SPECIAL ARTICLE

Medicine in the 21st Century: towards a Darwinian Medical Epistemology

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In this review we reflect upon the new science of Darwinian medicine. It is a tenet of modern biology that evolutionary theory as proposed by Charles Darwin and further refined via the new synthesis is the common thread that ties all of biological inquiry into a coherent whole. This review aims at making clear how evolution by natural selection is relevant to medicine. A set of pertinent examples linking *Homo sapiens sapiens'* present disease conditions to its evolution during the Late Pleistocene and Holocene epochs are discussed. The review concludes with observations as to the epistemological value of evolutionary theory as a heuristic tool for articulating a medical paradigm in accord with modern biology.

The Origin of Origin

July 1st, 1858: modern biology is born. The Linnaean Society of London sits quietly to listen to the reading of a combined paper on how natural selection underpins the variety and evolution of species. The authors were Charles Darwin and Alfred Russell Wallace (1). The paper and the meeting caused scarcely a stir (2). Was this muted event an extraordinary case of concurrent discovery? Hardly. Darwin alone went on to publish a transforming text: On the origin of species by means of natural selection, or the preservation of favoured races in the struggle for life. As the 2009 Darwinian anniversary is commemorated it is self evident that its legacy has been and is immense.

The Foundation for a Darwinian Medicine

Darwinian epistemology, as explained by Campbell (3), Popper (4) and Lorenz (5), needs be applied to medicine because *Homo sapiens sapiens* is subject to and is a product of evolution through natural selection. This results in the mosaic of interlocked adaptations that comprise the human phenotype upon which natural selection acts. Evolution with common descent implies a craggy, dynamic fitness landscape that has been and will continue to be navigated along unbroken pathways. The fitness landscape's possibilities exceed the sampling scope of natural selection: the ruggedness of the landscape constrains evolution to build off existing branches (6). Through universal common descent, life has evolved in this branching manner for four billion years (7). The root of the human phylogenetic tree lies in Africa. *H. habilis*, the first species of the genus *Homo*, arose about 2.4 to 1.4 million years ago (mya). *H. s. idaltu*, from Ethiopia, lived from about 160,000 years ago (Kya) and is the oldest known anatomically modern human. Overall, the weight of evidence from both genetic and paleobiological studies supports a recent common origin of all modern humans from a population originating in Africa (8).

Today *H. s. sapiens* is the only extant species of the genus *Homo* (9). Anatomically modern humans began their worldwide trek during the Late Pleistocene (10). Its numbers were originally small compared to the coexisting biota, and constrained by climatically induced reductions in population size followed by some level of recovery (genetic bottlenecks) (11).

The last of these occurred during the Late Pleistocene when our ancestors were squeezed through a bottleneck that brought the number of extant *H.s. sapiens* to about 10^5 individuals. Further along, ca. 73 Kya, a further reduction to around 10^4 occurred, seemingly an effect of the Toba supervolcano eruption, the largest explosive volcanic event of the late Quaternary (12), provoking a decadal climatological forcing (13). It lofted about 1015 g each of fine ash and sulfur gases to heights of 27-37 km, creating dense stratospheric dust and aerosol clouds leading to a six-year volcanic winter that decimated extant *H.s. sapiens* and numerous other species.

The bottleneck hypothesis is strengthened by corroborative findings in the Greenland ice core studies that support a six-year volcanic winter (14). The eruption greatly accelerated the glaciation already underway by inducing perennial snow cover, albedo and increased

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sea-ice extent at sensitive northern latitudes: the Würm glaciation event (15). It is estimated by mitochondrial DNA phylogeny studies that just before the Pleistocene bottleneck close to 40 additional evolutionarily successful lineages prospered in sub-Saharan Africa coeval with the migration of anatomically modern human out of Africa (16). The total population crossing the bottleneck amounted to at most several thousands (17). The population level reached was low enough for founder effects, genetic drift and local adaptations to produce rapid population differentiation. The number estimated for the residual population is of 1000-4300 individuals (18); the impact of this reduction led to a very constrained population bottleneck for *H.s. sapiens*: it was taken to the edge of extinction.

This event explains the markedly constrained genetic variability of the different human groups and the fact that genetic variability declines linearly as a function of distance from Africa: e.g., skull variability within individual populations declines with increasing distance from Africa (19). These Late Pleistocene paleoclimatic events affected not only *H.s. sapiens*, but also numerous animal and plant species: e.g., *Percichthys trucha* (20), European *Cyprinids* (21), *Crocidura suaveolens* group (Lesser white-toothed shrews) (22) and *Lilium longiflorum* and *L. formosanum* (*Liliaceae*) (23).

Dispersion, colonization, and incursions into novel environments characterize *H.s. sapiens'* evolutionary history. Such a process selects for rapid rates of reproduction and a generalized biology. Physiological viability across diverse ecosystems favors nimble phenotypic plasticity, thus protecting the genome from the violent selective pressures encountered as migrations progressed across unstable Late Pleistocene environments (24). A highly valued adaptation was the reduction of interbirth intervals and slow childhood growth (25). These allowed human females to provision more offspring simultaneously, increasing the reproduction rate in favorable conditions and thus favoring rapid recovery from population crashes or rapid population growth in new habitats. But reproduction entailed peril.

For the last 2 my prior to and after the Pleistocene bottleneck, humans lived as hunter-gatherers much the same way present ones, such as the! Kung and others socialize and live. Once *H. sapiens* left Africa, it encountered new ecosystems and pathogens, encounters that drove the evolution of the species (26). This process accelerated upon the domestication of animals (27).

Domestication is a reciprocal process causing reciprocal evolutionary adaptations: in plants and animals, modifications in biogeography, morphometry and pathology; in humans, transformations in demography, societal organization, health, and disease. Many infectious diseases common today originated with animal domestication (28). Measles and tuberculosis arose from *Bovidae* and influenza from the *Suidae* and *Anatidae* (29). The archaeological record of the Southern Levant provides an example of the possible role of animal domestication in the genesis and spread of zoonoses. More recently the emergence of a number of *Chiropteran* viruses has caused considerable alarm. SARS coronavirus, Australian bat lyssavirus, henipaviruses, Menangle virus, Ebola virus, and Marburg virus are also harbored by *Chiropterans* and probably are capable of infecting a variety of other species (30).

For 2 million years, until 10 Kya, the genus *Homo* lived as all hunter-gatherers: on current solar income (31). This frugal way of life, coupled to the need for very large ranges per individual, allowed for total numbers of probably less than 10 million persons globally, divided into small bands, each comprising from 50 to 100 individuals. For the hunter-gatherer lifestyle to be sustainable, access to large land areas is essential. It has been estimated that hunter-gatherers need approximately 20 km^2 in temperate zones and up to 1,500 km^2 of land per person in arid zones to sustain their lifestyle (32).

Furthermore, the space area required increases allometrically rather than isometrically with increasing population size magnifying range requirements (33). This spatial scaling relation is robust to differences in trophic foraging niches, ecosystems temperatures, energy availability, geographic location, and cultural phylogeny.

The hunter-gatherer lifestyle has been the predominant mode of social organization for members of the genus *Homo* for 2 million years, up to the advent of plant and animal domestication, making it *Homo's* most durable form of social organization (34). As agriculture became dominant, communities evolved that could support far more people. World population expanded to about 300 million by 1 CE and continued to grow at a moderate pace for close to two millennia. With the 18th century Industrial Revolution, living standards changed and deaths attributable to widespread famines and epidemics diminished. In 2000 CE, the world had 6.1 billion human inhabitants.

Driven by numbers, the species of *Homo* began to live in close quarters with each other, as well as with domestic animals. Numbers also required *Homo* to settle in ecosystems hitherto unknown to the species. This has multiplied the interactions between the total environment and *H.s. sapiens*, which has caused habitat degradation for numerous species, causing humans and the feral biota to come into previously nonexistent interactions and thus transforming disease dynamics. The so-called

emerging diseases are but the latest manifestations of this phenomenon (35).

Our most fundamental defense systems have been sculpted by evolution to cope with these new experiences. Thus, genetic variation within the highly polymorphic human leukocyte antigen class I region is an adaptive response to pathogen polymorphism, generating the potential for cytotoxic broad-based T lymphocyte-mediated defenses (36). But T-lymphocytes act as a selective force driving pathogen mutations that allow them to escape recognition (37).

In addition, variants of pathogens that are ever more aggressive are being generated via the promiscuous use of pharmaceuticals. Nevertheless, parasitism is a natural phenomenon. Indeed, all metazoans are a microecosystem and harbor a wide array of species comprising their normal flora. One need go no further than the most ancient and primitive of all metazoans, *Porifera*, which diverged from the ancestors of other metazoans 1.3 billion years ago (38). During the Paleozoic era *Poriferans* accounted for much of the benthic biomass (39). Today, they remain important members of benthic ecosystems, occupying as much as 80% of available surfaces in some areas (40). Such long-lived evolutionary and ecological success is due to their intimate association with highly diverse microbial symbionts: an evolutionary accomplishment extant in all multicellular aggregates.

Over 90 trillion microorganisms and some parasite species have accompanied *H.s. sapiens* since the species inhabited the African landscape (41). Animal domestication brought on new pathologic challenges. With the advent of agriculture and of life lived in close proximity to domesticated animals, bacterial as well as helminth parasitism, caused by such as *Enterobius vermicularis, Trichuris trichiura, Ascaris lumbricoides, Trichostrongylus sp., Strongyloides sp., taeniid* and *hymenolepidid cestodes*, became prevalent (42). Coprolithic research has shown that prehistoric hunter-gatherers were burdened by far fewer helminth parasites than settled agriculturalists (43). The adaptations over time of both humans and pathogens were sculpted by natural selection.

The Hunter-Gatherer Phenotype in the Present World

Ninety-nine percent of genus *Homo's* history was spent as hunter-gatherers. Because of the social nature of humanity, we are naturally selected, not for the extant set of problems, but for another set of problems rooted in the Pleistocene (44). Of the many phenotypic traits that define our species--notably the physically and metabolically enormous brain, advanced cognitive abilities, complex vocal organs, bipedalism and opposable thumbs--most (if not all) are the product of strong positive selection.

Many other aspects of human biology (physical development, reproductive strategies, host-pathogen interactions, alimentary adaptation), have also been the substrate of varying levels of positive selection. The evolution of early hominids required adaptation to unstable environments with their attendant cycles of alimentary scarcity and abundance (45). To cope, natural selection has favored thrifty genotypes and phenotypes (46). One of these adaptations was the capacity to store fat. However, it becomes a maladaptation when exposed to modern lifestyles because the present environment is more stable, as is the dietary energy fund. This has occurred because cultural evolution has modified our environment to such a point as to render some of our hunter-gatherer adaptations a liability. The rise in incidence of diseases such as metabolic syndrome (47), type II diabetes (48), hypertension in carriers of the salt-conserving genotypes (49) contribute powerfully to the overall rise of cardiovascular diseases and other chronic inflammatory diseases such as frailty (50).

Via antagonistic pleitropy these genotypes favor the emergence of late-onset disease while paying a meager evolutionary cost (51). Thus there is no selection force leading to negative selection of such genotypes, as exemplified by the 70% incidence of type II diabetes in Nauru Islanders (52) and Pima Indians (53). The median age for the onset of diabetes has been gradually decreasing in these populations, and as the age of onset overlaps reproductive age, detectable natural selection against the predisposing genotypes, even within recent decades, has been noticed. The lower frequency of type II diabetes in Europeans contrasted to non-Europeans matched for diet and lifestyle suggests that natural selection has already reduced European frequencies of those genotypes in previous centuries, as the western lifestyle was developing in Europe.

Lactase persistence is an important example of *H.s. sapiens'* evolution and of the impact of culture on evolution. *Ungulate* domestication was already established in the Near East by 10,000 Kya (54). Dairying appeared in Europe around 7900-7500 B.P. (55), coeval with cereal agriculture and animal husbandry. Lactose persistence gradually emerged as dairying spread (56). European cattle herders and milk consumers, notably Germans and Dutch, have evolved lactase persistence (with SNP C/T-13910 serving as marker); African pastoralists have also developed this adaptation (57).

Late onset diseases are the result of the collision of the hunter-gatherer phenotype evolved for the Pleistocene with the Holocene environment. Marked increments in Mendelian diseases (such as sickle cell anemia and glucose-6-phosphate dehydrogenase [(G6PD) deficiency]

and late-onset diseases such as hypertension, diabetes, obesity, asthma, and osteoporosis) are becoming more frequent with the accelerated westernization of the world's two most populous countries, China and India (58). Indeed, China has seen the incidence of type II diabetes and obesity increase several fold. In regions of mainland China where westernization has been more aggressively pursued type II diabetes has increased by 17% (59).

Similar diet-related disease epidemics, not just of diabetes, but of hypertension and other conditions, are underway among Africans and Australian Aborigines (60). Bone loss is another antagonistically pleiotropic process, because of age-associated stress accumulation and its negative impact on bone turnover, gonadal failure causing an increase in inflammatory cytokines, and cellular bone marrow changes leading to bone loss. Elongation of lifespan due to modern lifestyles is exposing the biological price of expanded life spans. *H.s. sapiens*, by lengthening its lifespan, has marched straight into an evolutionary wilderness for natural selection is weakly operant, if at all, during the post-reproductive period.

Compared to other primates, birth in the human primate is particularly difficult, a fact poetically highlighted in past myths (61). Bipedalism has evolved over the past 6 or 7 million years, and has resulted in a small pelvis, adapted to the upright posture. The fetal head's increasing intrauterine size makes childbirth perilous. A pelvic architecture that leads to obstructed labor is the evolutionary price paid for evolving an upright, bipedal posture and locomotion. This and progressively increasing brain size (encephalization) in hominids led to the present human obstetrical dilemma: larger offspring with larger brains in the presence of a narrow pelvis that favors bipedalism. Natural selection has yet to solve this problem; cultural evolution has: the Cesarean section. In spite of the conundrum, *H.s. sapiens'* brain is actively evolving. Two genes, Microcephalin and ASPM regulating brain size emerged in recent human history and spread quickly through the population (62).

Some 140 million persons live permanently at high altitudes (>2500 m) in North, Central and South America, East Africa, and Asia. Recent adaptations have emerged amidst *H.s. sapiens* living at high-altitudes. High altitude reduces infant birth weight as a result of intrauterine growth restriction and is associated with increased neonatal mortality. However, a novel adaptation has recently been identified (63). High-altitude native resident Tibetan females carrying genotypes for high hemoglobin oxygen saturation exhibit higher Darwinian fitness than females with low oxygen saturation genotypes. Offspring mortality for those with the genotypes for high hemoglobin oxygen saturation drops several-fold (0.48 deaths for high oxygen saturation offspring genotype compared with 2.53 deaths for low oxygen phenotype offsprings). These findings suggest that high-altitude hypoxia is acting as an agent of natural selection. This adaptation is different from the ones found amongst the residents of the Bolivian Altiplano or the Ethiopian highlands (64). Thus, Tibetans have a new inferred indicator of ongoing natural selection whereas the other two populations have not evidenced any novel adaptations (65).

Human evolution is an ongoing factual process. There is evidence of recent selection on approximately 1,800 genes, or 7 percent of all human genes (66). As can be seen from the above discussion, there are multiple traits that have played out over time that undergird a host of presently extant diseases (67). The conceptual grasp of disease is facilitated and made robust when the evolutionary history of a disease-favoring trait is known. One such impact heavily emphasized above is the impact of diet on the inappropriate expression of what were adaptive traits in *H.s. sapiens'* early development. The concept of antagonistic pleiotropy (68) goes a significant way into elucidating the evolutionary root cause of many present disease conditions. Genes that exhibit antagonistic pleiotropy increase the odds of successful reproduction early in life, but have deleterious effects postreproductively. Antagonistic pleiotropy is found not only in humans, but in widely differing species such as hermaphroditic snails *Physa acuta* (69), platyfish *Xiphophorus maculatus* (70), song sparrows *Melospiza melodia* (71), wild red deer *Cervus elaphus* (72) and the common guillemot seabirds *Uria aalge* (73). Understanding the role of this phenomenon in nature will deepen and broaden our understanding of epidemic late-onset diseases. It is compelling that we take into very serious consideration *H.s. sapiens* evolutionary history if we are to design strategies for undercutting the ravages of late onset diseases.

A quarter of a century has elapsed during which the role of evolutionary theory in medicine has been, albeit hesitatingly, ever more clearly delineated (74). Gradually the discipline we now term Darwinian Medicine is emerging as a valid and valuable concept. This approach to medicine is a means of strengthening our current understanding of the biomedical panorama (75). As evolution enriches our perception of medical phenomena, medicine reciprocally enriches our comprehension of evolutionary principles: a phase change from *what* questions to *why* questions (76). From the Pleistocene to the present, our evolutionary history has been inextricably linked to the vagaries of diseases as they emerged and faded. It is appropriate, therefore, that we practice and advance medicine on the light of Darwinian evolution. As Theodosius Dobzhansky sagely stated: "Nothing in biology makes sense except in the light of evolution."

Darwinian evolution, with its emphasis on descent with modification, provides the heuristics for understanding the evolutionarily selected multifactorial mechanisms of reproductive dilemmas as well as chemical carcinogenesis, atherogenesis and other late onset diseases, thus facilitating the identification of populations differentially at risk as well as guiding the proper prevention, early detection and therapeutic strategies: essentially, the scientific understanding of the role of disease in human biology. Our present definitions of disease and their etiology, treatments, etc., center on the here and now, bereft of reference to the evolutionary past and the milieu within which diseases unfolded. We are just beginning to realize that though the *H.s sapiens* species is remarkably genetically homogeneous there is sufficient variability to explain the profound differences in risk, incidence and outcome of major diseases. When the out-of-Africa migrations of anatomically modern humans are taken into consideration, a window is opened that points towards the emergence and nature of such variations and their attendant diseases.

One example is the secular adaptation of xenobiotic detoxification systems to shifting ecosystems beginning with *Homo erectus* during the Early Pleistocene and continuing with the succeeding members of the genus during the Middle Pleistocene and the eventual migration of anatomically modern humans out of Africa in the Late Pleistocene up to the Eocene. Dependent as they were upon foraging, they came in constant contact with numerous species of plants bearing chemicals toxic to them. We are the heirs of the advantageous adaptations that were essential to survival by deriving nutrients from such vegetable foodstuffs as well as the maladaptive ones, a fact leading us to the present situation in which the United States incurs a yearly cost of about $100 billion for the 100,000 deaths and 7% of all hospital admissions caused by adverse drug reactions (ADRs) caused by undesired P450 metabolic activity.

The cytochrome P450 family of enzymes, present in all living organisms, is critically involved in the metabolism of drugs and other xenobiotics and many of the observed deaths and ADRs. It is encoded in *H.s. sapiens* genome by 57 different active genes (77). Understanding the heterogeneity of the ubiquitous P450 family is crucial to solving this problem. For example, it has been shown that the aryl hydrocarbon receptor *(Ah)*, a ligand-dependent transcriptional regulator of the expression of the cytochrome P450 family, shows significant interspecies and geographical variability. Polychlorinated biphenyls (PCBs) are global environmental contaminants that bind the *Ah* receptor and induce cytochrome P450s. Ethnic variations amongst *H.s. sapiens* in specific mutations at codon 554 of the *Ah* gene affecting xenobiotic binding has been noted between Japanese, Ivory Coast African, Caribbean-African, Canadian, Chinese, North American Indian, French Canadian, Canadian Inuit and German Caucasian ethnic groups. This is of signal importance since this heterogeneity underlies their varying responses to pharmaceuticals and environmental or occupational chemicals. Understanding the operating mechanisms subtended by the heterogeneity will bring about the rational development of new risk assessment tools, preventive measures, diagnostic strategies, and drug design. Similarly, knowing the considerable variability in susceptibility to cardiovascular disease (e.g., low risk among the Inuit, despite a fat-rich diet, and among Italians, carriers of apolipoprotein AI gene, versus high risk among populations such as US Caucasians and Asian-Americans) will have an analogous impact for type II diabetes, degenerative dementias, metabolic syndrome, reproductive diseases, frailty, senility, and other such conditions. Furthermore, interspecies variability in P450 makes difficult and uncertain the extrapolation of results of drug tests in other species to *H.s. sapiens*, hampering the evaluation of new therapeutic agents.

Polymorphic alleles carrying multiple P450 family CYP2D6 active gene copies have been identified. These particular polymorphisms were caused by positive selection due to development of alkaloid resistance in Northeast Africa about 10,000-5000 BC, a period that coincided with the onset of agriculture. The knowledge about the CYP genes' geographic distribution due to migrations and their polymorphisms is of fundamental importance for effective drug therapy and for drug development as well as for understanding metabolic activation of carcinogens and other xenobiotics. P450 2C enzymes hydroxylate about 16% of drugs that are in current clinical use and participate in the metabolism of several clinically important substrate drugs. Frequency variation between Eurasian Tuvinians, Buryats, Altaians, Yakuts and Russians genotyped for the P450 enzyme family alleles CYP2C9*2, CYP2C9*3, CYP2C19*2, CYP2C19*3, CYP3A5*3 and CYP3A5*6 showed statistically significant interethnic differences marked enough to be relevant to drug design and related therapeutic efforts (78). Similarly, allele distribution at the CYP2C9*2 and CYP2C9*3 alleles in Israeli Ashkenazi, Yemenite, Moroccan, and Libyan Jews was contrasted to their distribution in an ethnic Japanese population. The studied alleles were found to be very rare among the Japanese. Allele distribution provides a more accurate guide than ethnicity to account for the observed variability in drug response, metabolism, adverse effects and drug interactions.

Prudence dictates that it is high time medicine broadened its scope beyond an evidence-based epistemology. The evidence-based methodologies are focused primarily on immediate problem-solving and proximate causation. Medicine must embrace the evolutionary paradigm that welcomes ultimate explanations as espoused in evolution into its epistemology. Through this door will enter into medicine the concepts of systems biology, dynamical systems theory, complex systems, complex networks, and chaos theory, to name some up-and-coming analytical methodologies that should pry medicine out of its linear thinking (79). Because *H.s. sapiens* is the product of an evolutionary process, we cannot hope to have a deep understanding of the major diseases of our age if we ignore our evolutionary past. In the depths of our minds as in our genes, we are all African hunter-gatherers.

Resumen

Este artículo recoge una reflexión en torno a la nueva ciencia de Medicina Darwiniana. La biología contemporánea plantea como el ente unificador de las diversas ramas de la biología, incluyendo la medicina, la teoría evolutiva propuesta por Charles Darwin y su ampliación vía la nueva síntesis. En este escrito pretendemos esclarecer la relevancia para la medicina de evolución vía selección natural. Se analiza un conjunto de ejemplos concatenando el estado actual de salud de Homo sapiens sapiens con la evolución de la especie durante las épocas del Pleistoceno y el Holoceno. El artículo concluye con una reflexión en torno a la valía de una epistemología evolutiva como herramienta heurística para plantearnos un paradigma medico armónico con la biología moderna.

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