



# Evolutionary Approach to Medicine

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**ABSTRACT:** A new discipline in the medical field, called Darwinian (or evolutionary) Medicine, has arisen to study how natural selection could shape a machine as complex as the human body without eliminating its vulnerability to diseases. It asserts that systems and organs that form our bodies result from millions of years of evolutionary advances and are designed to survive in order to reproduce. According to this principle, Nature does not strive for complexity or perfection—it is blind and random. Using the scientific knowledge that has revolutionized biology, Darwinian Medicine seeks to provide an explanation for diseases based on the evolutionary process. This new discipline, in short, can undoubtedly help physicians in their medical practice, though further research is necessary to improve understanding of the range of its clinical application.

DARWINIAN MEDICINE is a new field of medical science whose most important aim is to seek evolutionary explanations for the vulnerability of humankind to diseases,<sup>1,2</sup> namely, to study medical problems in the light of the Theory of Evolution. In simple terms, this theory states that the variation of genetic material occurs randomly in species in every generation, through cellular DNA mutations, and that the survival or extinction of a given organism is a result of natural selection, according to its capacity to adapt and reproduce itself within its own environment. Thus, through natural selection, genes providing greater reproductive success to the organisms are “selected” and remain in the genome during subsequent generations. Conversely, genes that result in less viable offspring are gradually eliminated from the population.<sup>1,2</sup> However, according to Darwin, natural selection was not the only process driving evolution: variability is also increased by sexual selection, thought to account for characteristics such as the behavior, shape, and physiology of organisms before, during, and after mating. Through this process, while competing with a member of the same sex and species, an individual gains reproductive advantages over a member of the opposite sex.<sup>3</sup>

One of the greatest mysteries of medicine is the presence, in an excellently structured machine such as the human body, of apparent failures and palliative mechanisms that cause most diseases.<sup>4</sup> The evolutionary approach offered by Darwinian Medicine sums up this “mystery” in two issues: why did the natural selection process not uniformly eliminate the genes that render us susceptible to diseases, and why did it not select all genes that improve our capacity to resist damages and perform “repairs”?<sup>3</sup>

To solve this paradox, it is necessary to make a careful distinction between the “immediate” explanations and the “evolutionary” explanations of diseases. The immediate explanations approach the pathogenic mechanisms of diseases and the body’s responses to it. Evolutionary explanations, on the other hand, go back in time trying to show why human beings remain susceptible to some diseases and not to others.<sup>1,2</sup> However, the evolutionary and immediate explanations are not alternative ones; ie, both are necessary for the overall understanding of the disease process.<sup>1,2</sup>

Evolutionists have advanced several explanations for the maintenance of deleterious genes in the human genome: (1) many diseases appear mostly after the peak reproduction periods; (2) anomalous traits tend only to reduce, not eliminate, the number of progeny; (3) recessive traits may be hard for natural selection to eliminate if they only partially compromise adaptation; and (4) even if it is maladaptive to have the entire set of genes that produce a

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given illness, having some of them may be advantageous in certain environments.<sup>5</sup>

The rationale of Darwinian Medicine begins by establishing a causal relationship between previous information on health/disease and a hypothesis concerning evolutionary adaptation. Thus, the process follows a logical sequence that attempts to answer issues such as the following: Do the features studied in the human body participate in some adaptive mechanism? If these features appear functionally undesirable, how did natural selection allow them to continue for so many generations? Could they have been adaptive features in ancient periods of human development and currently cause disease?<sup>1,3</sup> One of the basic principles of Darwinian Medicine states that the regulation of some defense mechanisms of the human organism (ie, anxiety, fever, and cough) were shaped by natural selection for maximal reproductive success. This means that these defense mechanisms will arouse a response whenever its cost is less than the likelihood of harm multiplied by the protection. Thus, if the cost is low, defense will be expressed in a way that seems too frequent and too intense, although the system is functioning normally or near optimum. This has been called the “smoke detector principle,” because of the frequent but normal and necessary false alarms from those systems.<sup>1,2,4</sup>

Undoubtedly, the Darwinian Medicine theory is eminently testable,<sup>5</sup> despite the fact that it concerns themes belonging to a time distinct from ours. We have to remember that evolutionary biology is a historical science, as opposed to chemistry and physics. Instead of using laws and experiments, researchers construct a historical narrative, ie, an attempt to reconstruct the particular scenario that led to the events and processes they are trying to explain.<sup>6</sup> Moreover, these field investigators have been using several skills to solve this challenge, such as the observation of physiologic and behavioral similarities between modern human beings and the higher primates (whose genomes are homologous at about 98%) and the study of human communities, which today still live as our forefathers did.<sup>7</sup>

Evolutionary principles have been widely applied to several fields of medical knowledge. For this reason, we are obliged to choose basic topics of this new discipline to achieve a synthesis of its main concepts.

#### WHY FEVER?

Several recent studies have shown that fever and its direct consequences are adaptations of

natural selection specifically to fight infections,<sup>8,9</sup> both by increasing the phagocytic and bacterial activity of neutrophils and by optimizing the cytotoxic activity of lymphocytes.<sup>10</sup> According to Kluger et al,<sup>8</sup> current evidence indicates that fever is a primitive immunologic response, with a long phylogenetic history. Fish, for instance, when inoculated with bacterial endotoxins or gram-negative bacteria, instinctively raise their body temperature by swimming toward regions where water is warmer. When lizards are inoculated with pyrogens or bacteria, they expose themselves to the sun to increase their body temperature up to feverish levels by means of the irradiated heat. Moreover, fever inhibition in rabbits infected with type III pneumococci increases their death rate.<sup>9</sup> Finally, for his work with artificial fever production, Wagner-Jauregg won the 1927 Nobel Prize in Medicine and Physiology. He treated syphilitic patients by inoculating *Plasmodium* spp (responsible for malaria).<sup>9</sup>

In an early study with rhinovirus-infected volunteers, Stanley et al<sup>11</sup> reported that aspirin therapy was associated with a significant increase in virus shedding when compared with placebo. In a subsequent study, Mogabgab et al<sup>12</sup> found no differences in this parameter between placebo-treated and aspirin-treated individuals. In a more recent placebo-controlled study done by Doran et al,<sup>13</sup> 68 children infected by varicella alternatively received acetaminophen or placebo for 4 days. The outcome was surprising: children who had taken placebo recovered 1.1 day faster (ie, time to total crusting) than those who had taken acetaminophen ( $P < .05$ ) and even presented fewer clinical symptoms on the fourth day. The researchers' conclusion was that besides not having relieved varicella symptoms, acetaminophen extended the course of the disease. In another double-blind, controlled study done by Graham et al,<sup>14</sup> 56 volunteers were intentionally infected with type II rhinovirus, and variables such as antibody levels and clinical symptoms were monitored. It was observed that the use of aspirin and acetaminophen was associated with the suppression of the neutralizing humoral immune response ( $P < .05$ ) and that aspirin was associated with an increase of nasal symptoms such as nasal obstruction ( $P < .05$ ).

However, an evolutionary perspective offered by Darwinian Medicine calls attention to the costs and benefits of an adaptation such as fever. If there were no disadvantages in having a 38°C body temperature, the body would always remain at this temperature to prevent infection

from emerging.<sup>1,2</sup> Nevertheless, even this moderate fever has its costs: for each 1°C rise in body temperature, there is an increase of 13% in oxygen consumption, besides an increase in caloric needs and the induction of a temporary infertile state in men. Episodes of even higher fever may cause delirium and stupor and accelerate muscular catabolism.<sup>10</sup>

Antipyretics are frequently administered without a compelling medical reason.<sup>15</sup> In most febrile illnesses, there is no evidence that fever is detrimental or that antipyretic therapy offers any benefit.<sup>9</sup> Likely exceptions to this principle may include pregnant women, patients for whom a hypermetabolic state could be dangerous, children with a history of febrile seizures, and patients who cannot tolerate a rise in intracranial pressure.<sup>9,10,16,17</sup>

Keeping in mind that bringing fever down by using medication possibly postpones recovery, increases the probability of a secondary infection, deprives one of clues as to the need for further examination or for changes in the therapeutic approach, and may provoke widespread side effects, physicians should treat feverish patients only when the expected benefits outweigh the possible risks.<sup>1,2,9,10,16</sup>

#### IRON "WITHHOLDING" SYSTEM

Our organism has another defense mechanism, known as iron "withholding," which physicians often unintentionally try to frustrate.<sup>1,2</sup> Iron is essential for all pathogens, and to obtain it from low concentrations present in host plasma, microorganisms have developed sophisticated mechanisms<sup>18</sup> such as (1) erythrocyte lysis, hemoglobin digestion, and heme assimilation; (2) binding siderophilins with iron extraction at the cell plasma membrane; (3) obtainment of host intracellular iron; and (4) use of siderophores that remove iron from transferrin.<sup>19</sup>

Conversely, the human organism has conceived primitive defense systems to both avoid tissue damages due to iron exposure and prevent the access of pathogens to this essential ion.<sup>20</sup> Among these host defense mechanisms are (1) *constitutive mechanisms* such as iron-binding proteins (transferrin in blood, lymph, and cerebrospinal fluid; ferritin in host cells; and lactoferrin in secretions of lachrymal glands, and of the respiratory, gastrointestinal, and genital tracts); and (2) *processes induced at the time of infection*, such as suppression of the assimilation of about 80% of dietary iron (activated by IL-1, IL-6, and tumor necrosis factor),

neutrophil release of apolactoferrin to bind iron at septic sites, synthesis of nitric oxide by macrophages to disrupt the iron metabolism of pathogens, hepatic release of hemopexin and haptoglobin (to bind heme and hemoglobin, respectively), and many others.<sup>19</sup> All systems mentioned play a central role in the maintenance of host iron concentrations at relatively low levels, which is essential for bacteriostatic and bactericidal systems.<sup>18,21</sup> However, these antibacterial systems are abolished when iron becomes freely available,<sup>21</sup> as for instance when an infected patient (who presents low protective serum iron levels) receives parenteral or oral iron supplementation.<sup>1,2,22</sup> This results in faster bacterial growth and increased virulence.<sup>19,21,22</sup> An analog effect was reported in patients with end-stage renal disease: overtreatment with iron increases the preexisting risk for episodes of infection caused by dialysis, malnutrition, and other factors.<sup>22</sup>

Moreover, iron loading is thought to increase the risk for neoplasia, infection, cardiomyopathy, arthropathy, and several endocrine and perhaps neurodegenerative disorders. Thus, certain populations (such as patients with hemochromatosis, alcoholism, and asplenia) may benefit from screening tests for iron loading, and this can provide important information concerning therapeutics, prophylaxis, and diagnosis of iron-related illnesses.<sup>19</sup>

In an explanatory controlled study done by Murray et al,<sup>23</sup> the incidence of infection was compared among 137 Somali nomads who showed constitutive low serum iron levels. One group received placebo, and the other received a food supplement with iron. After 1 month, 50.7% of the individuals who had received the iron supplement had episodes of infection, as against 10.6% of those who had received placebo ( $P < .001$ ). Moreover, experiments with *Escherichia coli* showed that the lethal dose for guinea pigs on intraperitoneal injection was  $10^8$  bacteria. Titration of the effect of iron compounds showed that bacterial virulence increased 100,000-fold with  $Fe^{3+}$ , and 10,000-fold with hemoglobin,<sup>24</sup> and this implies that resistance of these animals to *E coli* had been virtually eliminated.<sup>21</sup>

Thus, the evolved mechanism that regulates iron plasma and tissue concentrations is another specific illustration of the principle that physicians should be careful when distinguishing defenses from other manifestations of infection and before concluding that a defensive response from the body is an undesirable adaptation

problem.<sup>1,2</sup> This attempt to strengthen natural resistance can help, for example, in the treatment of septic peritonitis (where donated plasma could provide unsaturated transferrin, which binds free iron, and haptoglobin, which binds free hemoglobin)<sup>25</sup> and in the development of new antibacterial drugs based on interference with iron metabolism of microorganisms.<sup>21</sup>

#### A DISEASE OF CIVILIZATION

The transition of animal life from the oceans toward the numerous niches on the surface of our planet (specifically the progression of amphibians from the aquatic environment to land 300 million years ago<sup>26</sup>) has involved many cellular “stresses.”<sup>27</sup> These stresses were a direct consequence of several ionic and osmotic patterns to which the cells of primitive organisms were submitted. Life in the ocean, which has a salt concentration (3.5% saline) about four times higher than our extracellular fluid (0.9% saline),<sup>26</sup> has involved osmoregulatory stresses different from those found in the development of life on earth. In the latter, there was the risk of dehydration and, in many areas of the planet, salt deficiency.<sup>27</sup>

Since their appearance 40,000 years ago, modern human beings (*Homo sapiens sapiens*) lived in this NaCl-poor environment,<sup>26,28</sup> consuming about 690 mg sodium/day.<sup>29</sup> Because of the development of agriculture 10,000 years ago, salt intake became even lower, as plants made up 90% of the diet.<sup>26,29</sup> For this reason, our forefathers developed a mainly renal regulatory mechanism for the conservation of extracellular fluid concentrations. This maintenance of ionic patterns in prehistoric times was achieved by high glomerular filtration rate (GFR) and by an almost full tubular reabsorption of NaCl considering the limited consumption of this salt, low extracellular volume, and/or changes in the blood pressure (BP).<sup>30</sup> In this way, the self-regulation of renal plasmatic flow and GFR was crucial to prevent an even greater variation in fluid and electrolyte intake from altering the *milieu interieur* stability.<sup>26</sup> Therefore, it could be suspected that the persistence of such an intricate control mechanism of BP in the human genome assumes that it has adaptive value.<sup>31</sup>

This is the context in which hypertension appears as one of the greatest public health problems in developed countries. It is defined as the chronic rise of BP above 140/90 mm Hg. It is a common asymptomatic clinical entity, and frequently leads to lethal complications if not treated properly. The etiology is unknown

in 90% to 95% of patients, which is why it is called “essential hypertension.”<sup>32</sup>

However, various studies (including observational epidemiologic studies, migration studies, animal experiments, and randomized controlled trials) showed the strong link between the daily intake of sodium and the prevalence and etiology of hypertension,<sup>33,34</sup> as well as the importance of sodium restriction in the treatment and prevention of hypertension,<sup>35</sup> though there is still some controversy on this subject.<sup>36,37</sup> In a recent observational epidemiologic study,<sup>38</sup> examination of salt intake and BP in 663 individuals showed that a 3 mm Hg increase in systolic and 1.8 mm Hg in diastolic BP ( $P < .01$  for both) was associated with a 100-mmol higher 24-hour urinary sodium. Two recently published trials deserve mention.<sup>39,40</sup> Cappuccio et al<sup>39</sup> conducted a double-blind trial in which 47 untreated elderly patients were randomly assigned to a usual NaCl intake (10 g/day) or modest NaCl reduction (5 g/day). The authors reported that a reduction in dietary sodium intake of 83 mmol/day was significantly associated with a reduction of 3.2 mm Hg in diastolic BP and 7.2 mm Hg in systolic BP. On the other hand, Whelton et al<sup>40</sup> conducted a randomized, controlled trial with 975 hypertensive patients (aged 60 to 80 years). Obese individuals were randomly assigned to either usual care (ie, no active intervention), weight loss, sodium reduction, or combined sodium reduction and weight loss groups, and those who were in the normal weight category were assigned to either a usual care or sodium reduction group. At 30 months, 38% of those in the sodium reduction group vs 24% of those in the control group ( $P < .001$ ) were free of an endpoint such as a BP-related clinical complication, BP >150/>90 mm Hg, or resumption of an anti-hypertensive drug.

Moreover, Denton et al<sup>41</sup> provided direct evidence in favor of a causal relationship between hypertension and high NaCl intake. They studied 26 chimpanzees that were fed a vegetarian diet with a very low sodium content for 1 year. After this period, salt was added in increasing amounts to the diet of 13 animals (5 g/day for 19 weeks, 10 g/day for 3 weeks, and then 15 g/day for 67 weeks). After the 19 weeks of the 5 g/day salt addition, mean systolic BP increased by 12 mm Hg ( $P < .05$ ). After the addition of 10 g/day salt for 3 weeks and of 15 g/day for 62 weeks, mean diastolic BP increased by 10 mm Hg ( $P < .01$ ), and mean systolic BP increased by 33 mm Hg ( $P < .001$ ). Twenty weeks after the end of the salt supplementation period, BP

returned to baseline values. In fact, migration studies showed that populations with a very low salt intake have no hypertension, yet if such people migrate to more industrialized societies (with high salt intakes), almost 30% of them will show a significant rise in BP.<sup>26,28,33,34</sup> Four recent meta-analyses of published trials<sup>42-45</sup> showed a significant relationship between BP and sodium intake in both normotensive persons and hypertensive patients. More impressive are the results of the "Dietary Approaches to Stop Hypertension—Sodium" (DASH-Sodium) study, in which investigators randomly assigned 412 subjects with and without hypertension to either the "DASH diet" (rich in low-fat products, fruits, and vegetables) or a control diet at three levels of NaCl intake (8 g/day, 6 g/day, and 4 g/day) similar to that of the average American, both for 90 days. Then, the researchers changed the sodium level every 30 days. When individuals with hypertension went from the high-NaCl to the low-NaCl control diet, their systolic BP fell 8.3 mm Hg and diastolic BP fell 4.4 mm Hg. This drop is comparable with that achieved by pharmacotherapy. In the nonhypertensive individuals taking the control diet, going from high salt to low salt intake reduced systolic BP by 5.6 mm Hg and diastolic BP by 2.8 mm Hg.<sup>46</sup> In the future, according to He and Whelton,<sup>33</sup> prospective epidemiologic studies should be conducted to examine the relationship between daily salt intake and risk of coronary artery disease, stroke, renal disease, and left ventricular hypertrophy.

From the evolutionary perspective previously offered, we may notice that natural selection over generations has molded the adaptation of our forefathers to the low NaCl content in their environment.<sup>28</sup> However, in modern society access to salt is almost unlimited, with a sodium consumption of about 4,000 mg or more per/day (equivalent to 10 g NaCl).<sup>29</sup> Taking into account the fact that in the last 10,000 years the change in our genetic material was of at most 0.005%,<sup>6</sup> our genes are almost identical to those of our forefathers. Nevertheless, as stated by Eaton et al,<sup>29</sup> our genetically determined physiology and biochemistry now face circumstances vastly different from those that were selected by evolution, and this difference between the human organism and its life environment could account for the current high prevalence of chronic degenerative diseases such as hypertension, obesity, and atherosclerosis.

From all this, it could be concluded that the possible deleterious effects of a high sodium

chloride diet are not unexpected and essential hypertension may be a consequence of renal maladaptation to excessive salt consumption, a feature of modern civilization.<sup>1,26,29,46</sup> Finally, an intervention to lower BP in the general population—based, for instance, on a modest reduction of dietary sodium intake—should result in a large reduction in hypertension prevalence, as well as a substantial decrease in cardiovascular and renal events.<sup>34,48</sup>

## CONCLUSION

Darwinian Medicine is a new and revolutionary discipline of medical thinking that has gradually brought new evidence to support the principle that the interaction between the human organism and its environment is absolutely essential to the understanding of health and disease. One of the most important aims of this incipient science is to apply evolutionary principles to daily medical practice. However, this undertaking has faced several obstacles, the most important of which is physicians' difficulty in accepting the essential role of man's evolutionary history in the present panorama of health and disease. Nevertheless, many prevalent clinical entities have been discussed in the light of the Theory of Evolution, and new fields of biomedical research have arisen daily. Among topics of unquestionable interest not discussed in this article are (1) hormone replacement therapy seen, in some situations, as antagonistic to the possible adaptive value of menopause; (2) the icterus of the newborn seen, in milder cases, as an adaptation mechanism and not as a disease; (3) human emotions implicated in the genesis of psychologic disturbances taken as possibly negative aspects of sophisticated adaptive mechanisms essential for human survival in the past; (4) the abuse of illicit substances, so common nowadays and no longer a cause for moral judgment, which is beginning to be analyzed through man's evolutionary history; (5) the host-parasite-environment relationship from the evolutionary viewpoint stimulating new therapeutic approaches to fight viral and bacterial infections; (6) allergy studied as the "price paid" by humankind to develop immediate hypersensitivity mediated by IgE (molded by natural selection in fighting helminthic parasitic infections); and (7) rigid dietary recommendations suggested by health care professionals confirmed by humankind's nutritional experience throughout evolution.<sup>49</sup>

Even though today this new discipline is not extensively applied in medical practice (because

of its newness), what becomes clear is that it offers medicine an additional perspective, based on the scientific knowledge of evolutionary biology—so long treated as uninteresting by physicians. Nevertheless, evolutionary thinking applied to medicine does not aim to stimulate an alternative to medical practice. On the contrary, it seeks to add a new dimension, useful and inclusive to the understanding of health and the disease process. This field of research offers new opportunities to understand the etiologic mechanisms of a number of clinical entities. As stated by Smith,<sup>50</sup> the ideas presented by evolutionary medicine stimulate and encourage our questioning of why and how. As observed by Nesse and Williams,<sup>1,2,4</sup> it teaches us that disease does not result from malevolent and random forces but from a historical process of natural selection.

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