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Article

Evolutionary Medicine and Future of Humanity: Will Evolution Have the Final Word?

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Abstract: Evolutionary medicine in its classical form assumes that since cultural evolution is faster than biological evolution, ailments of modern people are a result of mismatch between adaptations to the past environments and current situations. A core principle is that we, humans, having evolved for millions of years in a specific natural environment (environment of evolutionary adaptation EEA) are biologically adapted to this past environment and the ancient lifestyle. This adaptation to the past produces major mismatch of our bodies with the present, highly anthropic and thus "artificial" living conditions. This article provides two areas of possible future evolution, diet and physical activity levels which have been dramatically altered in industrialised societies. Consequently, micro-evolution is an on-going process.

Keywords: Darwinian evolution; mismatch; Lamarckian selection; diet; sedentism; physical activity levels

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Introduction

Evolutionary medicine uses knowledge of evolution of mammals and of hominins to explain diseases and ailments of modern people; it also uses principles of evolution to explain changing responses of pathogenic microorganisms to treatments [1–5]. Its core principle is that we, humans, having evolved for millions of years in specific natural environments (environment of evolutionary adaptation EEA) are biologically adapted to this past environment and the ancient lifestyle, while fast cultural evolution grossly changed our environments and lifestyles in recent years. The concept of EEA is based on the consideration that until the last several thousand years, humans did not produce food, but obtained it by gathering and hunting in natural environments. This had numerous implications for human lifestyle—nomadism, low population density, good natural diet, stimulating exercise. Details of EEA varied depending on geographical location and climate—coastal environments were different from semi-deserts, life in the vicinity of advancing glaciers was different from that in the tropics. Some elements of the supposed EEA lifestyles can be gleaned from early modern descriptions of present-day hunters-gatherers. Although these descriptions concerned peoples who, for various reasons, were relegated to marginal environments inappropriate for agriculture and animal husbandry, we can see that the supposed EEA lifestyle was not especially physically demanding though daily physical activity was required. Supposed human biological adaptation to the past produces major mismatch of our bodies with the present, highly anthropic and thus "artificial" living conditions. Inasmuch as some of our biological characteristics may not be best served by present environments, this approach assumes that biological evolution is slow, and that it happens gradually over thousands of generations. In this way, evolutionary medicine can only indicate one solution for the future of humanity: manipulate technological, social and cultural changes of the recent years to restore our ancestral ways of life, or face increasing threats to health.

While a great deal of research in evolutionary medicine discusses the mismatch between ancestral and current environments and their consequences for health and illness, this paper will focus on future human evolution. The emphasis on categorisation in science makes it difficult to incorporate in our thinking the on-going evolution of human beings. Current approaches to evolutionary medicine started to consider ongoing biological changes in recent human generations—the microevolution—as an important factor shaping our health [5]. Natural selection is still operating at different levels on extant humans [6–9]. This should not be ignored. Unprecedented human population size in the 21st century has increased opportunities for sexual selection and mutation. Moreover, novel human environments may allow for new directions in micro-evolution. While the extent of possible micro-evolution is beyond the scope of this paper, we provide an overview of various areas of future concern: genetic load, diet and sedentism.

Bio-Cultural Evolution

Evolutionary theory is based on the premise that biological reality is highly variable. This variability concerns individuals and extends through time. Life is a system of dynamic complex interactions of a multitude of variable organisms with their diversified environment. In this view, the recent human history re-shaped our biological makeup and this makeup is presently undergoing further changes in response to quickly altering living conditions. We are a part of a dynamic and continuously evolving system. This system includes technologies, social organisation and knowledge that are produced and stored extrasomatically, but serves to maintain human organic life and supplement its biological substance. Hence, human evolution is a bio-cultural phenomenon rather than just a biological one. Current evolutionary medicine takes this into account [5].

The entire human system is still subject to interactions with the rest of the world that imposes constraints and produces challenges, but the responses of the human system are not entirely predictable by the rules of Darwinian evolution. In the Darwinian view, information, upon which, functioning of biological systems relies, is coded in the genes, passed through time from generation to generation. Its modifications appear randomly, by means of errors in the chemical structure of the DNA, and are then discarded or incorporated into the endowment of new generations by means of either natural selection that produces sensible adaptations, or by random vagaries of gene transmission depending on the size of gene pools and on mating systems. Humans, due to their cognitive abilities [10] and physical ability to manipulate external elements of their environments, code a large portion of the information relevant to their survival in carriers that are not integral parts of their bodies. This extrasomatic mode of the transmission of information is not constrained by the rules of biological reproduction and by chemical processes of genetic and epigenetic coding. It is partly subject to phenomena similar to those of Darwinian evolution, but it is not identical with it [11,12].

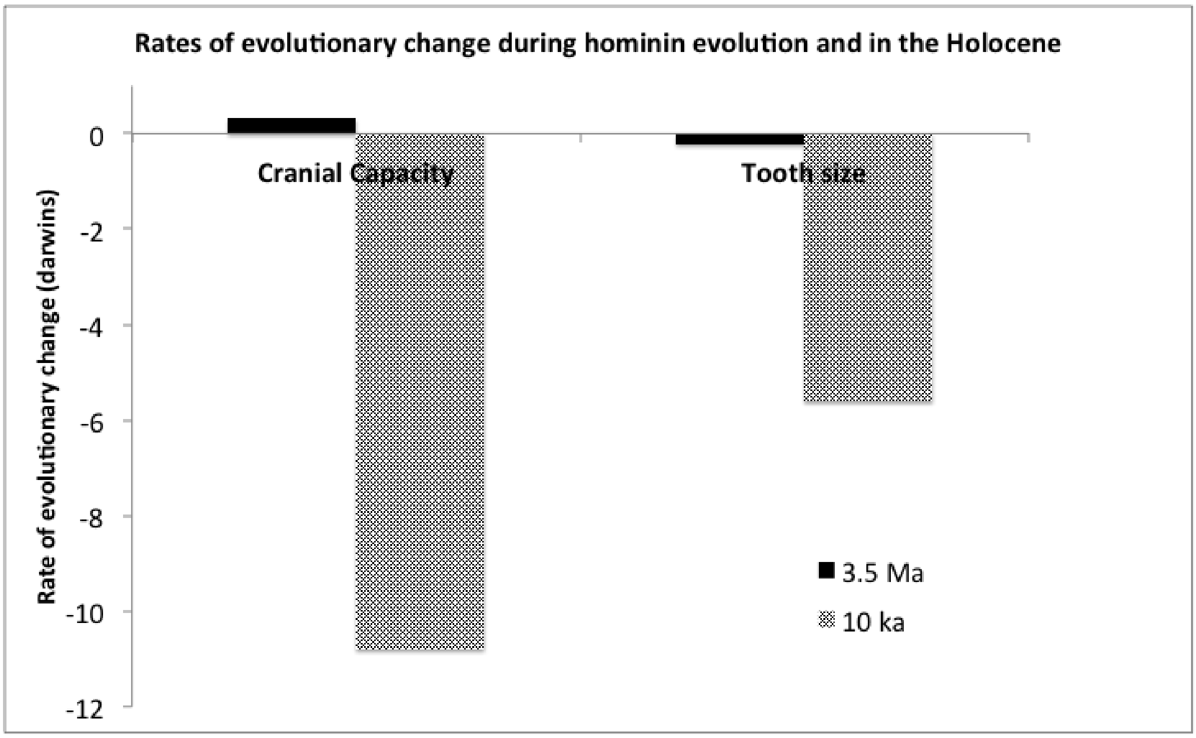
Extrasomatic mode of information transmission has a potential to be more effective as a mechanism of adaptation. This is due to a multitude of coding mechanisms (construction of infrastructure—shelters, dwellings, roads *etc.*, modification of plants and animals through domestication, art, writing, electronic storage), to the ability to transmit information laterally within the same generation without the need for biological reproduction, and targeted, non-random generation of new information based on focused collection of data and their logical processing in the context of previous knowledge. Evolution based on this extrasomatic transmission of biologically relevant information can be shown to be more adaptively efficient in digital simulations [13]. Results of actions based on these more adaptively efficient evolutionary phenomena are transforming environments, which human bodies encounter during their lives. Our bodies are also subject to direct modifications resulting from the technologically constructed environments.

Bodies of modern humans are a result of millennia of bio-cultural evolution. *Homo* is no longer a mammal adapted to the natural environment, but rather an animal adapted to the environment modified by technology and social organisation—to culture *sensu lato*. Changes of human morphological characteristics, such as the tooth size, or brain size, in the last few thousand years were much faster than those occurring during the Pleistocene (Figure 1). While the total occlusal surface area of teeth continued in the last few thousand years its general evolutionary decline, albeit at a faster rate, brain size change was the reverse of the previous trend. In the 3 million years of hominin evolution, cranial capacity increased in size from about 450 mL to about 1,450 mL, but in the last seven thousand years, it decreased from that value to 1,350 mL—a fast negative change [7,14].

The process of post-Pleistocene human adaptation to conditions resulting from food production and sedentary lifestyle may be, though inadequately, described as self-domestication [6]. Unlike domestication of animals, which are selected for specific, consciously defined purposes, human bio-cultural adaptation has been a natural process involving all aspects of our lives. Everything that increased Darwinian fitness of human populations was incorporated into the repertoire of our biological and cultural traits.

Darwinian fitness is measured by the energetic efficiency of reproduction [15], and this criterion applies to all aspects of human life. Anything that improves ability to reproduce members of human populations will be, in the long run, perpetuated at the expense of those characteristics that limit survivorship and reproduction.

Figure 1. Rates of evolutionary change of cranial size and tooth size in the hominin evolution (the last 3.5 million years) and in the Holocene (the last 10 thousand years) [7]. Units are darwins: d = (lnX1 − lnX2)/t where X1 initial state of a character, X2 final state of a character, t—time. Note that rates in hominin evolution are just fractions of one darwin, while rates in the last 10 ka are several darwins. Rate of cranial capacity change in hominin evolution is positive, in the Holocene—negative. Tooth size rates for both periods are negative, they only differ in size.



As a criterion, Darwinian fitness applies only to the entire cycle of population reproduction, from conception to death, but not to its separate elements (*e.g.*, just to fertility). Populations with lower fertility, but also with lower mortality, may have better net reproductive rates and thus, be ultimately more successful than those who simply have high fertility. The recent need for birth control to limit natural increase of some populations seems to be an exception to the rule of increased efficiency of reproduction of populations. Alas, it is not. Rapid numerical increase of populations lacking ability to supply energy necessary to continue life is counter-adaptive. The energy invested by the mother's body into foetal growth and then into feeding and caring for a child is wasted when the child dies after several months or several years of its life. This energy could have been invested into improved length of life of others or into production of useful items.

For the vast majority of human evolutionary history, reproductive success of individual genomes was low. Reproductive success can be measured by the Biological State Index [16,17], a probability that a newborn individual will be able to participate fully in the reproduction of the next generation. Values of the Biological State Index (I_{bs}) indicate that from the Middle Palaeolithic until the Middle

Ages, mortality and fertility combined to give an average newborn only about 30% chance of passing its genes to the next generation [16,17]. Thus, the opportunity for natural selection depending on variance of reproductive success [18] was large. A simple measure of this opportunity is a ratio of the number of individuals who will not be able to pass their genes to new generations to those individuals who are able to participate in reproduction. This ratio can be calculated as one minus value of the Biological State Index divided by the Biological State Index: $(1-I_{bs})/I_{bs.}$

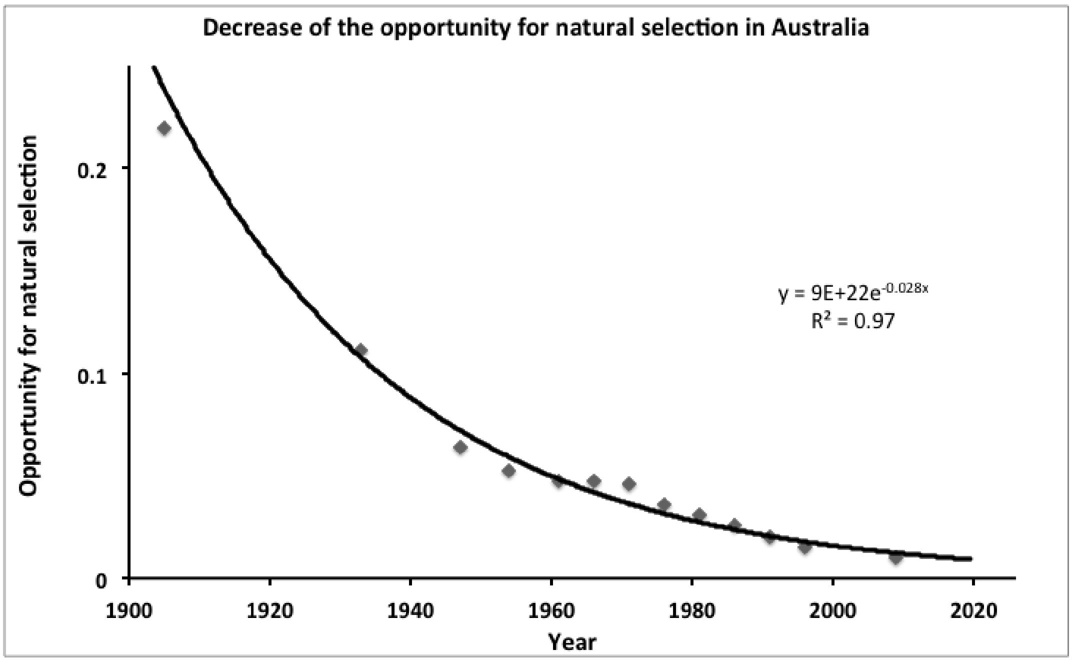
In the past, with only about 1/3 of individuals being able to pass on their genes, this ratio was approximately 2.0 (0.66/0.33). This large opportunity for natural selection was mostly due to differential mortality that allowed only ~50% of newborns to reach the age 15 years and continued to eliminate adults during their reproductive life span [17,19–23]. The situation changed only when industrialisation caused the demographic transition in the later 19th century [22]. Since that time, premature mortality declined significantly to produce values of the Biological State Index approaching 99% in developed countries by the end of 20th century [23].

This drastic decline in the opportunity for natural selection in the 20th century caused by the decline in premature mortality, coupled with widespread birth control—both negative and positive in the form of assisted reproduction—produced for the first time in human history virtual lack of the operation of natural selection on biological traits of humans. There still remains an opportunity for gametic selection and selection during intrauterine life, though with improving care during pregnancy, even this opportunity becomes limited. Therefore, deleterious mutations, previously eliminated by natural selection, will increasingly accumulate in the human gene pool creating a "genetic load" [24]. Considering that greatly increased global human population creates more chances for occurrence of mutations, we are faced in the near future with a spread of a significant number of new genes that, according to the Probable Mutation Effect [25], will be deleterious in their majority [26]. The index of the opportunity for selection became 0.01/0.99; that is about 0.01 (Figure 2).

This prospect, however, does not need to endanger human life because our knowledge and technologies may be able to compensate innate faults of future organisms in a way similar to what happens now—prosthetics, corrective surgery, pharmacological adjustment of faulty metabolic and immunological processes. As long as we will be able to produce new relevant knowledge, design appropriate chemicals and devices and use them efficiently, human life will not be in danger, though its biological form will change in response to new genetic and epigenetic processes. This, of course, assumes that no major natural or human-made disasters will occur. Such catastrophes, however, cannot be predicted with regularity.

Abilities to produce new knowledge and implement its use economically are the major challenges to the future human evolution. These, however, belong in the realm of social sciences. Complex social and technological processes will still need to be informed by the quality of individual human lives and by demographic dynamics, but these are just a few of many determinants of cultural development.

Figure 2. Decline of the opportunity for natural selection in Australia during the last 100 years. The opportunity is measured as a ratio of individuals unable to pass on their genes to the next generation to those able to participate in reproduction of new generations. Based on data from [23] and supplemented by new information [27].



Present day Mismatches and Lamarckian Selection

There has been considerable theoretical attention focussing on the role of mismatch in evolutionary medicine. Evolutionary mismatch refers to discordance between present day humans and the environment. Thus, this theory proposes that human genes have not had sufficient time to adapt to modern lifestyles [2,4,5]. The notion that modern human bodies still bear the hallmarks of adaptation to the EEA (environment of evolutionary adaptation) is current, even as evolutionary medicine recognises microevolutionary changes in some modern human biological characteristics. Also, implied in the mismatch hypothesis is that alleles that may have been adaptive in the past are maladaptive in novel environments [28]. There is little doubt that modern lifestyles in relation to dietary regimes and levels of physical exertion have dramatically changed from the Palaeolithic period. This discordance has probably exacerbated many present 'diseases of civilisation'. Moreover, extant *Homo* has been exposed to a tremendous amount of environmental pollutants and has had its sleep patterns changed due to the advent of electrical lighting at the turn of the 20th century, with subsequent disturbance to circadian cycles [29].

Additional to prevailing ideas of the mismatch hypothesis are arguments highlighting that ancestral humans may have been genetically protected against chronic degenerative diseases afflicting industrial societies [29–31]. For example, recent epigenetic research on human populations notes that prolonged exposure to industrial environments may become expressed as unfavourable phenotypes which occur *in vitro*. Factors influencing embryological development may also include chronic maternal psychological distress [32] and lifestyle choices of fathers. In the latter, it has been shown in an animal model that a father exposed to a high fat diet (HFD) may negatively influence metabolic programming of offspring ([33], p. 963). In humans, obesity can affect sperm morphology, motility and increase DNA damage, induced by HFD exposure [34].

The recent concern of epigenetic factors in producing vulnerable phenotypes indicates a possible re-direction of evolutionary medicine. In short, epigenetics has re-introduced Lamarckian inheritance as an invaluable adjunct to Darwinian Theory. Epidemiological studies reveal that fathers exposed before mating to various toxins, drugs (*i.e.*, endocrine disruptors) may cause deleterious behavioural development in their future children [35]. Studies also demonstrate that substance abuse such as paternal smoking and alcoholism may cause post natal weight changes, hyperactivity and reduced cognitive functioning [35–37]. What these, and many other studies indicate, is Lamarckian inheritance in which environmental factors influencing parents may be passed on to their progeny via germline elements [38–40]. To make matters more concerning, lifestyle factors and environmental exposures of grandparents may also inform metabolic disorders and longevity in their grandchildren [41,42].

On this note, Gregory Bateson suggested that a sub-system is affected by and affects other sub-systems [43]. Bateson's point was that organisms and ecosystems should be viewed in terms of relationality, where each unit is inter-connected to other units. A poignant example of this is how an organism's deleterious environmental exposure may have unforeseen and long term 'spill on' effects to an entire eco-system. In Darwinian terms, the current genetic load of humanity, albeit a by-product of improved medical practice and informed by moral systems, may have unexpected consequences for future humans.

Diet and Sedentism: Will Evolution Leave Humans to Their Own Fate?

Current dietary regimes and chronic sedentism in industrial societies have been extensively researched from an evolutionary point of view over the last twenty years. Modern diets have been attributed as a co-factor for increasing "diseases of civilisation" (e.g., cardio-vascular disease, stroke, type-2 diabetes, hypertension, depressive disorders, cancer). The World Health Organization predicts there will be 2.3 billion overweight adults in the world by 2015 and more than 700 million of them will be obese [44]. This number will continue to rise, causing massive health burdens on societies, especially poorer nations which cannot afford to provide adequate medical care to its citizens. Evolutionary medicine has highlighted that human nutritional needs evolved in environments which were radically different from contemporary dietary regimes [4,45–47]. Indeed, contemporary diets found in industrial societies are higher in simple sugars, sodium and fats, but lower in fibre and complex carbohydrates [48]. Incipient bio-markers such as increasing adiposity and insulin resistance, hypertension and chronic degenerative diseases are prevalent in these societies while being virtually absent in extant hunter-forager cultures [49–52]. Modern hunter-gatherers (especially those cultures which have had minimal exposure to western lifestyles) maintain excellent and persistent insulin sensitivity, lower body mass index and fasting insulin plasma concentration than westerners [29].

While analyses of modern hunter gatherers/horticulturalists offer a relevant insight into how ancestral *Homo* may have lived in relation to diet, such an exploration inevitably constrains our scientific scope within a past/modern dualism. This in itself needs to be addressed in relation to drawing hypotheses of future human evolution. Our objective here is to play the devil's advocate, by proposing that human evolution has been an on-going process, and did not cease at the end of the

Palaeolithic period. A noted micro-evolutionary change during the Neolithic period was lactose persistence (LP) which underwent selection in central Balkans/central Europe approximately 6,256 to 8,683 years BP. The lactase allele −*13,910 C/T*) underwent selection during this period, probably due to increased reliance on dairy products by Neolithic populations [8,9]. A similar evolution toward lactose tolerance may have occurred as recently as 2 ka in East Africa, among cattle pastoralists. Consequently, East African pastoralists have higher levels of lactose tolerance than among other African groups who have only recently been introduced to dairy foods.

A concomitant feature of poor dietary practices in industrial societies is chronic sedentism, due to technology and lifestyle changes which have reduced physical activity in modern *Homo*. The rise of sedentism has been a looming calamity with adverse, long term implications for the future. To put it in perspective, for the previous 87,000 generations human ancestors were active hunters and foragers, which placed premium on physical fitness. Ancestral life was physically demanding in every way. Consequently, ancestral *Homo* evolved robust, strong bodies, capable of prolonged endurance and resistance to environmental stresses. Ancestral *Homo* became genetically adapted to various environments of evolutionary adaptation (EEA) ([53], p. 1082). *Homo erectus* was the first hominin that may have engaged in long distance running. Long distance running became an adaptation to hunt down game and avoid predation [54]. This form of persistent endurance activity was positively selected via the modification of phenotypic features including sparse body hair, eccrine glands and comparatively large body surface (improved thermoregulation response); swivel shoulders, elastic tendons, plantar arch, short toes, long legs (improved locomotion for endurance); evolved central nervous system, and capability for prolonged cardio-vascular and metabolic responses (improved CNS bio-feedback processes) [55]. The higher physical activity level (PAL) from *Homo erectus* onwards represents the larger body size of *Homo erectus* which needed more energy. Activity patterns from *Homo erectus* onwards markedly increased. By 1.8 Ma, total energy expenditure (TEE) for males would have increased by 85%, and for females, levels exceeding Australopithecines [56]. What is evident is that, from the origin of the genus *Homo* onwards, archaic hominins show higher levels of physical activity than non-human primates and australopithecines.

In comparison, the agricultural revolution, a seminal feature of the Neolithic period (10,000 ka), accounts for 350 generations, while the industrial age came into existence only seven generations ago The current digital age (two generations) has witnessed a systematic reduction in physical activity in many cultures, exacerbating physical disability and chronic disease ([53], p. 1082).

Attention to evolutionary elements of human diet and physical activity level is important in order to hypothesise future evolutionary scenarios. Modern human populations are undergoing unprecedented technological and social changes which are radically altering human ability to stave off disease. One reason for this malaise has pointed to the recent increase in hygiene in many human populations. Loss of helminths and beneficial microbiota, which modulated human immunological response during the Pleistocene and Holocene periods, has led to a pandemic allergic and auto-immune disorders [57,58]. This is usually referred to as the 'Hygiene Hypothesis', which notes that many individuals in the developed world lack the exposure to infections, parasites, pathogens and microorganisms and until recently, had minimised auto-immune disorders [59–61]. While the Hygiene Hypothesis has not been the focus of this article, its prevalence in the developed world is involved in epigenetic processes. Although, not all auto-immune diseases are inherited, modifications to hygiene characterised by cleanliness may trigger allergic auto-immune disorders which may otherwise have remained latent. Concomitant with impaired immunoregulation are depressive and anxiety disorders. Evidence suggests that depressive symptoms in both humans and animals may be induced by pro-inflammatory cytokines that impair neurological processes [62–65].

If modern day humans do possess 'stone age' bodies which have evolved for high physical activity levels (PAL), present sedentism may play an integral part in compromising future human biological systems. One major reason for this could be due to reduced levels of brain derived neurotrophic factor (BDNF) which plays a crucial role in inter-neuronal connectivity, neuronal integrity, increases efficiency of neuronal mitochondria, and maintains somatic homeostasis [66–68].

It is now believed that high PAL of ancestral *Homo* optimised BDNF in the brain and body to the point that BDNF was positively selected due to its neuronal protective role during the period of hominin brain evolution. Persistent hunting in ancestral *Homo* would have required an increase in BDNF which in turn assisted in the growth of the prefrontal cortex and hippocampus—key areas involved in decision-making, emotional control and spatial mapping [55]. The results of a recent study indicate that increase in brain size in many mammalian species evolved in conjunction with increasing PAL rather than as selective pressures on cognitive faculties [69]. A reduction of BDNF in the prefrontal cortex is associated with psychiatric disorders. Indeed, many behavioural disorders point to hippocampal dysfunction and reduced neurogenesis in this area, probably caused by chronic stress response which impairs the hypothalamus-pituitary-adrenal axis (HPA) [70,71]. Exercise is strongly implicated in increased neurogenesis (especially the hippocampus region), countering cognitive and mood disorders, and enhancing cognitive performance [72]. Vascular Endothelial Growth Factor (VEGF) has also been implicated in increasing hippocampal neurogenesis in an animal model in which mice were given a running regimen [73]. Additionally, exercise may stimulate neurogenesis in the dentate gyrus hippocampal region due to the increased expression of Serotonin 5-HT_{2C} found there [74].

Our concern is that the translocation to clean environments combined with changes in dietary practices and increased sedentism may lead to accelerated epigenetic processes which may compromise the body's psychoneuroimmunlogical systems. Microevolution of the human body can occur at relatively faster pace than previously thought by evolutionists ([7], p. 57). There is a large amount of evidence to support that epigenetic changes may trigger deleterious transgenerational responses due to dietary practices, as discussed earlier. While *Homo* has been in a period of accelerated adaptation during the last 80,000 years, the sheer population size of extant *Homo* which had recently reached 7 billion people means that mutation rates will dramatically increase in response to this unprecedented demographic growth [26]. A more ambitious claim that the last 10,000 years has caused accelerated evolution in *Homo* has been made [75].

Conclusions

Will evolution have the final word? Past and present human ability to tinker with its own evolution due to symbolic consciousness will continue to create opportunities for further genetic change in ways which we cannot imagine. The possibility of the future human body being physically reduced and immunologically compromised, as had occurred during the first epidemiological transition, cannot be discounted [76,77]. Such a weakened body may need to be routinely supplemented with technologically produced artefacts that will become a constant feature of our lives. Evolution is an on-going process of unknown possibilities [78].

Conflict of Interest

The authors declare no conflict of interest.

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