AN EVOLUTIONARY PERSPECTIVE ON INFECTIOUS AND CHRONIC DISEASE

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The integration of evolutionary biology with traditional medicine can elucidate novel mechanisms of contemporary disease. Whereas the goal of traditional medicine is to treat and cure the proximate causes, evolutionary biology aims to understand the driving forces behind why humans are susceptible to disease. To form the basis of this hypothesis we postulate that modern man’s current genetic information was programmed at a time, and in an environment, that is not relevant to today’s human populations. The discordance between these genes of our ancestors and the environment of contemporary humans is thought to be a major reason for the increase in chronic diseases. Accordingly, the “Old Friends” Hypothesis is presented here to help understand the environment in which our ancestors evolved, emphasizing the relationship between humans and microorganisms that have an adaptive role in the human immune system. Furthermore, as societies and civilizations progressed throughout history, the human disease-scape began to change. The rise in epidemic infectious disease is tied to the advent of agriculture, and continues to be a major cause of mortality in developing nations. In Westernized nations mortality from infectious disease has decreased and life expectancy has nearly doubled in the last century. However, quality of life for many has diminished by the emergence of complex, chronic diseases such as cardiovascular disease, obesity, and type II diabetes. Current research supports the idea that an understanding of the evolutionary history of humans and their pathogens can be used as a complement to traditional approaches in disease treatment and prevention.
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CHAPTER 1

INTRODUCTION

Medicine and evolutionary biology are two profoundly distinct fields within the realm of basic science. Medicine stresses basic principles of chemistry, physics, and human biology, while also unifying these principles to understand physiology, embryology, and proximate causes of disease pathology. The primary goal of medicine is to cure the individual, to heal by taking solely what is applicable from these basic theories. Medicine aims to cure by solving the proximal causes of disease because these proximal causes are typically the most obvious and allows for the opportunity to “act and react” in attempts to quell disease manifestation or progression.¹ On the other hand, evolutionary biology is a collection of theories used to understand the variation in living beings.¹ Those in the field of evolutionary biology seek to understand the ultimate processes that shaped the diversity of life on Earth. In the simplest terms, medicine shows us how, and evolutionary biology shows us why. Thus, integrating these interdisciplinary pursuits seems logical because such a union may shed light on the “missing piece” of countless medical phenomena. However, despite contemporary advances in each respective field, full integration has been difficult to accomplish.

Charles Darwin’s contribution to evolutionary theory has helped explain the diversity of living organisms and has influenced how we observe life and its origins. His
writings have been applied to medicine since their emergence; however, it is important to note that two products of his theories, medical Darwinism and Darwinian medicine, are fundamentally different and are far from interchangeable.\(^1\) Medical Darwinism materialized soon after the 1859 publication of *Origin of Species*. Darwin’s own writings stressed the principle of pathological heredity, that inheritance of disease proved inheritance of variation, which became a backbone of his theory of natural selection.\(^2\) Classical Darwinism (1880-1920) was centralized around a typological approach: through the selection of traits, “types” are shaped. These “types” each have certain commonalities that may be structural, functional, or behavioral and are akin to what we know as phylogenetic families, groups, or species.\(^1\) The formation by natural selection of these certain types is a result of the elimination of unfavorable traits and the accrual of favorable ones that improve survival or reproduction of individuals. Those who applied Darwinism to medicine thought that natural selection was an all-or-nothing process and that traits were either strictly good or entirely harmful.\(^1\) It was thought that natural selection allowed for the “better” traits to be conserved, the “lesser” traits to be eliminated and that pathology was a result of traits that escaped natural selection.\(^1\) This “black and white” approach lead to the idea that natural selection was not applicable to modern man.\(^1\) English surgeon Lawson Tait was one of the first physicians to accept Darwinian theory and posed the notion that “the deteriorating constitutions of modern man [is] proof that medicine was keeping alive many who would have otherwise perished.”\(^3\) However, the erroneous belief that natural selection worked to eliminate through mortality rather than modify through differential reproductive success lead to the foundations of the eugenic paradigm.\(^4\) Aiming to improve the human race and counter the
perceived failures of natural selection, the founding of the eugenic paradigm and its grim consequences rendered medical Darwinism unpopular in the United States.\textsuperscript{1,4} The decline of medical Darwinism can also be attributed to the Flexner reform, which stressed medical research and experimentation rather than abstract application of ideas, as well as religious issues, as the teachings of Darwin were prohibited in many schools in the United States in the first half of the 20\textsuperscript{th} century.\textsuperscript{5}

In 1991, George Williams and Randolph Nesse published the first comprehensive paper on evolutionary principles as a foundation for modern biomedical science titled \textit{The Dawn of Darwinian Medicine}.\textsuperscript{6} This publication is considered to be the birth of “Darwinian medicine,” both the term and as a discipline. The phrase “medical Darwinism” was only used by medical historians to describe the previously discussed school of thought and was never actually used by Darwinian clinicians of the late 1800s and early 1900s.\textsuperscript{1} In contrast, Nesse and Williams intended to create a new discipline, coining the phrase “Darwinian medicine.”\textsuperscript{1}

Several advances have occurred within evolutionary biology over the last sixty years and preceded development of a new discipline.\textsuperscript{1} Firstly, contrasting with previous ideas of medical Darwinism, it is now known that natural selection operates at the level of genes and not at the level of individuals or species.\textsuperscript{6} Natural selection is the result of differential representation of genes across generations, and genes become more frequent in populations if they increase reproduction.\textsuperscript{6} It is worth noting that natural selection and an increase in gene frequency in order to increase reproductive success do not always lead to beneficial outcomes for the individuals of a species, as selection tends to flow towards an increase in genetic representation in the next generation regardless of an
expense to health after reproductive age. Essentially, one can personify genes as being “selfish,” as if the ultimate goal of genes is to use a body as a vector in order to be passed on to the next generation at any cost, so long as there are no negative effects on reproduction and fecundity of an individual. Traits that extend life or make life easier to live are evolutionarily irrelevant unless they also increase reproduction. In contrast with medical Darwinism, natural selection does not favor “good” traits over “bad” traits; the outcomes of selection may be positive or negative, working to potentiate genes that positively affect reproduction. Examples of this could be pathogen resistance or ability to choose a healthy, fertile mate. A second advancement that contributed to the development of Darwinian medicine was the discovery of genetic polymorphisms (or polymorphic alleles), which are natural variations in genetic material and are fairly common within populations. The study of genetic polymorphisms is a way to quantify what makes individuals unique within a species, for example, eye color, hair color, and blood type in humans. A third important finding in the field is the concept of genetic pleiotropy, or the idea that a certain gene can control many phenotypic traits, potentially having both positive effects on one trait and negative effects on another. This gives rise to a tradeoff among two or more traits, which is described by Fabio Zampieri as an “evolutionary enhancement in the contribution to fitness of one trait that is linked through development and physiology to an erosion in the contribution to fitness of another trait.” For instance, genes that apparently cause detrimental effects later in life may actually be preserved by natural selection if those genes have beneficial effects at a younger age. The converse is also true: a gene that repairs or prevents the abnormalities associated with aging will not be favored by natural selection if it imposes even the smallest cost early in life. Built
upon Darwin’s theories, these three ideas suggest that the adaptations produced via natural selection are compromises that are far from perfect and may also have concurrent maladaptations.\textsuperscript{6,7,12} To put this into the scope of medicine, one must be aware of some of the accumulated compromises shaped by natural selection in order to thoroughly understand the human body and the causes of disease. A concept described by Nesse and Williams in their book, \textit{Why We Get Sick: The New Science of Darwinian Medicine}, the adaptationist program refers to conceptualizing known aspects of human biology as functionally significant adaptations. This “functional adaptation approach” may subsequently lead to the prediction of unknown facets of human biology, and, through investigation, one may determine if the functional adaptations are clinically relevant.\textsuperscript{13}

So, why do we get sick? Nesse and Williams attempt to answer this question based not on disease itself but vulnerability to disease. Because natural selection results in imperfect compromises, the structures and functions that are shaped by selection are vulnerable to disease.\textsuperscript{7,13} In the discussion of disease vulnerability, it is important to remember not only the accumulated adaptations as well as maladaptations that selection has not overcome, but also the evolutionary history of humans and our pathogens. There are six causes of disease vulnerability:

1) A mismatch between our evolutionary design and our environment, for example, premature death by heart disease caused by diet and exercise choices due to a metabolism shaped in an environment where over-abundance of scarce nutrients were rare. Selection in favor of our current food environment has not yet occurred.\textsuperscript{7,14}
2) Competition with pathogens and other organisms due to selection occurring at a higher rate in pathogen populations than in host populations. This is seen in the case of antibiotic resistance.\textsuperscript{7,15,16}

3) Tradeoffs between traits occur because any potential improvements to one trait will inevitably result in the dysfunction of another trait.\textsuperscript{7,17} Our bones could be much thicker and less prone to breakage, however, doing so would require much more strength to move them as well as put unnecessary stress on delicate or complex joints, such as the pectoral girdle.

4) Natural selection can only work with what is already present, which may provide limits in future generations. For example, bipedalism allows us to run and move quickly, hold our offspring, use tools, and see greater distances; however, the price paid for these benefits is pain in the neck and lower back.\textsuperscript{7}

5) Selection is often misunderstood as something that will lead to improvements of all traits, however, selection acts to improve reproductive success.\textsuperscript{7} If a gene increases reproductive success it will continue to be selected for, even at the expense of health, happiness, or longevity later in life.\textsuperscript{9}

6) Many defenses, such as cough, fever, pain, nausea, vomiting, fatigue, and anxiety are misinterpreted as disease rather than defense.\textsuperscript{7} Much of the time these defenses are seen as the problem. The expression of these defenses in the presence of disease often leads clinicians to treat by blocking these mechanisms, which may not be problems at all, but the body’s solution to an underlying dysfunction. Blocking a defense may have harmful repercussions.\textsuperscript{15}
Using research from evolutionary biology and biological anthropology, we can apply an evolutionary perspective to diagnosing and treating disease in the modern world. For instance, when treating an infectious disease, as described above, it is crucial to be able to distinguish what is a cause of the disease and what is a consequence of the disease. It is also important to determine if the symptoms presented are a host defense or a parasite manipulation of the host, which would determine the course of action for treatment. For example, treating a cold with an anti-inflammatory drug has shown to lengthen the course of some infections due to suppression of pain as well as inflammatory responses that would otherwise aid in fighting the infection. Also, the coevolution between pathogens and their hosts has caused host traits to evolve in response to the evolution of pathogen traits that determine virulence, and vice versa. A pathogen’s virulence can further evolve in response to changes in population density, transmission, interaction with other pathogens or noninfectious conditions, antibiotic use, and countless other ways, which may render current or previous treatment plans ineffective.

The mechanisms by which the body handles mechanical damage or toxins can also be considered in an evolutionary context. For example, the swelling around a joint after an injury is not simply a bothersome side effect: it restricts movement and inflicts pain when used, facilitating the healing process. Emotions that are part of the stress response, such as fear or panic, may seem to be a weakness in the development of our psyche. From an evolutionary standpoint, these responses are extremely useful tools in the perception of potential impeding danger, yet are calorically expensive and can produce harmful effects if they persist chronically. As for toxins, humans are able to detoxify a considerable array of toxins and instinctively prefer a varied diet in order to
avoid toxin overload. Virtually all plant matter produces some kind of toxin to protect itself from predation, even if present in trace amounts. The most widely consumed drug in the world, caffeine, makes us feel great but is produced by coffee seeds to deter or kill any small animal or insect that preys on them. Pregnancy sickness is another way selection has shaped traits that influence the production of offspring. The protective mechanism of aversion to bitter taste experienced by most women during their first trimester of pregnancy indicates the presence of toxins. Consuming toxins within this stage of gestation can lead to problems with tissue differentiation, and it has been found that miscarriages are more common in women who are not afflicted with pregnancy sickness.

Another key concept in the field of evolutionary medicine is the hygiene hypothesis and its derivative the “old friends hypothesis.” This hypothesis is based on the idea that in developed, modern nations, lack of exposure to certain infectious pathogens, parasites, or symbiotic microorganisms leads to immune dysregulation. Our immune system has been selected to defend against the continuous bombardment by microorganisms while also developing a somewhat symbiotic relationship with particular bacteria, helminthes, and other parasites along our evolutionary journey via diet or lifestyle. However, in the present, many humans no longer live in an environment that facilitates regular contact with these microorganisms, including ones that may have been beneficial to our health. These organisms are virtually absent from individuals in developed nations, such as the United States, but are still present in some developing nations. There is evidence that exposure to these microorganisms mediate the development of immune responses and are thought to keep the immune system...
functioning at a particular baseline.\textsuperscript{25} Lack of exposure and thus disruption of the immune system’s basal function can lead to the development of allergic disorders and autoimmune diseases, both of which are widespread among developed countries and occur with little to no prevalence in developing nations.\textsuperscript{22} Described by S. Boyd Eaton, it is as if “the human immune system is now underemployed.”\textsuperscript{26}

One of the greatest challenges in modern medicine today is how to deal with the emergence of chronic diseases such as diabetes, cardiovascular diseases, asthma, and cancer. Since our beginning, we have undergone shifts in the diseases that have afflicted human populations over time, also known as epidemiological transitions.\textsuperscript{27} As civilizations emerged, famine or infectious diseases were the primary causes of mortality.\textsuperscript{27} However, in societies that have become more developed, mortality from infectious agents has dropped yet populations are afflicted with chronic, degenerative diseases.\textsuperscript{28} While overall life expectancies have increased, quality of life has decreased for many individuals who suffer from chronic illness.\textsuperscript{29} Some may argue that these diseases emerge simply because we are living longer. However, although these diseases emerge late in life, their biochemical origins occur decades earlier. Studies of younger age-matched subsistence horticulturalists compared with those living a more Westernized lifestyle show that the biomarkers for the development of chronic disease such as insulin resistance and high blood pressure are very common in the Westernized individuals and rare in the horticulturalists.\textsuperscript{30-32} It is hypothesized that there is a discordance, or mismatch, between the lifestyle our genes have been selected for and the lifestyle in which many of us currently live, which is relatively new on the evolutionary timescale.
It may seem as if we have fallen on our own sword, with the modern advances of antibiotics, sanitation, and industrialized food production come the consequences of antibiotic resistance and immune system and metabolic dysregulation. Evolutionary applications to medicine are new and unconventional, and in many ways, seem to go against traditional medical education. Further, teaching medical students about natural selection and lifestyle differences between the past and today may seem irrelevant to the causes of disease in the present. However, understanding that many diseases that afflict modern society are a result of genes inherited from our distant ancestors may offer a fresh perspective, allowing students to recognize the cause-and-effect relationship between our modern lives and disease manifestation. Connecting the evolutionary basis with the physical outcome may allow scientists and clinicians to produce a more efficient way to treat certain complex, multi-faceted diseases. The purpose of this paper is not to criticize or to discuss the shortcomings of modern medicine, but to illuminate certain aspects of infectious and chronic conditions that may have been overlooked yet have potentially valuable clinical implications and may aid in the treatment or prevention of disease.
CHAPTER 2

THE PALEOLITHIC DISEASE BASELINE AND THE “OLD FRIENDS” HYPOTHESIS

An updated variant of the hygiene hypothesis, called the “old friends” hypothesis, is based upon the lack of exposure to microorganisms that evolved to have an established role in our immune system and therefore contributing to the rise in chronic inflammatory disorders. The predominant diseases that afflicted human populations several millennia ago are different from the ones that primarily affect humans today for several reasons. However, comprehensive knowledge of contemporary human disease can be facilitated by an appreciation for the disease profile of pre-agricultural populations. It is speculated that the transition from foraging to agriculture that occurred roughly 10,000 years ago in several civilizations marked the first epidemiological transition for humans.

Researchers have used a variety of data in order to reanimate the disease patterns of the pre-agricultural era, including knowledge of habitat, genomic analysis of humans and their pathogens, as well as studying diseases in current hunter-gatherer societies. Prior to the development of agriculture, populations were small, dispersed, and had little contact with each other and therefore could not support epidemic diseases, and thus the presence of diseases such as measles, smallpox, and influenza were not likely. The types of pathogens that afflicted early humans fall into two categories: heirloom species and souvenir species. Heirloom species are those that have had a long lasting relationship with our ancestors and continued to infect them as they evolved into hominids; head and
body lice, pinworms, and bacteria such as *Staphylococci* and *Salmonella typhi* are some examples.\textsuperscript{35,36} Souvenir species are pathogens that hominids have “picked up” along the evolutionary timeline as they maneuvered through daily activities, such as zoonoses acquired from insect bites or the hunting and slaughtering of animals and preparing them as food.\textsuperscript{35,36}

Foraging populations of the Paleolithic period were also in greater contact with commensal microorganisms.\textsuperscript{37} From what we currently understand of their diet, our ancestors ate a wide variety of unprocessed foods that was stored in the soil, where it became enriched with fiber-fermenting *Lactobacilli* bacteria.\textsuperscript{38} Several strains of this and other health-promoting genera were likely to be found within the intestines our ancestors, and as a result, our ancestors probably had a much greater amount of commensal gut flora that we do in the present. For example, it has been found that most humans living in modern, Westernized societies have less than 1.3kg of commensal flora, while those living in developing, rural nations and eat a diet rich in plant matter have commensal flora weighing 2kg or more.\textsuperscript{38}

The significance of our millennia-long relationship with microorganisms can be explained through the concept of evolved dependence. Evolved dependence is when an organism becomes adapted to sharing an environment with another organism as if they have formed a partnership, and, over time, both organisms depend on one another and survive poorly without each other.\textsuperscript{24} Studies suggest that certain aspects of biology, including immunologic function, become “entrusted” to the symbiont species.\textsuperscript{24,39,40} For example, a study involving human symbiont *Bacteroides fragilis* demonstrates that the bacteria can regulate immune pathways, reducing inflammation.\textsuperscript{40} Using germ-free mice,
which are known to have dysregulated immune function compared to mice raised with a whole bacterial composition, Mazmanian and colleagues used an experimental colitis protocol and found that defects in immune cell development are corrected by the commensal *B. fragilis* via a surface molecule called polysaccharide A (PSA). Germ-free mice have higher levels of pro-inflammatory cells, yet when inoculated with *B. fragilis*, the immune balance is restored to that of mice that were not raised in a germ-free environment. Further, in immune-compromised mice, PSA from *B. fragilis* protects from *Helicobacter hepaticus*-induced ulcerative colitis. This protective effect was found to occur via suppression of pro-inflammatory cytokines tumor necrosis factor-alpha (TNFα) and interleukin-23 (IL-23), and expression of the potent anti-inflammatory cytokine, IL-10. *B. fragilis* PSA is the first single bacterial molecule found to reduce and even reverse mammalian intestinal inflammation by regulating immune pathways and has been classified amongst a new set of molecules called “symbiosis factors.” While the specific interactions between PSA and immune pathways have yet to be determined, isolation of this molecule for clinical purposes may have promising results.

Helminths are another class of organisms that have had a long-standing relationship with our ancestors. Traditionally, helminth infection has been associated with the domestication of animals to be used for livestock during the development of agriculture around 10,000 years ago. However, evidence discovered by Hoberg, et al. suggests that the ancestors of the modern tapeworm in the *Taenia* genus began to parasitize humans much earlier than previously believed. It is thought that our Homo ancestors underwent a habitat shift around two million years ago from forests to open savannahs, forcing our ancestors to forgo an herbivorous diet and adapt an omnivorous
diet due to the change in available food resources.\textsuperscript{43,44} Savannah-dwelling animals such as antelopes and other bovids became a new food source for these early humans.\textsuperscript{45-47} For the Taeniidae, the typical definitive hosts are carnivores, such as large felids or hyaenids, and the intermediate hosts are herbivores, such as bovids; in this case, our early ancestors became the definitive hosts, which resulted in the parasitizing of \textit{Homo} by the \textit{Taenia} worm.\textsuperscript{42} The modern lineages \textit{Taenia saginata}, \textit{Taenia asiatica}, and \textit{Taenia solium} all use humans as a obligate definitive hosts and, through phylogenetic and molecular clock analysis, were found to have diverged anywhere between 160,000 to one million years ago, suggesting that the \textit{T. saginata}/\textit{T. asiatica} lineage, and likely other helminth lineages, has been associated with humans and our ancestors since well before the domestication of animals.\textsuperscript{42}

Today, like many of the saprophytic bacteria that were constantly present in our ancestors, helminthes are largely absent from our daily lives; yet, like certain bacteria, helminthes are also relevant to immune regulation.\textsuperscript{41} According to the “old friends” hypothesis, early in our evolution certain harmless organisms needed to be tolerated by the body because they have always been present in food and water sources, and although some helminthes are not necessarily harmless, complete elimination may have caused tissue damage.\textsuperscript{41} Essentially, our bodies outweighed the negative effects of the pathogen for the benefits of nourishment, and our early immune systems learned to deal with the infection rather than initiating unnecessary and potentially destructive immune responses.\textsuperscript{41} Currently in developed societies, there has been an increase in allergies and autoimmune diseases, and these societies are void of intestinal helminth exposure\textsuperscript{48}. In contrast, individuals in developing nations with a heavy helminth burden are less likely to
be allergic or have an inflammatory or autoimmune disorder. Research has shown that helminth infections are associated with the release of anti-inflammatory molecules and serve somewhat of a protective function in our immune system.

Traditionally, the hygiene hypothesis was based on the balance of two types of cells in our immune system: type 1 helper cells (Th1) and type 2 helper cells (Th2). Th1 cells are associated with bacterial and viral infections as well as autoimmune disease. Th2 are associated with allergies and helminth infections; they also produce the allergic atopic response, characterized by elevated pro-inflammatory cytokines such as IL-4, IL-5, and IL-13, which stimulate immunoglobulin (Ig) E, eosinophil, and mast cell production. Some have argued that Th1 cells and Th2 cells act antagonistically, and that low exposure to bacterial and viral infections in childhood fails to stimulate Th1 cells, which in turn results in over-activation of Th2 cells leading to allergy. In developed nations, Th1-mediated disorders such as type 1 diabetes, multiple sclerosis, and inflammatory bowel diseases as well as Th2-mediated allergic diseases are on the rise. On the other hand, in less developed nations, people infected with helminthes, which enhance Th2 responses, are less likely to be afflicted with allergies or have inflammatory disorders, yet treating the helminth infection leads to an increased sensitivity to allergens. However, it is this paradoxical relationship that suggests a more complex mechanism at play than simply an imbalance between Th1 and Th2 responses. In individuals who are free of helminth infections and suffer from allergies or chronic inflammation, there is speculation that the true problem behind immune dysfunction is the failure of the immune system to cease unnecessary responses while allowing intended responses to continue. The unwanted responses are no longer thought to be a result of the Th1/Th2 relationship.
but are attributed to a reduction of regulatory T cell activity. Regulatory T-cells are thought to guide the complex network of immuno-modulatory molecules toward an appropriate response.\textsuperscript{50} According to Graham A.W. Rook, rather than the immune system deciding when to respond with an immune attack, which can be caused by failure to recognize harmless antigens, the most likely mechanism behind a correctly-functioning immune system is the decision of when \textit{not} to respond because an allergen is harmless or could be part of the gut itself.\textsuperscript{54}

Several experiments involving children of developed and developing countries display an inverse relationship between helminth infection and sensitivity to allergens or manifestations of asthma.\textsuperscript{56-58} In both the highly developed and less developed countries, around one-third of the children exposed to allergens via skin prick test produced an atopic immune response characterized by elevated levels of IgE antibody for a particular allergen.\textsuperscript{56-58} Despite raised IgE levels in children from the less developed countries, respiratory symptoms of asthma were less prevalent and overall less severe than children tested in more developed nations.\textsuperscript{56-58} Interestingly, the degree of helminth exposure shows varied immune responses. Light helminth infections produce an increase in allergen-specific IgE responses and high skin reactivity, while heavy helminth infections were less likely to show skin reactivity.\textsuperscript{59-61} Removing the worms from the lightly parasitized individuals alleviated allergic symptoms, yet resulted in a worsening of symptoms in the heavily parasitized individuals.\textsuperscript{59-61} The complex relationship between helminth exposure and a reduction in allergic symptoms despite high levels of IgE and Th2 cytokines is not well understood but is currently thought to be mediated by regulatory T cells.\textsuperscript{50}
In animal models, helminth therapy has been shown to attenuate inflammatory bowel disease as well as airway inflammation and allergic responses.\textsuperscript{62-64} Due to this success, human clinical trials have commenced and with promising results.\textsuperscript{65-67} *Trichuris suis*, the porcine whipworm, does not complete its lifecycle in the human host but is a close relative to the human whipworm, *T. trichuria*.\textsuperscript{68} *T. suis* is not a natural human parasite and brief colonization following hatching does not have any known associations with disease, thus making *T. suis* a good candidate for therapeutic use.\textsuperscript{66} In patients with active Crohn’s disease, treatment with *T. suis* ova for 24 weeks produced an 80% response rate and 73% remission rate.\textsuperscript{66} Additionally, the same research group studied the effects of *T. suis* therapy on patients with active ulcerative colitis which did show improvement, however, few remissions occurred.\textsuperscript{65} This may be related to the fact that many patients participating in the trial had longstanding and severe forms of active disease, suggesting that early intervention with *T. suis* therapy may provide the greatest benefit to ulcerative colitis patients.\textsuperscript{65} The hookworm *Necator americanus* has also shown to be well-tolerated in humans in low doses for use in the treatment of asthma, as indicated in a dose-ranging pilot study.\textsuperscript{67}
CHAPTER 3

THE FIRST EPIDEMIOLOGICAL TRANSITION: A RISE IN EPIDEMIC INFECTIOUS DISEASE

The idea that the Agricultural Revolution marked the first major epidemiological transition is well-documented. Changes in human behavior, habitat, and food niche exposed populations to novel pathogens or infectious agents that were previously encountered sporadically in isolated incidents. Although the advent of agriculture is associated with a spike in population growth, some argue that this period represents the beginning of an overall decrease in health among human populations due to the rise in infectious disease.

There are many reasons for the increase in infectious disease following the development of agriculture. Firstly, agriculture allowed our ancestors to modify the surrounding environment, making it possible to settle and produce food virtually anywhere. This was the first time humans could not only choose where they wanted to live but support themselves while doing so. However, settling in novel locales exposed populations to new pathogens, for example via insect bites during crop cultivation.

Secondly, stationary settlements allowed the people in these growing populations to be in close contact with one another, thus increasing the transmission of droplet-spread respiratory diseases as well as making human waste disposal a potential problem increasing the occurrence of fecal-borne disease. The static nature of these settlements also provided a contiguous living area with domesticated animals and
“peridomestics” such as rodents allowing the transmission of bacterial diseases including anthrax, brucellosis, and tuberculosis, or Q fever. While stationary settlements allowed people to accumulate and store food for times when food would be scarce, this storage also increased the possibility of food poisoning. Thirdly, due to the dependence on domesticated crops, people in agricultural settlements had less dietary variation than their foraging predecessors, which may have negatively impacted health. Traditional agricultural communities eat only around ten to fifteen different types of plant species, while hunter-gatherer societies today, such as the Kalahari San Bushmen or Congo Pygmies, eat more than 100 different plant species. The lack of variation in diet may have had nutritional and health consequences increasing the impact of infectious disease in malnourished individuals. Finally, the increase in population size and human contact following agriculture allowed for acute infections to be supported by a population facilitating the maintenance of epidemics. Small population sizes prior to the agricultural revolution were typically not large enough to support epidemic disease. These fundamental reasons underlie the causes of morbidity and mortality in nearly every society undergoing urbanization since the dawn of agriculture. The ever-present threat of infectious disease becomes so commonplace that it is entwined within culture, with every culture having a cluster of infectious diseases that represents it. Cross-continental trade from Asia during the early Renaissance delivered the Black Death to Europe, with its epidemics of the 1300s killing an estimated third of the European population. Seemingly innocuous diseases in one population were sometimes devastating epidemics in another. Thus, during the age of global exploration, introduction of diseases to novel populations and environments often resulted in changed transmission dynamics and
increased virulence, as seen with the introduction of smallpox to Native American populations.\textsuperscript{75} The Industrial Revolution facilitated the spread of disease, bringing people, as well as their diseases, from far-reaching rural areas to urban environments for work and opportunity for a better life. These densely populated urban centers became foci for poverty enhancing the transmission of diseases such as tuberculosis, typhus, diphtheria, measles, and yellow fever.\textsuperscript{75} Throughout history, infectious disease has influenced societies by evoking fear, dividing classes, decimating populations, and shaping human behavior.

3.1 **Infectious Organisms: Symptoms and Virulence**

Infectious organisms include bacteria, viruses, types of fungi, parasitic protozoa and helminthes, which live all or part of their life cycle inside the host. Exploitation of host resources is the primary way in which these infectious organisms survive and proliferate.\textsuperscript{15} Colonization of an infectious agent usually disrupts host homeostasis in some way, manifesting as symptoms. When we experience uncomfortable symptoms such as fever, headache, coughing, sneezing, and G.I. upset, we know something is wrong, and we usually seek some way to suppress the symptom in order to go about our day. However, it is important to recognize that the symptoms are occurring for two reasons: 1) the infectious organism has established residence in one’s body and is manipulating host physiological processes for its benefit, and 2) the host is responding to the invader and attempting to protect itself from damage by the pathogen.\textsuperscript{15} Some examples of defense symptoms include fever, iron sequestration, nausea, pain, and behavioral defense such as vomiting, malaise, or skin scratching.\textsuperscript{13} Fever, pain, and malaise work to keep the host less active, making it easier to allocate metabolic energy to
fight an infection. Many pathogens require high bioavailability of iron for proliferation and have evolved strategies to obtain iron from hosts. However, hosts have evolved a response to this by the development of iron sequestration mechanisms through a variety of iron-binding proteins. Nausea and vomiting have evolved a psychological component: both provide a strong, one-time learning experience to avoid subsequent infection from ingesting contaminated food. Manipulative symptoms that can benefit the pathogen include excessive sneezing or diarrhea to facilitate transmission, or secretion of compounds that misguide host immune responses. The bacterium *Vibrio cholerae* releases a toxin that increases the activity of the cystic fibrosis transmembrane conductance regulator (CFTR). Activation via *Vibrio cholerae* toxin leads to irreversible activation of this channel, resulting in dehydration and electrolyte loss in the form of diarrhea. This mechanism facilitates dispersal of the parasite via manipulation of host resources. In some cases, symptoms can benefit both the host and the pathogen at the same time. The bacterium that causes dysentery, *Shigella*, produces bloody diarrhea resulting from invasion of intestinal epithelial cells. The diarrheal symptom can be interpreted as manipulative because it facilitates transmission of the bacteria. However, this symptom can also be interpreted as a defense because ridding the body of the bacteria in this way minimizes the time that the bacteria stays inside the body, therefore reducing destruction of intestinal tissue. Experimental infections with *Shigella* showed that treating the patient with an anti-diarrheal prolonged the infection until treatment was terminated, while untreated patients eliminated the bacteria and overcame the infection. From this example, one can see that symptomatic treatment may not always be the most effective in curing the patient of the disease. Described in Paul Ewald’s book *Evolution*
of Infectious Disease, in a case where a symptom benefits both the host and the parasite, treatment providers must be cautious because although prevention of a symptom may decrease transmission of an infection, symptomatic treatment may actually harm the patient. Thus, he asserts that treatment providers should make decisions with the knowledge of the compromises that will result from the selected method of treatment and that they will have to consider the expected harm to the patient versus the benefits to others who may otherwise contract the infection if it is allowed to spread. By understanding the symptoms of an infection and categorizing them as a manipulation or defense, and then further into host-benefit, pathogen-benefit, or beneficial to both, clinicians may be able to select the most optimal method of treatment.

Some symptoms of an infection are often correlated with a pathogen’s virulence. Virulence is defined by the degree of harm inflicted upon the host. A highly virulent pathogen exhibits higher levels of host exploitation, morbidity, and mortality. In evolutionary terms, virulence is the degree of parasite-induced decline in host fitness. Traditionally, evolutionary theory suggested that pathogens and hosts would coevolve towards a benign relationship with one another and result in less virulent infections. Currently, the updated theory is that natural selection will increase fitness for both the host and the pathogen, yet not necessarily moving towards a benign, symbiotic relationship. Virulence differs among pathogens for many reasons; however, differences in transmission play a large role. Ewald has formulated general predictions about virulence:

1) Pathogens requiring insect or animal vectors in their transmission are highly virulent in the human host. This is because the pathogen does
not require the host to be mobile in order to disperse and infect others, malaria is a common example: an ill, powerless, stationary host facilitates transmission because it allows many potential vectors access to the plasmodium.\textsuperscript{15} Also, any damage to the vector would reduce pathogen dispersal and thus virulence in the vector will be low.\textsuperscript{15}

2) Pathogens spread by water and other inanimate objects are more virulent than those that are not. For example, if a person is immobilized and suffering from severe diarrhea, the pathogen will be released into bed linens and clothing.\textsuperscript{85} Washing this clothing will release the contaminated water. If this water mixes with drinking water, many people will become infected from the bacteria released from only one host.\textsuperscript{85} Immobilization of the host does not affect pathogen dispersal, so virulence will continue to increase.\textsuperscript{85}

3) Pathogens spread by “cultural vectors” are highly virulent.\textsuperscript{84} A common example is attendant-borne transmission in hospital settings because hosts are usually immobilized patients with compromised immune systems, such as infants or the elderly. In this case, the hands of healthcare providers serve as the vectors, and the vectors rarely become infected due to hand-washing and stronger immune systems than the hospitalized patients.\textsuperscript{15,80} Interestingly, infections have been found to increase in lethality as they cycled for longer periods of time within hospitals.\textsuperscript{86}
4) A change in transmission will result in a change in virulence. For example, changing transmission from vector-borne to direct transmission from host-to-host should result in a decrease in virulence because host mobility is required for transmission.  

5) Parasites with a high frequency of vertical transmission, or from mother to offspring, are less virulent than those transmitted by horizontal transmission and may even lead to benign, mutualistic relationship with the host. A decrease in host fecundity or survival would be a massive cost to the pathogen.

The predictions regarding virulence provide a set of guidelines when studying and interpreting the effects of infectious disease. Many diseases fall under more than one of these predictions, making the pathogen unique in terms of transmission and virulence potential. For example, *Yersinia pestis*, the etiologic agent of the Black Death, is what Ewald describes as a “sit-and-wait” pathogen. A “sit-and-wait” pathogen is the ultimate opportunist and can be transmitted from an immobilized host in two ways: the pathogen can be transported by a vector, or the pathogen can sit and wait for a potential new host to come in contact with the infected host via respiratory droplets. These types of pathogens reap the benefits of being able to multiply inside the host while also paying little to no cost of a languid host. Due to the high rate of spreading, it is thought that the Black Death was primarily transported through respiratory droplets, but it could also be transported through an arthropod vector if the opportunity presented itself. The crowded, unsanitary living conditions of Europe during the Middle Ages facilitated the rapid
proliferation of the disease through person-to-person contact, making the Black Death one of the most destructive diseases in human history.\textsuperscript{80}

Despite major scientific advancements such as the development of antibiotics, vaccines, and improved sanitation, infectious diseases are still the major source of mortality worldwide.\textsuperscript{87} These diseases fall into one of three categories: 1) new infectious diseases that have emerged and are previously unknown to have affected humans, 2) re-emergence of infectious diseases that were thought to be under control, and 3) persistence of unmanageable infectious diseases.\textsuperscript{88} Examples include West Nile virus, dengue hemorrhagic fever, prion diseases, and some influenza strains.\textsuperscript{88}

Human activity such as mass transportation of products, livestock, and people increase the contact between humans and pathogens.\textsuperscript{81} Decreased compliance with vaccination protocols has led to the re-emergence of previously controlled diseases such as measles and pertussis, while misuse of antibiotic or antimicrobial agents have contributed to treatment-resistant strains of bacterial pathogens.\textsuperscript{87,88} Although increased surveillance, rapid diagnosis and early containment are critical to disease control, these public health measures alone are insufficient in the fight against infectious diseases.\textsuperscript{87} Pathogens adapt and evolve rapidly in response to human behavioral and environmental alterations, making it easy to assimilate into new ecological niches.\textsuperscript{15,87} According to Paul Ewald, it may be possible to decrease a pathogen’s virulence by altering the environment. For example, when water sanitation improved in North America, South America, Europe, and Asia, diarrheal pathogens \textit{V. cholerae} and \textit{Shigella} evolved toward lower virulence because in the absence of water as a vector, these pathogens rely on host mobility.\textsuperscript{15,85} An understanding of the perpetual evolutionary “arms race” between humans and their
pathogens may provide insight into the development of treatment plans, and if employed correctly, lead to decreased virulence and ultimately reduce the harm inflicted by many infectious diseases.\textsuperscript{15}
CHAPTER 4

COMPLEX, CHRONIC DISEASE

Currently, in industrialized countries, we live in an era where mortality rates from infectious disease pandemics have declined while life expectancy has increased to 70 years or beyond and population growth has increased exponentially.\textsuperscript{26,89} This is due to many advancements including the development of medical practices such as implementation of germ theory, improved nutrition, and public health measures.\textsuperscript{34}

However, although life expectancy has increased over the past two centuries, quality of life for many has been reduced due to the emergence of complex diseases that are chronic and degenerative.\textsuperscript{34,90} This transition of disease prevalence and mortality from infectious pandemics to chronic degenerative disease is known as the second epidemiological transition.\textsuperscript{27,34}

Complex chronic degenerative diseases are distinguished by vague etiology, long latency period, prolonged course of illness, functional impairment, and in many cases are not curable.\textsuperscript{26} Examples of these diseases include cardiovascular diseases such as stroke and heart attack, some cancers, asthma, and diabetes. In the United States and other developed countries, these chronic diseases are responsible for approximately 70\% of deaths and are thus known as “diseases of civilization.”\textsuperscript{6,26,91} One common attribute to chronic diseases is the necessary interaction of multiple contributing agents, known as risk factors, which implies that many genes are involved in the regulation of these diseases.\textsuperscript{26} The risk factors involved seem to be related to diet and lifestyle choices and
their interactions with our genes. Our genes have been selected through adaptations that occurred over millions of years, and despite migrations and developments such as agriculture, industry, and technology, there is evidence that our gene pool has differed little since anatomically modern humans diverged around 200,000 years ago. Some speculate that the rise in the “diseases of civilization” are due to the mismatch between our genes and the cultural changes that have occurred relatively recently on the evolutionary timescale.

There are many types of discordance between our genes and our environment. Most discordance is related to nutrition, physical exertion, reproduction, infection, growth and development, and psychosocial elements. However, for this section of the paper, only discordances of nutrition and physical activity will be discussed.

4.1 Nutrition

Nutrition is perhaps the greatest difference between our ancestors and contemporary humans. Much of what we currently eat is derived from domesticated or commercially produced and processed sources, whereas our pre-agricultural ancestors had to forage plant matter and hunt wild game for survival. Most foods that make up a large portion of the contemporary diet today such as dairy, refined sugars, cereal grains, refined vegetable oils, and alcohol were largely absent from pre-agricultural diets. Ancient wild cereal grains are small in size and difficult to harvest and digest without processing, making it difficult for our ancestors to utilize grains as food until the emergence of stone mortars and other grinding instruments anywhere from 40,000 to 10,000 years ago.
Using current hunter-gatherer societies as a model, it is estimated that our ancestors’ carbohydrate intake was around 20-40%, consisting of mostly fruits and vegetables as opposed to refined grains and sugars. Today, American caloric intake typically consists of over 50% carbohydrates from cereal grains and refined sugars, which have a higher glycemic index, are more insulinogenic, and have a lower antioxidant capacity than the fruit and vegetable caloric equivalent. The total fat proportion consumed by pre-agricultural and modern-day humans remains the same at approximately 35%, however, the composition was different. The fatty acid profiles of wild game consist of more long-chain mono- and polyunsaturated fatty acids than their domesticated grain-fed counterparts, meaning that our ancestors consumed less saturated fats and more long chain unsaturated fatty acids. The pre-agricultural essential fatty acid ratio of omega-6 to omega-3 was estimated to be 3:1, while current Americans have closer to 10:1, which has inflammatory effects and is thought to promote atherogenesis. Despite dietary cholesterol being high due to the consumption of wild game, serum cholesterol-raising fat was lower compared to present Western diets. According to an analysis conducted by Sebastian et al., pre-agricultural humans most likely ate a diet rich in protein and non-grain plant food groups such as nuts, legumes, fruits, and vegetables. This type of diet is found to have a net alkalotic effect on the body via increased bicarbonate production, promoting an anabolic effect on bone and increasing bone mass. Contemporary diets, however, have replaced non-grain plant foods with cereal grains, refined sugars, and separated fats, resulting in reduced bicarbonate production and an acidotic effect. This net acidosis has catabolic effects and eventually results in bone loss, osteoporosis, and muscle degradation.
Over most of the human evolutionary journey, food production and physical exertion were intimately coupled and if one needed to eat, one was obligated to physically work. Today, social structure and industrialization has uncoupled the food-work relationship. We no longer need to hunt wild game, forage for plant foods, or even make our own tools to do it all.

The levels and types of activities varied among different groups living during the Stone Age and were dependent on geographical location and seasonal patterns, yet there is a consensus that overall energy expenditure exceeded that of an average contemporary American. These groups had a wide range of daily physical activities, which included: walking while gathering and hunting; running after prey; carrying their kill, plant foods, or firewood; building shelters; making tools and digging for roots and tubers; butchering and cleaning game meat; ceremonial and recreational dancing; and carrying their children. Although these daily activities required muscular effort and stamina, it is likely that these individuals spaced out their activities rather than working for many hours at a time. For example, men usually hunted on 2-4 nonconsecutive days per week, while women usually foraged every 2-3 days. During these days, individuals would walk or run in fast bursts, jump, leap, climb, carry, stretch and more in order to obtain food or water. These patterns of physical activity are analogous to modern cross-training with aerobic, resistance, and flexibility exercises. Current data on physical activity suggests that exercise programs containing various types of exercises and intensities are beneficial in terms of lowering the risk for cardiovascular disease. Considering the activity level of our ancestors, one would assume that they must have
been extremely muscular and strong. Using skeletal remains in conjunction with studying current hunter-gatherers, evidence confirms that our ancestors had greater strength and muscularity than most people living today.\textsuperscript{92} This finding is true whether the groups being studied lived 10,000 or 1,000 years ago, suggesting that the increased robustness is a result of habitual activity and not an evolutionary shift.\textsuperscript{101,104,105} The obligatory activity level of our ancestors resulted in an increased lean body mass and a decrease in adipose tissue, which would have reduced their risk of type II diabetes.\textsuperscript{106}

In the present day, discordances resulting from abnormal body composition as well as consumption of a typical American or Western diet have lead to a host of diseases that have now become public health concerns: atherosclerosis, type II diabetes, obesity, and hypertension. While all are part of a cluster of diseases known as “metabolic syndrome,” type II diabetes is becoming one of the fastest-growing diseases worldwide.\textsuperscript{107,108}

4.3 TYPE II DIABETES AND INSULIN RESISTANCE

Insulin resistance is the center of the metabolic syndrome and is linked to reduced activity levels and a surplus of metabolic energy.\textsuperscript{109} Individuals who are insulin resistant are at high risk for not only type II diabetes, but also hypertension, coronary artery disease, peripheral vascular disease, and polycystic ovarian syndrome.\textsuperscript{26} Insulin resistance and type II diabetes mellitus are strongly associated with obesity among all ethnic groups, causing more than 80\% of cases.\textsuperscript{110} While obesity is a strong contributor, BMI and weight are not as critical for the development of type II diabetes as body composition.\textsuperscript{106} There appears to be an inverse relationship between the proportion of lean muscle tissue and the likelihood that an individual will develop insulin resistance.\textsuperscript{26}
According to a model described by James Neel, some of our ancestors possessed what he terms the “thrifty genotype,” meaning that during times of fluctuating food availability, selection favored those who could release insulin most effectively during plentiful times while also being able to easily store energy during times of scarcity. Our taste preferences have also evolved to aid in this process: we instinctually prefer fats, sugars, and salt due to their rarity in the past and their high energy value. Now, reaping the benefits of a sedentary lifestyle in times of plenty, this once adaptive genotype results in hyperadiposity, sarcopenia, and insulin resistance.

The chemistry of adipose cells (adipocytes) and muscle cells (myocytes) differ in terms of insulin sensitivity. Insulin receptors on adipocytes and myocytes compete for insulin released from the pancreas. Although muscle fitness determines exactly how much glucose is cleared from the blood upon insulin receptor binding, insulin binding to muscle receptors clears approximately 7-10 times more glucose from the blood than when binding to adipose receptors. Thus, people who have more muscle tissue relative to adipose tissue are more insulin-sensitive as opposed to those who have a higher adipose to muscle tissue ratio. The imbalance of insulin receptors in those with more fat than muscle tissue means that the pancreas must secrete more insulin per amount of carbohydrate ingested.

Location of adipocyte cells in the body as well as body shape also seem to play a role in the way insulin is utilized. Fat cells in the liver are exposed to all of the insulin released into portal circulation from the pancreas, and the insulin receptors on the adipocytes in the liver “steal” some of the insulin molecules that would normally go to the rest of the body. Thus, there are fewer insulin molecules available for myocytes in
the body per pancreatic insulin release, and insulin sensitivity will decrease as liver adiposity increases.106

By now, many have heard that a “pear” body shape, or those with more subcutaneous fat in the lower body, is more beneficial to health than an “apple” body shape, or those who have excess visceral fat in the abdomen.114 One reason for this may be that blood flow patterns differ between visceral fat and skin or subcutaneous fat.114 Visceral blood flow requires 25% of cardiac output at rest, and rises to 35% during digestion, while cutaneous and subcutaneous flow requires only 5% of cardiac output at rest and even less during digestion.106 Visceral adipocyte insulin receptors can therefore outcompete subcutaneous receptors for circulating insulin because they are exposed to 5-7 times more insulin molecules than subcutaneous fat cells.106 Again, this means there is less insulin available to bind to myocyte insulin receptors, and due to the reduced efficacy of fat cells to clear glucose from the bloodstream compared to muscle cells, blood glucose remains high and the pancreas continues to secrete more insulin to compensate leading to repetitive hyperinsulinemia.26

The development towards insulin resistance seems to have two phases.26 As described above, the first phase is characterized by the imbalance of insulin receptors due to body composition that differs from the ancestral norm: too much adipose tissue, not enough muscle tissue, and low muscular fitness.26 The recent dietary addition of high glycemic-load foods produces repetitive hyperinsulinemia. This first phase is an excellent example of the discordance that arises when our ancient physiology attempts to adapt to our modern environment and is likely the reason behind the increase in type II diabetes over the past thirty years.26 The second phase of insulin resistance is more complex.
Repetitive hyperinsulinemia resulting from the first phase activates genetically determined cellular mechanisms that ultimately leads to reduced sensitivity of the myocytes and adipocytes to insulin stimulation.\textsuperscript{26} The exact mechanisms responsible for this second phase of insulin resistance are not well understood but are currently being addressed in biomedical research.\textsuperscript{115,116}

As previously discussed, foods that are relatively new to humans include refined grains, sugars, and dairy.\textsuperscript{95} These foods have a potent effect on raising serum insulin levels.\textsuperscript{117} This may be due to the fact that refined grains and sugars are rapidly absorbed by the intestines and are thus known as “high glycemic index” foods.\textsuperscript{95} These foods also have what is known as a “high glycemic load,” which means that they have a high proportion of carbohydrate per unit of weight.\textsuperscript{26,95} The digested carbohydrate delivers a rush of glucose into the bloodstream, which results in large amounts of insulin release from the pancreas.\textsuperscript{95} For mechanisms presently unidentified, dairy products seem to cause an acute rise in serum insulin levels despite having a low glycemic index.\textsuperscript{26,95}

Studies have shown that individuals placed on a Paleolithic-style diet (i.e. no grains, added refined sugars, separated oils, dairy, or alcohol) have better glycemic regulation, decreased blood pressure, and reduced blood markers for cardiovascular disease in diabetic individuals and even in as little as ten days for healthy, non-obese individuals.\textsuperscript{117-119} Rather than one sole dietary component being responsible, there appears to be several elements at work that cause many chronic diseases today related to glycemic load, fatty acid composition, macronutrient profile, fiber content, acid-base balance, and sodium-potassium ratio.\textsuperscript{95} Dietary elements and other lifestyle factors interact with our ancient genome to produce these complex, multifaceted “diseases of civilization.”\textsuperscript{120} The daily
lives of our ancestors provide insight towards understanding why diabetes and other chronic diseases have become increasingly widespread. Incorporating aspects of ancestral diet and activity patterns may be the key to chronic disease prevention.\textsuperscript{121}
CHAPTER 5

CONCLUSION

Millions of years of selection has shaped the human body into a collection of compromises. We get sick because of these compromises formed by natural selection. Selection works to optimize reproduction, not steer us towards perfect health. Many genes that make us vulnerable to disease often have an advantage early in life, or conversely, do not present a significant disadvantage until late in life and thus selection cannot act to eliminate them. The slow nature of human evolution through selection also contributes to disease susceptibility. Pathogens can out-evolve humans, causing disease simply because human immune systems cannot keep pace. Further, humans have not yet adapted to many novel circumstances that were not present in the environment that humans evolved. Costs and benefits of selection have been continuously weighed against each other throughout evolution, with the balance point being vulnerability to disease.

To summarize, as described by Steven C. Stearns, et al., here are some of the key principles that guide evolutionary medicine:

1) Organisms are not perfectly engineered machines. Organisms are bundles of compromises accompanied by tradeoffs and limitations.

2) Due to the fact that biological evolution occurs much more slowly than cultural change, many diseases are a result of the mismatch between our bodies and our environment.
3) Pathogens evolve much more quickly than humans therefore infection is inevitable.

4) Common heritable diseases are usually caused by many genetic variants in a population that interact with environments and other genes during development to influence disease phenotypes.

Tinbergen and Mayr stressed among the evolutionary biologists that every trait in every organism requires two types of explanations: proximate ways in which mechanisms work and evolutionary explanations of why the mechanisms developed.\textsuperscript{122,123} Understanding both proximate and evolutionary explanations can provide a complete picture of a disease rather than simply knowing the proximate reasons alone. The practical implications of applying evolutionary principles to medicine are abound, however, it is not common practice to include evolution in the medical curriculum.\textsuperscript{124} Many clinicians have never had any formal course in evolutionary biology or even questioned the evolutionary mechanisms behind proximate causes of disease. In 2009, the American Association of Medical Colleges and the Howard Hughes Medical Institute (AAMC-HHMI) proposed a set of scientific competencies for future physicians and undergraduate students who plan to attend medical school.\textsuperscript{125} Rather than requiring that universities teach specific courses, the committee recommends that certain competencies should be addressed in the separate areas of mathematics, scientific methods, physics, chemistry, biochemistry, cell biology, physiology, and homeostatic adaptations to external and internal changes.\textsuperscript{125} However, a new competency recommendation has emerged: evolutionary biology.\textsuperscript{126} The idea is that better education about evolutionary biology needs to begin before entry into medical school and continue to be integrated into
the medical curriculum, because evolutionary biology is a unifying principle that can be used to organize the basic sciences. Members of the committee also assert that this integration will allow students and physicians to think of our bodies as products of evolutionary processes, not as machines. For example, the proximate mechanisms behind obesity and type II diabetes make more sense when described in an evolutionary context, including the environment that shaped those mechanisms. Understanding that our bodies are the consequences of natural selection will allow students and physicians to have a more comprehensive view of the human body and why we are vulnerable to disease.
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