004; 9(3); 56-75.

This article takes a very sociological point of view on the topic of obesity, presenting several public health suggestions to help solve the epidemic. Through a critique of how Western media frames obesity in advertisements, Lawrence suggests shifting the blame of being fat from the individual to the society as a whole, helping us move forward together to solve the problem.

Ozcan, Umut, Cao, Qiong, Yimaz erkan, lee, Ann-Hwee, Iwakoshi, Neal N., Ozdelen, Esra, Tuncman, Gurol, Gorgun, Cem, Climcher, Laurie H., and Hotamisligl, Gokhan S. "Endoplasmic Reticulum Stress Links Obesity, Insulin Action and Type 2 Diabetes." *Science* 2004; 306: 457-461.

This scientific experiment looked at cell cultures and mouse models in order to show that obesity causes endoplasmic reticulum stress. This is important because this type of stress is a key feature in insulin resistance and type 2 diabetes at the molecular and cellular levels. Through such experiments scientists hope to manipulate chemical pathways in order to treat these common diseases.

Peralta, Robert L. "Thinking Sociologically about Sources of Obesity in the United States." *Gender Issues* Summer 2003; 5-16.

This article also focuses on external social and behavioral trends that cause obesity in order to encourage a more community oriented framing of the obesity problem. Because obesity is linked to disparities of race, social class, and gender, individuals cannot necessarily be blamed

for their ill-health and every one must encourage one another in order to overcome obstacles to fitness. The authors stresses that without an understanding of the reasons leading to being overweight, the responsibility for reducing risks will solely, and unfairly, rely on the individual.

Roberts, Christian K., Barnard, James. "Effects of exercise and diet on chronic disease." *Journal of Applied Physiology* 2005; 98: 3-30.

This article in the *Journal of Applied Physiology* itemizes several types of chronic diseases associated with diet including, coronary artery disease, hypertension, diabetes, and cancer based on gene-environment interactions. This article is detailed in its descriptions and statistics.

Rogge, Mary Madeline. "The Case for Immunologic Cause of Obesity." *Biologic Research for Nursing* 2002; 4(1): 45-53.

This article presents another evolutionary argument, separate from the thrifty gene hypothesis and the fetal origin hypothesis, based on the immune response to fat. This theory is based on the idea fat accumulation is due to an infection of some sort that causes an immune response. By investigating the types of fat cells and their individual functions, this researcher suggests a longitudinal study to examine associations between infections or immunizations and the development of obesity.

Saris W.H.M, Blair, S.N., van Baak, Eaton, Davies, DiPietro, Fogelholm, Rissanen, Scholler, Swinburn, Tremblay, Westerterp, Wyatt. "How much physical activity is enough to prevent unhealthy weight gain? Outcome of the IASO 1st stock Conference and consensus statement." *Obesity Reviews* 2003; 4: 101-114.

Focusing on the physical activity aspect of obesity, this article addresses specific recommendations that are made to individuals trying to lose weight. Based on hunter/gatherer energy expenditures, this article emphasizes exercise as a primary means of obtaining health in our modern society.

Schreyer, Sandra A., Chua, Streamson C., and LeBoeuf Renee. "Obesity and Diabetes in TNFalpha receptor-deficient Mice." *Journal of Clinical Investigation* 1998; 102: 402-411.

This detailed scientific article presents findings done on mice that are genetically engineered to have either one receptor, two, or neither. These mice were fed a high-fat diet to induce obesity. It was determined that the receptors did not a major contributor to obesity-associated insulin resistance, in fact it was determined that the mice with both actually worked in order to protect the mice against diabetes.

Snyder, Eric E., Walts, Brandon, Perusse, Louis, Chagnon, Yvon C., Weisnagel, John, Rankinen, Tuomo, and Bouchard, Claude. "The Human Obesity Gene Map: The 2003 Update." *Obesity Research* 2004; 12 (3): 369-439.

This resource is very detailed, entailing all of the updates though 2003 on the genetic studies pertaining to research on the obesity gene. As of October 2003, 41 syndromes relevant to human obesity were already mapped to specific genomic regions, and causal genes or strong candidates had been identified for most of the syndromes.

Further reading on Evolution and Mental Health:

Allen, NB and Badcock, P. 2006. Darwinian models of depression: A review of evolutionary accounts of mood and mood disorders. *Progress in Neuro-Psychopharmacology & Biological Psychiatry* 30: 815-826.

This article reviews the evolutionary hypotheses for mood disorders and presents the evidence for and against the arguments used in the attempts to explain clinical depression as an adaptation. Included are hypotheses that have not been included in the case study of depression used in this chapter. One example is the social navigation hypothesis.

Zammit, S., and Owen, MJ. 2006. Stressful life events, 5-HTT genotype and risk of depression. *British Journal of Psychiatry* 188: 199-201.

This article reviews the evidence for and against an association between genetics and environmental stressors in increasing risk for depression. Conclusion for the review highlights the need for caution when interpreting the results produced from gene-environment interaction studies.

Nesse, RM. 1999. Proximate and evolutionary studies of anxiety, stress and depression: synergy at the interface. *Neuroscience and Biobehavioral Reviews* 23: 895-903.

This article provides a review of the evidence and arguments of the dysregulation model using proximate and evolutionary explanations and the importance of such studies in providing a conceptual framework. The article highlights the challenges of Darwinian medicine, but also its importance in providing a way of better understanding individual variation for disease susceptibility.

McLoughlin, G. 2002. Is depression normal in human beings? A critique of the evolutionary perspective. *International Journal of Mental Health Nursing* 11: 170-173.

This article provides the strengths and weaknesses of using an evolutionary perspective on depression, specifically the arguments Randolph M. Nesse utilizes in providing an evolutionary framework for depression.

Kirk, KM., Blomberg, SP., Duffy, DL., Heath, AC., Owens, IPF., and Martin, NG. 2001. Natural selection and quantitative genetics of life-history traits in western women: a twin study. *Evolution* 55(2): 423-435.

This study tested the conditions necessary for natural selection to select for a particular trait in a human population. The study looked at the relationship between reproductive fitness and the three female life stages, age at menarche, first reproduction and menopause. A high heritability for fitness was found and the authors conclude that natural selection is acting on traits different from our ancestors.

Licinio, J., and Wong, M-L. 1999. The role of inflammatory mediators in the biology of major depression: central nervous system cytokines modulate the biological substrate of depressive symptoms, regulate stress-responsive systems, and contribute to neurotoxicity and neuroprotection. *Molecular Psychiatry* 4: 317-327.

This article reviews the evidence for the etiology of depression resulting from the dysfunction of the inflammatory system and addresses the links between some chronic diseases and depression. Of importance in reviewing the evidence is the discussion of developing

interventions that utilize research findings on the biology of major depression in reducing risk for chronic diseases.

Pani, L. 2000. Is there an evolutionary mismatch between the normal physiology of the human dopaminergic system and current environmental conditions in industrialized countries? *Molecular Psychiatry* 5: 467-475.

The article argues that there is some evidence for an “evolutionary mismatch” in the human central nervous system for specific mental disorders.

Korf, J., Klein, HC., Versijpt, J., den Boer, JA., and ter Horst, GJ. 2002. Considering depression as a consequence of activation of the inflammatory response system. *Acute Neuropsychiatria* 14: 1-10.

This article addresses the etiology of depression as perhaps resulting from the activation of the inflammatory response in the brain. There is some evidence that infection either from bacteria or virus can lead to depression. The article looks at the implications that may contribute to the development of treatment in cases where antidepressants do not work in treating resistant depression.