Selection For Hereditary Immunity To Infections
During The Evolution Of Humankind

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Abstract

This article is devoted to the discovery of the evolution of hereditary immunity exhibited by the majority of modern humans in relation to most known infections. The research methods were based on a comparison between different factors of natural selection through the principal stages of the descent of both humankind and its predecessors. Special attention is given to the inherent features of human hereditary immunity that can be considered, in retrospect to be evidence of previous infectious selection. The results of this research revealed that relevant traits of modern human have not been inherited from our ape ancestors. The vigorous immunogenic selection began in the savannah stage of human evolution (3.5 mya) and led to the appearance of Homo sapiens (1.8 mya). Selection continued during the establishment of H. sapiens in the region of the species? genesis (0.15 mya) and and during the subsequent dispersion of humankind around the world that began 0.06 mya and resulted in the unique diversity of this species. Anti-infectious hereditary immunity in modern humankind was therefore created during our paleoevolution. The resulting traits affect the main features of current epidemics. This research has also revealed the key role that infectious selection for hereditary immunity has played in the process of human descent in the Pleistocene.

Keywords: Anthropogenesis, Hereditary immunity, Health care, Natural selection, Paleoecology, Paleoepidemiology, Pleistocene

Introduction

This article is devoted to the discovery of the evolution of hereditary immunity exhibited by the majority of modern humans in relation to most known infections. The research methods were based on a comparison between different factors of natural selection through the principal stages of the descent of both humankind and its predecessors. Special attention is given to the inherent features of human hereditary immunity that can be considered, in retrospect to be evidence of previous infectious selection.
the fewness of preparative processes selective agents may be very different in quantity, quality, intensity and efficiency in regard to their influence on the direction and rate of evolution. The rate and quality of natural selection can be accelerated, improved and directed by the multifariousness of selective factors, by the intensity of its selective influence and by the fitness of the selective agents to meet environmental challenges at different stages of evolution.

The main selective forces of evolution hold sway over the inevitable biotic interactions existed in consumptive ecosystems, for example in predator/pray and microbe/victim interactions. The agents of predatory selection are relatively few and stable. They do not directly influence the primary, i.e. the molecular level of the evolutionary process. The impact of predatory selection should be prepared in advance by many stages of foregoing molecular ecological selection [4;6].

The evolution of a body as well as of its organs, tissues and cells is secondary to the evolution of the biomolecules of which they are composed. Any level of evolutionary transformation of populations and species is initially based on the processes of molecular evolution. This basic level of evolutionary transformation is also performed under the control of natural selection [3] during interactions between living beings and their biotic environment by means of molecular ecological substances synthesized by the co-actants [4]. The most intensive, extraordinarily specific, and very diverse selection is performed by interactions in the microbe/victim ecosystems through every stage of biological evolution including the natural history of Homo sapiens [4;6]. The interactions include the mutual impact of both selective agents and the self-preservation response of the victim species in the form of hereditary immunity.

Immunity is a state of being immune, i.e. having a degree of inherent or individually acquired resistance to a disease [7]. Four innate principles of immunity maintenance are known today. Human and vertebrate animals possess all four innate systems of immunogenesis (Illustration 1). Constitutional and phagocytic mechanisms are performed by specific factors that are inherent and present in the body before the primary act of infection happened. They are ready to counteract infection at the moment the infectious agent begins its attack. They serve as a first line of specific defense and can provide the victim of infection with immediate protection. In case they prove to be ineffective, the attacked organism still has a chance to be rescued by the response performed by the simplest innate response system as well as by specific immunoglobulins produced by the fourth innate system, the lymphatic system that is individually performed immunogenesis that may begin to function during the course of the infection or after vaccination. Illustration 1. Main principles of immunogenesis: constitutional (1), simplest responsive (2), phagocytic (3), and lymphatic responsive (4).

In most infectious incidents, the majority of people are spared from illness by hereditary protective factors that were present in their body before the primary act of infection happened. The entities responsible for this kind of immunity are constitutively expressed inhibitors of infectious agents. Their activity does not require any microbe-triggered signalling or intercellular communication. These activities are strongly specific to each kind of infectious agent. They comprise the front line of victim defense against infection because they are active and, in some instances, most effective in the context of the very first microbe-cell interaction that heralds the attack of a microbe to a genetically armoured being.

One of the implicit dogmas of immunology in the 20th century was that the design and strength of immunity is provided mainly by immunoglobulins elaborated by lymphocytes. Recently the key protective function of the lymphatic system began to be doubted, because its response to a first microbial attack is more inert and lazy [8;9] than infectious pathogenesis. Its mechanism of immunogenesis is reactive and begins to function only after infection triggers a sufficient quantity of microbial antigens to mount an effective response. Moreover, the adaptive response of the lymphatic immunogenic system includes transport of microbial antigens into lymphoid organs, recognition and differentiation of antigens by T- and B-lymphocytes, clonal expansion and differentiation of effector cells, biosynthesis of specific immunoglobulins, and their transport to infected organs. For example, the circle of anti-anthrax immunization consists of a series of six doses. The first portion of the series must be given at least four weeks before exposure to the infection.

In contrast, inherent factors of constitutional immunity are characteristic of a body independent of attack by disease-causing agents. Like all other body characteristics, constitutional immunity is formed during individual development and growth in accordance with the individual genetic component [10-12] but without induction by relevant infection or vaccination. Constitutionally immune individuals are resistant although they have not been exposed to the infection before and have no trace of agent-specific immunoglobulines in their body. Their immunity is provided by virtue of genetic features that are characteristic of their molecular constitution. Constitutional immunity is inherent, but it is not
adequate in all members of a species. There are variations between populations and individuals. For example, a prevalent proportion of humans have genetic immunity to typhoid fever. Humans have a hereditary immunity to foot-and-mouth disease. Only one of ten thousand people (0.01 percent) has been affected with a light form of the disease after close contact with sick cows [13].

The high specificity and unprecedented power of this kind of immunity is provided by chemical and stereo-chemical incongruence between molecular factors of microbial pathogenicity and relevant molecular structures of a targeted organism. All steps of microbial pathogenesis are performed by means of specific microbial molecular ecological agents (adhesins, toxins, enzymes, cytolsins, polynucleotides, etc.) that interact with the specific molecular structures of the infected victim. Success of these interactions depends on the chemical and stereo-chemical complementarity of interacting molecules. A competent mutation that precludes intermolecular complementarity creates constitutional insusceptibility.

Constitutional anti-microbial immunity encompasses several specific structures. These structures present a variety of molecular doorways or barriers such as specific cell receptors, modification of? the specific cell receptor, modification of specific nutrients, lack of a specific nutrient, presence of specific antibiotic and/or poison, and other mechanisms [8;14-16]. Alleles bring about modification of the molecular target in the potential victim reduce or even eliminate intermolecular interactions and, accordingly, reduce the potential of microbial aggression [14;17].

The pathogenic effect of microbes or microbial molecules depends on the genetically determined molecular structure of targets in the body of a potential victim, thereby defining either constitutional susceptibility or hereditary immunity to infection. The huge variation in individual sensitivity as well as in clinical course and severity of response to identical infecting pathogens is the result of genetic variation in relevant components of molecular constitution of infected persons [18].

Illustration 2. Evolutionary transformation of a human population initiated by an epidemic process.

Organisms possessing a mutantly modified molecular constitution rendering them incapable of being infected with the microbe are constitutionally immune to a particular disease. They give rise to immune progeny while susceptible individuals of the same species become ill and die without reproducing [3]. On repeated exposure of many generations to a given pathogen, the progeny of immune variants eventually predominate in a population (Illustration 2); an individual protective variation becomes the property of a group, then of a population and, finally, of most of the species [15;19].

This article is devoted to the discovery of the evolution of hereditary immunity exhibited by the majority of modern humans in relation to most known infections. The research methods were based on a comparison between different factors of natural selection through the principal stages of the descent of both humankind and its predecessors. Special attention is given to the inherent features of human hereditary immunity that can be considered, in retrospect to be evidence of previous infectious selection. The results of this research revealed that relevant traits of modern human have not been inherited from our ape ancestors. The vigorous immunogenic selection began in the savannah stage of human evolution (3.5 mya) and led to the appearance of Homo sapiens (1.8 mya). Selection continued during the establishment of H. sapiens in the region of the species? genesis (0.15 mya) and and during the subsequent dispersion of humankind around the world that began 0.06 mya and resulted in the unique diversity of this species. Anti-infectious hereditary immunity in modern humankind was therefore created during our paleoevolution. The resulting traits affect the main features of current epidemics. This research has also revealed the key role that infectious selection for hereditary immunity has played in the process of human descent in the Pleistocene.

The article presents the initial results of an attempt to integrate bioecological, epidemiological, clinical, immunological and evolutionary approaches to decipher the chronology of infectious selection over appearance and further evolution of humankind both at the phenome and genome level. The discovery was based on the analyses of appropriate data from observations and experiments performed by the author with his team as well as published by other researchers. The study pursued four consecutive aims: a) discovering traces of ancient selection amongst relevant hereditary traits of modern humans, b) establishing chronological milestones of the process, c) interpolating achieved results in the current paradigm of evolutionary anthropology, and d) interposing of achieved results in the paradigms of current infectology and epidemiology.

Traces of Infectious Selection

The traces of infectious selection can be found in the architecture of both phenome and genomes of human individuals, ethnocenes and entire species. To appreciate the creative significance of infections in the context of human evolution, it is important to consider...
the selective effects of infectious diseases, focusing on their current individual and ethnic features. In recent years, there has been considerable progress in identifying the traces of infectious selection that have been performed under pressure of a wide variety of epidemics [14]. Today, researchers can unearth the remnants of archaic human selection for inherent immunity against significant infectious agents. Humankind always had, and continues to have, the most extensive and broad ecological contacts with the world of microbes [4:19-22]. Selection for hereditary immunity in humans probably involved all infectious agents known today. As a result, most modern people are hereditarily immune to most known infectious diseases.

Natural influenza typically arose either as respiratory or food-borne illness. The self-reproduction and dissemination of the virus occurs from diseased organisms. In the bodies of sensitive animals, the microbes multiply explosively, causing the victim to have the disease and die. Both the diseased and dead victims serve as new sources of subsequent dissemination of the virus. The affection of the next victim is performed through the nutritional or respiratory tract. The Spanish influenza H1N1 (1918?1919) was the deadliest human pandemic known in the written history of humankind. It spread across the globe and killed more people than any other disease of similar duration. Nevertheless, it annihilated only 172% of the worldwide population at the time (Illustration 3).

Illustration 3. The worthiest Spanish influenza H1N1 (1918?1919) was able to kill only 2% of the current population. The majority of humankind possesses hereditary immunity to influenza, a sign of specific ancient selection.

The remaining 98% escaped death without vaccination or specific medication but through their own hereditary make-up of self-defense elaborated over ancient natural selection that developed during previous epidemics [22;23]. The formation of human constitutional immunity to influenza could have been induced by humans? historically continual, and ecologically inevitable, intensive carnivorous contact, primarily with aquatic birds and various infected animals and their remains [23]. Aquatic birds possess constitutional resistance to influenza infection, which is considered a result of their evolutionary adaptation to inevitable coexistence with this virus over a great many generations [24]. In contrast to humans (Illustration 3), aquatic birds (Illustration 4, b, c) and other omnivorous animals, the populations of domestic poultry do not have regular contact with natural sources of the influenza virus and thus do not experience natural selection for genetic immunity to the agent (Illustration 4, a) [23].

Illustration 4. Avian influenza virus H5N1 is nearly nonpathogenic for humans (current mortality is less than 0.01%), wild ducks, and geese (A, C; mortality less than 1%), but highly pathogenic for domestic poultry (B; mortality up to 90%).

Mutual affection by tuberculosis in both members of married couples is observed to be more rare (7 percent) than in a pair of dizygous twins (25 percent). Monozygous (identical) twins share susceptibility to tuberculosis; if one is ill, the other one has an 87 percent chance of also being ill [59]. Tuberculosis is also accounted as one of the world’s most pernicious diseases. However, the disease kills approximately 0.027% of the current world’s population each year. Only a minority of individuals develop the clinical disease, and most attacked individuals fail to progress to the full-blown disease. The inter-individual variability of clinical outcomes is mainly a result of variability in the human genes that control victim’s defenses [25]. Recent studies have indicated that humans were exposed to tuberculosis-mediated molecular selection pressure much earlier than was previously assumed [26].

Natural anthrax is also mainly a food-borne illness. Self-reproduction and dissemination of B. anthracis occurs in and from diseased animals. In the bodies of sensitive animals, the microbes multiply explosively, producing toxins that cause the victim to go into toxic shock and die. The dead victim is then attacked by scavengers, most of which can resist anthrax. Human infection with anthrax is carried out especially by nutritional contact with diseased bodies, including their uncooked or poorly cooked flesh, bone and hide, as well as hair, excrement and soil inseminated by any of these substances. The infection can also be initiated by inhalation of inseminated dust. In April 1979, an accident inside a biological weapons production factory in the city of Sverdlovsk, U.S.S.R., caused military-grade anthrax to waft out in a plume over a south district of the city [22]. The harmful aerosol cloud that formed then spread over 60 km from the military facility to the southernmost suburb. Approximately 7,000 people lived in the area of doubtless deadly concentration of the aerosol (up to 4 km from the facility) where its effect resulted in a total...
of 68 fatalities from anthrax and 11 survivors of a light form of the disease [27]. Thus, the accident demonstrated the lethal potential of anthrax aerosols on 1 percent of exposed peoples (Illustration 5).

Illustration 5. Correlation of damaged and unaffected persons among Sverdlovsk (USSR) population exposed to weaponized anthrax aerosol. The majority of current humankind is characterized by hereditary immunity to anthrax, a sign of specific ancient selection.

In the area between 4 km and 60 km, the potency of the deadly cloud was less and killed only sheep, which are far more susceptible to anthrax infections than humans, dogs, and even pigs [22]. The October 2001 anthrax incidents in the United States were consequent to the dispersal of anthrax spores by means of posted mail [28;29] distributed on a territory stretched out over 1000 km along the very populated East Coast of the country. The anthrax-tainted letter attacks induced 22 victims of anthrax, 5 of whom died. [29] The 22 cases of anthrax were identified in residents of seven states: Connecticut (1 case), New York City (8 cases), New Jersey (5 cases), Pennsylvania (1 case), Maryland (3 cases), Virginia (2 cases), and Florida (2 cases). Salmonella infection affects its prey exclusively by eating the flesh of the affected organism. According to a WHO estimate [30], the infection annually kills 0.01% of the world’s human population. Reported mortality associated with salmonella infection varies among different ethnic populations. For instance, the incidence of mortality due to S. typhi infection in Indonesia and New Guinea is higher than in other countries in southeast Asia [31;32].

2. Observations of Diseased Persons

Anthrax infection in human occurs mainly in secure cutaneous form, which accounts for over 95% of cases on record. The focal lesions of the cutaneous form vary in size from about 2 cm to several centimeters across, and begin to resolve about 10 days after first appearance. The resolution takes from 2 to 6 weeks and leaves minor scarring. Hyperacute and acute forms are characteristic of anthrax disease in herbivorous animals. In contrast, neither the deadliest nor serious forms of anthrax illness is common in humans [33]. The most common naturally occurring skin form of anthrax infection in humans affects 2,000 people around the world annually [34]. This form is unpleasant but secure (Illustration 6). In the United States, 224 cases of cutaneous anthrax were reported between 1944 and 1994, that is, nearly 4.3 cases yearly.

Illustration 6. This case of most usual (cutaneous) form of anthrax infection illustrates the traces of foregoing ancient selection and subsequent heterozygous interbreeding.

The largest reported epidemic occurred in Zimbabwe between 1979 and 1985, when more than 10,000 cases of anthrax were reported, nearly all of them cutaneous, that is, secure [35]. Some healthy people were reported to carry hundreds of anthrax spores in their noses and throats without incurring any disease [36]. These incidents of anthrax contamination failed to produce illness.

Stochastically disseminated foci of specific damages are clearly demonstrated in many kinds of infectious exanthemas. Mosaic distribution of damages is characteristic of herpes infection (Illustration 7), hepatitis, syphilis, tuberculosis, smallpox (Illustration 8) and all other infections [37;38]. Any epidemics is resulted both in fatal and nonfatal cases, which are prevalent. This diversity is a result of heterozygous interbreeding between parents with opposite grades of hereditary immunity. It highlights both individual and intra-individual differences in susceptibility of various parts of the organism under consideration [39].

Illustration 7. Localized mosaic distribution of specific lesions in a case of herpes infection, the result of foregoing ancient selection and subsequent heterozygous interbreeding.

Illustration 8. Like any other infection, smallpox reveals the coexistence in the affected person of hereditarily both immune and susceptible components, the traces of foregoing ancient selection and subsequent heterozygous interbreeding.

Each infectious disease is expressed in the infected organism in at least two categories of the same tissue, outwardly identical and differing only in their relationship to a given microorganism. Constitutional (hereditary) immunity explains why parts of one category are affected by a given microbe, while at the same time, other morphologically identical components of the organism remain uninvolved. Both exist under the same conditions and may be equally attacked by the infectious agents. These morphologically identical parts differ only in resistance. Thus, within the human body, there are at least two co-existing homologous parts with both unequal make-up and relations to an infectious agent. The parts exist in a form of separate patches of different sizes and locations being stochastically dispersed around the body. The quantitative correlations between such patches within specimens of a species are variable in size and location. This is the reason for the organism’s varied predisposition to different diseases and to their existence, spread, relevance, courses, and severity.
This kind of biodiversity arises as a result of sexual self-reproduction that inevitably forms this or that grade of heterozygosity. Each case of intra-individual biodiversity considered here is a result of hybridization between two genetically different organisms: one of them was constitutionally immune to the relevant ecological or physiological agent, whereas its mating partner was constitutionally sensitive to it. As a result, the descendant’s body cells are formed under control of two codominant allelomorphic genes. Such biodiversity in infectious diseases is predestined by the organism’s heterozygosity, resulting in coexistence of two active allelomorphic genes and two allelic cell clones in the body. Both of these alleles function dominantly. The heterozygous individual shows both alleles expressed equally, although in different locations of the body. One of these cell clones possesses the genetic immunity to an infection whereas the other one possesses the alternative feature of the other parent, i.e., genetic susceptibility to the same infection [39]. The mating of resistant and susceptible individuals gives rise to progeny with intermediate degrees of susceptibility to the infection and extent of infectious foci.

3. Experimental Infections
Volunteer infection studies [40] have established individual variations in minimal infective dose for Salmonella typhi from 100,000 to 1,000,000,000 microbial cells (Illustration 9). Like any infectious agent, salmonella cannot cause illness in all members of an observed human population. In some individuals, the microbes cause illness, while the majority displays hereditary immunity to the infection. The ecological chances of different animal species contracting anthrax depend on the natural mode of their nutrition. The data of experimental infection with anthrax [41] allow to conclude that razing herbivorous animals can occasionally catch the disease by the swallowing or inhalation the infectious agents. Many typical herbivorous animals, such as guinea pigs, mice, rabbits, cattle, sheep, horses, mules, camels, and goats, are the most susceptible to both natural and experimental infection with anthrax (Illustration 10).

In contrast, predators, carnivorous animals, and some omnivores (minks, dogs, cats) possess constitutional immunity to anthrax (Illustration 11). This kind of biodiversity arises as a result of hybridization of two or some kinds of botulinum toxins (Illustration 11).

In a try to evaluate the botulinum toxin bioweapon the Soviet experts performed the difficult, dangerous and precise tests on themselves. They demonstrated that although, botulism type A is more dangerous for men than types B, E, and especially C and D are, humans seem over 500-1000 times more resistant to type A botulism than horses, rabbits and guinea pigs are and that, for botulism toxins, dogs are the animal model most relevant to humans [14;42;43]. Thus, like other carnivores and many omnivores, humans possess hereditary immunity to botulism, the traces of ancient selection.

4. Cytological Investigations
Besides the above data concerning epidemiological, clinical and experimental observations, traces of previous natural selection can also be unearthed by in vitro testing of the influence of relevant microbes, or their molecular ecological agents, on the cells extracted from the organism under consideration. Cells of constitutionally immune individuals are not susceptible to a pathogenic agent whereas cells of constitutionally sensitive individuals are destroyed by the same pathogenic agents [11;44;45]. Thus constitutional immunity is a consequence of immunity of cells. We have discovered a key step of meningococcal infection - the attachment of Neisseria meningitidis to outer membranes of mucosal and blood cells of humans and animals. It was known that meningococcal infection can infect only some humans but not other species. In vitro testing revealed adhesion of meningococci only to cells of some human individuals, whereas analogous cells of naturally immune animals (mice, guinea pigs, rats, hamsters,
rabbis, goats, sheep, donkeys, horses, bulls, and hens) were absolutely immune to this key step of cell invasion by the parasite [11].

Bacteria of the Salmonella genus can provoke destruction of victim cells, although this effect is not manifest in every case. Salmonella strains were investigated for the organism's influence on mesenchimal cells of 10 biological species as well as 1,565 humans. All representatives of the four herbivorous species investigated possessed cells with very high sensitivity to destruction by salmonella. In contrast, the cells of omnivorous species were not destroyed by salmonella; they were genetically immune to these infectious agents. Only some individuals in the second group possessed cells weakly sensitive to some strains studied. Most representatives of an examined chicken population (1,042 out of 1,059) demonstrated hereditary immunity in their cells and only 1.6% (17 individuals) had weak sensitivity to destruction by some of the salmonella strains [46;47]. The nature of the differences in Salmonella infection found between constitutionally immune and susceptible chicken lines in vivo indicates that resistance is also expressed at the level of the mesenchimal cell, for instance in the mononuclear phagocyte system [16].

Analogous immunity of human cells was revealed in most representatives of urban populations in St. Petersburg (Russia), Kishinev (Moldova), Tartu (Estonia), and Alma-Ata (Kazakhstan). Only some individuals had cells sensitive to one or more of the salmonella strains tested. Nearly 90% had cells resistant to salmonella [46-48;48].

While Salmonella infections affect their victims by means of nutrition (via the alimentary tract), the origin of differences in cell sensitivity to salmonella discovered between mainly herbivorous species (guinea pigs, horses, rabbits, and white mice) and mainly omnivorous ones (humans, dogs, cats, hens, monkeys, and sheep) can be considered a result of their unequal interaction in this specific ?microbe-victim? ecological system. The above data also confirm both the genetic origin of the diversity in species and individual sensitivity to the molecular ecological agent of salmonella virulence [47].

Expressive traces of lengthy ecological interactions have also been revealed by in vitro observation of the interaction of the rabies virus with mesenchimal cells of 10 animal and avian species. Rabies infection exists thanks to the alimentary influence of predators on the species that inhabit dry land spaces. In contrast to aerospace inhabitants (the goose, rhesus monkeys, and vervet monkeys), the cells of land inhabitants (chickens, rats, guinea pigs, rats, sheep, and humans) were immune to rabies virus intrusion [14;49]. Thus, the farther a species has moved away from the ecologically determined possibility of interacting with the source of rabies infection (foxes and wolves), the higher its level of cell susceptibility to the virus, and vice versa.

Analogous ecologically understandable traces of foregoing selection have been found during the testing of animal cells for immunity/susceptibility to intrusion of tick-borne encephalitis virus. This infection is transferred by ticks, that inhabited the woods. Maximum sensitivity to the virus has been found in donkeys, the well-known inhabitants of the steppes. Bulls, whose pre-descendants lived in the woods, revealed high resistance to the virus. Goats revealed features intermediate between donkeys and bulls [14].

Analogous species and individual variations have been observed [23] in relation to the intrusion of influenza virus types A (subtypes H0N1, H1N1, H3N2), B, and C in the cells of 12 vertebrate species (chickens, dogs, guinea pigs, mice, Syrian hamsters, horses, donkeys, pigs, cats, goats, sheep, rabbits, and humans). The highest levels of cell sensitivity to intrusion of most viruses tested have been revealed in domestic poultry (the leghorn chickens). The lowest indices of cell sensitivity to all tested viruses were found in rabbits. The highest levels of cell immunity to most viruses were found in the other eight species. The greatest diapason of individual differences was observed in humans (in relation to all viruses, up to 40-fold), donkeys (in relation to virus H3N2, up to 32-fold), and horses (in relation to virus B, over 64-fold). The intra-species differences in sensitivity to influenza viruses types A among leghorn chickens were substantially less (up to fourfold) than among humans. Human cells also revealed relatively less sensitivity to viruses B and C, which reflects the lower epidemic potential of these viruses among human populations.

5. Molecular Investigations

The protective power of hereditary immunity results from the evolutionary disappearance of mutual complementariness (congruence) between molecular combining regions of both a microbial agent and its target in the attacked body. The choleraic toxin is able to interact only with such ganglioside macromolecules on the attacked cell membranes, which contain the subunits of ceramide, lactose, galactosamine, galactose, and the only radical of sialic acid joined with the radical of lactose (Illustration 12, a). The cells are able to resist the same toxin if their outer membranes contain gangliosides of other types, for instance, such as ones that do not contain galactose, or have an additional radical of sialic acid in the end position [50].
Botulinum toxin can interact only with those membrane ganglioside macromolecules that contain two sialic acids joined with the radical of lactose at the same position as in a case of Illustration 12b. Hereditary immunity to tetanic toxin depends on the absence in the cell membranes of gangliosides molecules (Illustration 12c).

Illustration 12. The organism?;s vulnerability to microbial agents is dependent on the presence in cell membranes of gangliosides (1-7) congruent either to choleraic (a), botulinum (b), or tetanic (c) toxins. Influenza A viruses (H1, H2, and H3 subtypes) cannot attach to attacked cell membrane receptors that do not contain terminal a-2,6-linked sialyl-galactosyl (a2,6 SA) moieties [51]. In addition, a relevant density and arrangement of receptors on the cell envelope are needed for virus binding to ensure that the virus particle is well attached; no fewer than 3,000 ganglioside receptor molecules are required for the attachment of a single virion [52]. The intensity of interplay between HIVirus-1 and its chemokine receptors on the cell surface has a fundamental role both in cell penetration by HIV-1 and in immunity to this clue step of the infection thus determining of the diversity characteristic of HIV infection [53;54]. Malarial parasites demonstrate selectivity toward a particular age group of erythrocytes. The factor involved in such a phenomenon may be that the young erythrocytes contain more lipids in their membranes than the older cells. [55]. Age-related changes in resistance of cells to mengo virus and encephalomyocarditis are conditioned by corresponding changes in maturation of the cell membrane?;s molecular composition, namely, the structure of the molecular receptor [56]. Moreover, there is a possibility that the large ribosomal RNA component in malarial ribosomes is provided, in part or entirely, from the victim?;s cell ribosomes. In the young red cell, the total volume of ribosomal RNA is greater than in the older red cell, and this volume decreases with age [55]. In addition, there may be a factor that prevents the plasmodium from entering cells of a certain age due to changes in the red cell surface receptor sites that are known to bind merozoites.

An "insignificant" change of amino acid composition in the hemoglobin molecule makes it inaccessible for nutritive systems of Plasmodium malariae and thus creates insusceptibility to malaria [57]. These mutant haemoglobin molecules constitute the red cells of aborigines in malarial regions, who are therefore not subjected to this infection because of previously performed natural selection for this trait. The non-availability of uncombined asparagin in guinea pigs makes this organism immune to the aggression of such varieties of plaque microbes, which cannot exist without the given amino acid. Such "defectiveness" of molecular constitution in these animals is conditioned by the presence of a large quantity of the ferment of asparaginase in their blood; this ferment splits the given amino acid as soon as it appears to be in an uncombined state [58]. The unequal contents of glycoproteins and glycolipides in the cellular membranes of rats and people is a cause of the inability of definite bacteria to affect the cells of the rat tongue in contradistinction to the human cells [59].

The absence of gangliosides susceptible to sialidase in horses? erythrocytes provides them with immunity to the action of a molecular factor that performed implements the pathogenicity of hemolytic vibrios [60]. The variations in the quantity and order of arrangement of definite gangliosides on the surface of the cellular membranes make them invulnerable to the affecting action of parainfluenza viruses [52]. The invulnerability of some molecules of collagen to the baneful action of the microbial collagenase is also determined by the specific and individual peculiarities of the structure of this protein molecule.

6. Investigation of Genome Make-up

Genes that control constitutional immunity to some infections in humans and animals have been identified and mapped to specific chromosomal locations [61-65]. The structure of the chemokine co-receptor for the HIV virus coded by the CCR5 gene has been mapped to a chromosome [54]. The mutant allele CCR5- [Delta]32, which is characterized by a 32 bp deletion in the single coding exon of the gene, was identified as responsive for coding the receptor structure not compatible to relevant molecular ecological agent of the HIV virus [53]. The CCR5 gene 32-base pair deletion provides strong constitutional immunity of human homozygotes to HIV infection [66]; in the heterozygous state, it may provide relative immunity, thus delaying the progression of HIV infection to AIDS in affected individuals [67].

The modified co-receptor along with CD4+ receptor for HIV-1 is incapable of promoting cell penetration by HIV. Individuals homozygous for CCR5- [Delta]32 display no clinical symptoms and appear to be healthy. They possess structural (constitutional) cell immunity to the infection. Heterozygous individuals also exhibit slower progression of AIDS. Thus, the risk of acquiring HIV infection is individually modulated by genetic polymorphisms in the chemokine receptor ligand. The CCR5 gene 32-base pair deletion provides strong constitutional immunity of human homozygotes to HIV infection [66]. In the mosaic heterozygous state, it may
provide relative immunity, thus delaying the progression of HIV infection to AIDS in affected individuals [67].

This mutation occurs at an allele frequency of 9% and a carriage frequency of 15%-18%, among white European individuals, which should be considered a trace of natural selection for genetic immunity against HIV. The frequencies in other major racial groups are negligible, which reflects probable ethnic differences in ancient performance of specific selection. Additional variants, most of which are codon-altering, have also been identified. Some of these variants may also protect against HIV-1 infection as a result of severe alteration in the conformation of the molecule. The effects of host genetic variation on acquiring HIV infection are inextricably bound to the well-established and powerful genetic variants that can function at different stages of infection [53;68].

Recent reports focusing on the inherent basis of genetic immunity to salmonella infection in animals contained information on a number of different lines of chickens that have been shown to be either resistant or susceptible to systemic salmonellosis. Immune lines show only moderate pathology and low mortality rates, whereas susceptible lines display extensive pathological changes and higher levels of mortality following salmonellosa infection. Genetic immunity to the salmonelloses in chickens was dominant and not linked to sex, MHC, or Slc11a1 (formerly known as Nramp1), which leads to resistance in mice and other species. A novel locus-encoding immunity to salmonella infection has been identified on chicken chromosome 5 and designated SAL1 [16].

Discussion

Decryption of the Traces of Infectious Selection

The unique set of human traits includes not only multiple physical features [69] but also numerous physiological and cognitive features [70]. The development of specific human traits should be initiated by relevant changes in a genome molecule, followed by subsequent transformation of the molecular phenotype performed by natural selection. The human genome contains roughly more than 3.4 billion base pairs and between 20,000 and 25,000 protein-coding genes. The overall difference between the genomes of the human and chimpanzee make up about 2% of the entire genome [69], equaling more than 68 million base pairs and between 400 and 500 protein-coding genes. Each of these specific human genes has been singled out for future existence by particular selective forces. The union of current anthropological, immunological, ecological, genetic and evolutionary methods can now lead us in deciphering the origin of these forces. Special attention should be paid to the traces of natural selection could be performed among human ancestors by predators and infectious agents.

The evolutionary importance of infectious selection is conditioned by many exclusively substantial circumstances. First, all decisive events in antagonistic microbe-victim ecological systems take place exclusively at the molecular level, the starting point of any evolutionary transformation [4]. The plethora of extraordinary features underlying the process of infectious selection was recently evaluated in detail for the first time [6;14]. Second, microbial parasitism sharply surpases any other marauding forms of symbiosis in many of its characteristics.

The penetration of infectious agents inside the victim’s body is mainly carried out by means of the victim’s ecological communications, through which the regular physiological functions are provided. It carried out mainly through feeding (as an alimentary intrusion) and breathing (respiratory intrusion). Of the two, the alimentary transfer of infectious agents functions most widely and effectively [19]. The affected victims, their excrements, corpses, or partial remains serve as a source of microbes to new victims.

The microbial world is characterized by a very broad variety of species, subspecies, and populations that are all different from one another in their molecular ecological properties and qualities. The significance of such biotic interactions participating in the processes of human evolution has not been especially studied until recently [6].

The number of microbial species that become potentially dangerous for a victim species can vary from a dozen to many hundreds, depending on the ecological features surrounding the victim. Considerably more than 500 species of potentially deadly microbes continue to threaten human settlers around the Earth today [71]. The variety of infectious agents that exists allows their interaction with a large number of various biomolecules (lipids, carbohydrates, proteins, nucleic acids, etc.) and their structural derivates, providing natural selection with many versions of the co-actors? molecular constitution [4;14]. Molecular agents of microbial pathogenicity and their molecular targets inside of the attacked body are unique and thus extraordinarily specific for each existing microbe-victim system. The ways in which microbial parasitism is realized are multiple and very diverse.

The antagonism of life-threatening molecular relations
between microbes and their victims induces responsive changes of relevant features of both co-actors. From these evolutive interactions, the victims of harmful microbes elaborate hereditary immunity, the traces of foregone selection for the molecular means of self-defense against infections. Next, the mutual evolution of microbes leads to improvement in their aggressiveness. These mutual responses function as effective forces in the mutual evolution of co-actors [6]. Thus, both microbial pathogens and their victims are in a continual evolutionary struggle?each side exploits new avenues of attack while simultaneously patching breaches in its defenses (Illustration 13). Illustration 13. Evolution of microbe-victim ecological systems; transformation of molecular make-up of a human population from the fight against different epidemics (A, B, C, D and so on).

In contrast, the members of predator-prey ecosystems are unable to gain relevant responses by means of a primary mutation. To improve their capacities, both the predators and their prey need to be performed with a chain of consecutive genome mutations. As a result, the evolution of this kind of ecosystem is slowly being performed during the change of generations.

The discussed primary molecular ecological mechanism cannot be considered the sole driving force and regulator of molecular evolution. Other types of ecological interactions should be mentioned as well. One may also suppose that in the processes of molecular evolution, there may act a regularity?similar to the correlation rule by J.Cuvier [72]?according to which any change of one organ entails a change in all other organs connected to it. Molecular components of any body constitution, as well as the organs, are also closely connected both anatomically and functionally. That is why the descent of a new version of a molecule must inevitably entail the conjugated transformations of other molecules [4]. These secondary changes also play a part in the fitness of organisms, thus additionally improving the efficiency of natural selection, which creates new forms trait by trait.

Chronology of Infectious Selection

The signs of ancient selection can be studied in various levels of the species architecture. Mutual achievements in both biology and medicine in the discovery of specific inherent traits of current populations reveal features that may be considered constitutive relicts of natural selection. This information has initiated a filling-in of the gap in our knowledge. It is now also possible to use an ecological approach in the study of evolution on both a phenome and genome-wide scale.

The multiplicity of current evidence for past infectious selection can now be combined for the try to locate when, where, and how the function of this creative force influenced the evolution of humankind. What is more, the data can enlighten on what influence infectious selection will have on the subsequent stages of humankind evolution. The myriad steps of anthropogenesis are usually divided into three principal stages: the tropical forest stage; the savannah stage; and the dispersion stage, when humankind migrated from the region of genesis toward other parts of the Earth. In addition to these stages, six principal periods of human evolution should be considered at integrative analysis of the same process (Illustration 14). Illustration 14. The duration of principal stages of evolution from earliest mammals to ancient humans: The tropical forest stage: The descent of insect-eating mammals, 33.8 my (1), and the subsequent descent of apes, 59.7 my (2);

The savanna stage:

a) The descent and disappearance of Ardipithecus and Australopithecus (3), 3.5 my;

b) The descent of the Homo genus, 1.8 my (4);

c) The stage of humankind?S establishment in the region of genesis, 0.15 my (5).

d) The stage of humankind?S dispersion around the world, 0.06 my (6).

The relatively quick evolutionary process (Illustration 14, point 4) has resulted in the establishment of Homo sapiens with a plethora of its unprecedented features that made humans unique in comparison with any other animal species, including its nearest primate relatives, the African apes. All of the uniquely human features arose as a result of natural selection, which acted specifically toward the achievement of specifically human descent. Now these features are considered as the traces of ancient selection.

There are no published ideas about what specific ecological events happened during this period of time. It is known only that the Pleistocene epoch was characteristic of global cooling. Without any doubt, climate conditions alone could not induce the unique lot of evolutionary transformations that specifically affected only one lineage amongst the plethora of existing ones. There was likely an unprecedented set of diverse, numerous, and very fertile selective agents that impacted on every level of relevant transformations, beginning from the molecular level.

The above-described abundance of human specific protective traits signifies traces of ancient infectious selection. It immediately leads to a question about the circumstances and chronology of the probable emergence of the traits. This can be discovered by comparison of relevant circumstances existing in...
consecutive stages of evolution of living matter toward the humankind.

1. In The Tropical Forest Stage

a) Descent of Early Mammals

In the Late Cretaceous epoch (near 99.6 million to 65.8 million years ago [mya]), tropical angiosperm forests began to spread across the Earth. Over this epoch, which lasted 33.8 my, some small, insect-eating mammal climbed into the trees, presumably in search of pollen-distributing flying insects, as well as ants and termites, and their eggs, larvae, and corpses, which would provide them with proteins, carbohydrates, vitamins, and minerals.

The tropical forest was not a relatively easy place for insect-eating mammals to find and catch this kind of food. These small, carnivorous predecessors of humankind served as a food for some other mammalian, avian, and insect predators, among whom there could be the juice-sucking predecessors of modern bloodsucking insects. Those bloodsuckers could introduce into the victim?s body some harmful transmissible infectious agents, for instance, the predecessors of today?s Plasmodium malariae, viruses of tick-borne encephalitis, microbes of duple fever, and some others.

Gradually, the former insect-eating mammals were granted the possibility of eating an abundant plethora of very moist, herbal, tropical products that were extraordinary rich in carbohydrates, vitamins, and minerals as well as a suitable quantity of proteins. The existing abundance of vegetarian food created favorable prerequisites for both their intensive self-reproduction and very wide diversification. Some former insect eaters adopted this potential, and this new strategy profoundly influenced the evolutionary destinies of these mammals.

At this stage, the evolution of the earliest human predecessors could be performed by natural selection as a lifesaving response to life-threatening challenges existing in this zone. The relevant life-threatening selective factors included predators, some poisonous plants and insects, as well as some infectious agents transmitted by bloodsucking insects. One can suppose that the selective power of these life-threatening challenges was too weak to perform a quicker evolution of a given human predecessor toward its next stage. Really, this period lasted too long (33.8 my) and led to the formation of the earliest herbivorous primates.

b) Descent of Apes

The next stage of human evolution, the descent of apes, started from the beginning of the Tertiary period (near 65 mya) when tropical forests had spread across all of the continents. The strategies that early primates adopted to cope with the dietary challenges of the tropic, arboreal environment profoundly influenced the evolutionary trajectory of the primate order. The descendants of some insect eaters came to rely on edible plant parts from the forest, and this change set the initial stage for the emergence of the primates. Natural selection strongly favored the complex of traits that enhanced the efficiency of arboreal foraging. As plant foods assumed increasing importance over evolutionary time, selection gradually gave rise to the suite of traits that most facilitated movement and foraging in the trees. For instance, selection yielded hands well suited for grasping slender branches and manipulating found delicacies [73].

Being dependent on plants for meeting their daily nutritional requirements, the plant eaters must also have sought a variety of complementary nutrient sources. Selective pressures also favored considerable enhancement of the visual apparatus (including depth perception, sharpened acuity, and color vision), thereby helping primates to travel rapidly through the three-dimensional space of the forest canopy and to easily discern the presence of ripe fruits or tiny, young leaves. Such pressures favored increased behavioral flexibility as well as the ability to learn and remember the identity and locations of edible plant parts.

Foraging benefits conferred by the enhancement of visual and cognitive skills, in turn, promoted development of an unusually large brain, a characteristic of primates since their inception. The selection for relevant abilities has been performed mainly by malnutrition, that is, by the lack of proper nutrition, caused either by not having enough to eat, not eating enough of the right things, or being unable to use the food eaten. Its influence has been fulfilled by physical agents and could not induce intensive primary molecular selection.

As time passed, primates diverged into various lineages: first prosimians (the lemurs, lorises, bushbabies, tarsiers) and then monkeys and apes. Each lineage initially arose in response to the pressures of a somewhat different dietary niche; distinct skills are required to become an efficient forager of a particular subset of foods in the forest canopy [73]. Tropical woods first allowed apes, monkeys, and prosimians to find food and obtain adequate nutrition. Having found a preferred food, they did only not sate themselves; instead, they seemed driven to obtain a mixture of fruits (rich in easily digested forms of carbohydrates) and leaves (more rich in protein) drawn from relevant plant species.

These characteristics of both jungle primates and their
descendants, including humans, have been derived from these early ancestors thanks to natural selection that has mainly performed by means of hunger and predators. Fresh vegetable food could not not be a source of any infectious threat to life. Selection by poisonous fungi, plants, and insects could be prevented by behavioral reactions. Direct molecular selection could be performed by a restricted range of infections transmitted by bloodsucking insects. The proper and diverse types of tropical foods provided apes with the capability for intensive self-reproduction. Diversification and multiplication of adaptive traits was intensified by genetic admixture through interbreeding between relative species (Illustration 15).

Illustration 15. The investment of interbreeding in the descent of humankind; the expression of idea by artist Mrs. Patricia Piccinii (2005).

The hybridization and exchange of genes between mutual ancestors of chimps and humans may have occurred over period of just a few million years. They may have interbred for a long time after their two lineages began to split apart evolutionarily [74]. Nevertheless, the rate and intensity of their further evolution would have been restricted by the sluggishness of selective agents (cats, leopards, eagles, wolves, snakes and other predators) existing at that time.

The lengthy process continued during five epochs of the Tertiary period, lasting totally near 59.7 my (Illustration 12). The selective power of life-threatening challenges existing at this time was too weak and slow to encourage more rapid evolution of the human predecessor toward its next stage. Millions of generations of apes?that is, consecutive human ancestors?changed during this period. Many different vegetarian apes began to emerge [75]. Over 100 species of herbivorous apes emerged at 23.8?5.3 mya, including the predecessors of modern chimps that humans shared a common ancestor with at 5?7 mya [76;77].

2. At The Edge of The Savanna Stage
a) Descent of Ardipithecus Genus
The paradise-like situation changed dramatically toward the end of Pliocene (5.3 mya), when global cooling began to dry out the tropical forests. These began to shrink and were gradually replaced by woodlands and then by savannah grasslands. The former inhabitants of jungles were forced to walk across woodlands. Among over 100 ape species existing at that time, only one, the predecessor of Australopithecus, was selected as the most probable ancestor of future hominids. Ardipithecus kadabba, the earliest known member of the Ardipithecus genus, inhabited the woodlands almost 6 mya. The best-known fossils, named Ardipithecus ramidus, are between 5.2-5.8 million years old. This species was probably the first ape that could evolve the initial qualities required to walk upright [78]. But in their prime, Ardi moved slowly, whether upright or on all fours. These apes were able to alternate cruising along tree branches on feet and the palms of the hands with the walking on two legs. Like other apes, Ardipithecus continued to emphasize vegetarianism. Its kind possibly evolved into the first Australopithecus species [79].

b) Descent of Australopithecus Genus
The acknowledged nearest ape ancestor of humankind, the Australopithecus genus, evolved more than 4.5 mya. The descent and subsequent extinction of Australopithecus lasted 2.7 my (between 4.5 mya and 1.8 mya). Like Ardipithecus, and many other apes contemporary to it, Australopithecus was a small-bodied (between 1.2 to 1.4m tall), small-brained, vegetarian hominid. Australopithecus might have been apelike in all respects, apart from its initial adaptation to upright walking. It was well adapted to find food products provided by either tropical forests or woodlands where it obtained adequate nutrition with a certain amount of energy, vitamins, and amino acids. Like all apes of this range, these apes obtained an estimated 94% of their annual diet from plants, primarily ripe leaves and fruits, supplemented with insects [80].

The rate and intensity of their further evolution would have been restricted by the sluggishness of selective agents (cats, leopards, eagles, wolves, snakes and other predators, blood) existing at that time. Direct molecular selection could be performed by a restricted range of infections (malaria, some encephalitis) transmitted by bloodsucking insects.

3. In The Savannah Stage
a) Extinction of Most Apes
As most tropical forests shrank and were replaced by savannah grasslands, the existing primates (over 100 species of herbivorous apes) forcibly lost the forest paradise-like environment and appeared in the grasslands. The primates in expanding savannah areas faced many new dietary challenges. Their hunger forced them to obtain high-calorie foods to ensure more effective moving across the savannah?s long distances. New ecological conditions forced yesterday?s vegetarians to eat whatever was at hand. Instead of the plethora of moist, tropical products, the hominids had the choice to eat either dry grass, which provided low energy for a former tropical feeder, or the corpses of killed and dead animals, which were extraordinary rich both in easily digested forms of...
proteins and carbohydrates as well as vitamins and minerals. Thus, the former fruit eaters were forced either to become the predators—the consumers of carrion—or to die. The importance of meat eating for human evolution has been theoretically accentuated by numerous anthropologists. [80;81] However, the mechanism of natural selection trough meat eating remains undiscovered. No good food source can drive natural selection on its own. Some specific features of a meat-eating diet should be taken into account [6;82].

On the one hand, the proper and diverse savannah food could provide apes with the capacity for intensive self-reproduction, this, with relatively large quantities of various mutations. But on the other hand, besides supplying proper food, the new mode of nutrition brought the new omnivorous feeders in contact with a plethora of very harmful infectious agents that inhabited the bodies of hunted or dead animals. Even the abridged list of potential infectious agents existing in animal sources [71] includes over a hundred of them, most of which were absolutely new to the eaters of tropical fruits.

The small-bodied hominids became the catches of many of the savannah's predators, including wild cats (tigers, lions, leopards, leopards), dogs, wolves, hyenas, foxes, snakes, crocodiles, and birds (hawks, raptors, toucans, owls) [83]. Thus, in contrast with analogous tropical challenges, the selective influences of predators became far stronger on the savannah stage. In addition, animals that are stressed by climate change are more vulnerable to being bumped off by infections and predators. It is well known that diseased animals or birds are caught by hunters more easily than healthy ones.

As a result, the absolute majority of vegetarian apes, including Ardipithecus and Australopithecus, appeared to be unable to survive these new conditions and therefore died. The fauna of the Earth lost 90% of its vegetarian apes within this period of time. At the same time, some of the predecessors of modern chimps, gorillas, and macaques remained in the remnants of the previous tropical forests, thus avoiding the worst influences of global cooling.

In the beginning of Pleistocene, 1.8 million years before present, the last of the consecutive species of the Australopithecus genus went extinct. But one branch of the genus appeared to become constitutionally immune and thus better able to counteract the life-threatening challenges of infectious agents existing in savannah at the time. The selected survivors developed many unique traits including larger brains and became the founders of the Homo genus.

It should be especially noted that the situation became dangerous only for the woodland herbivorous animals, including the primates. The factors that created this punishing environment impacted various species very differently. Their creative selection appeared effective only toward the descendents of the Homo genus. They did not force, for instance, the evolutionary progress of chimpanzees and other apes that humans shared a common ancestor with at 5.7 mya [76;77]. Besides this, the environment did not change the principles of nutritional ecology for the traditionally carnivorous animals like the cats, dogs, bears, hyenas, weasels, civets, raccoons, and mongooses, which continued their regular mode of carnivorous feeding. The nutritional ecology of predators, as well as carnivorous and omnivorous animals, such as the originality of their foraging, forced their predecessors to confront microbial enemies far earlier than the savannah stage for the apes. The traditional predators acquired genetic immunity to relevant sets of infections even before the Tertiary period. This achievement restricted their further selection by means of infectious diseases and thus slowed their evolutionary progress.

b) Descent of Homo Genus

One of many mysteries surrounding human ancestry is the unprecedentedly swift soar in the rate of human evolution from chimpanzee-like ancestors to Homo sapiens in Pleistocene. The earliest known fossil of anatomically modern humans dates from around 1.95 mya. [84]. In comparison to the foregoing stages, the Savannah stage of anthropogenesis was exceptionally short but unprecedentedly productive [14;82]. While proprietary descent of Homo sapiens took roughly 2.0 my, it was 32 times shorter than the preceding evolution of its primate predecessors which lasted 63.2 my.

During this period, the earliest Homo sapiens, the descendents of a tribe of the Australopithecus genus possessed human-like anatomy and many other traits that made them distinct from their ape-like predecessors. Except for the bipedality inherited from Ardipithecus through Australopithecus, the early Homo sapiens differed in that they had a naked body and the ability to run, could use primitive tools and elaborate on them, and also had a crude ability for conscious thought and speech. Undoubtedly, this set of very complicated physiological functions comes after 1.8 my period from a wider set of both genetic and phenetic structures, which may have arisen as a result of subsequent selection by extraordinary various and powerful agents. Neither climatic nor other bioecological influences could perform such selection by itself. This high tempo of evolutionary transformation can be achieved only by extraordinary...
The Human or Homo genus began to be selected at the end of Pliocene, when global, which were replaced by savannah grasslands. The primates in the expanding savannah areas have faced very difficult challenges, especially dietary ones. New ecological conditions forced them to eat the remains of animals that had either died of infectious disease or been killed by other species. This feed was extraordinary rich in easily digested proteins, carbohydrates, vitamins and minerals but disseminated with the plethora of animal consuming pathogens, including viruses.

The majority of vegetarian apes were unable to survive in these new conditions and disappeared. At the same time, anatomically modern humans emerged from the northern Africa’s savannah became predators and consumers of carrion. They were selected for hereditary and thus for the ability of infectious meta-eating and could withstand the savannah environment that been deadly for most of their herbivorous primate predecessors.

Early species of Homo were similar in body size and shape to Australopithecus but had particularly larger brains and relevant skills. These species were replaced by even larger-brained H. heidelbergensis, H. habilis, and H. erectus, and then by H. neanderthalensis and early H. sapiens, which, of course, had the largest brain of all. In parallel with the increases in brain size, many other amazing anatomical and physiological changes were also occurring in the Homo genus.

The meat-eating strategy forcibly adopted by some selected primates to cope with the dietary challenges of the savannah’s environment profoundly influenced the evolutionary trajectory of the primate order, particularly that of the anthropoids. The savannah foods put them in contact with widest range of new and very strong selective agents. As animal foods began to have increasing importance for the primates, they inevitably met a widest range of harmful infectious agents. In the response to this challenge, natural selection gradually gave rise to a specific suite of traits, most of which facilitated surviving the fight against infectious parasites [6;14]. One can suppose that the hereditary immunity against anthrax, botulism, tetanus, influenza, salmonellosis, plague, tularemia, brucellosis, smallpox, rabies and so on were obtained during the savannah stage.

Now the traits; first of all, the constitutive (i.e., genetic) immunity to a plethora of harmful microbes is regarded as characteristic of both modern humans and other carnivorous animals [6;14]. The molecular selection and subsequent evolution of human’s molecular constitution became far more intensive and extensive. It was a most significant event that molded human natural history. As the relicts of such intensive selection that began 1.8 my ago, most modern humanhood is characteristic of very strong hereditary immunity against various known infectious diseases. As a secondary result of this process, a unique set of macro-anatomical and physiological transformations [69;70] appeared.

4. During The Dispersion Around the World

According to the generally accepted ‘Out of Africa’ theory and its latest developments [85], anatomically modern humans emerged in one place, probably the northern African savannah? territory that has experienced abrupt, periodic switches between arid and humid climates. The earliest known fossil of Homo sapiens dates from around 0.195mya [84]. Early sapiens possessed an anatomical make-up essentially like our own, but the mutual evolution of humankind and its microbial co-actants was not completed at that time.

Nearly 0.06 mya, different tribes of early Homo sapiens began to sweep out of Africa??Lost Paradise??and disperse around the world, while some groups stayed behind in the African savannah. There may be three main directions of the migration: the tropical African way, the Euro-Asian way and the South Asian way. In that time, different human populations adapted to a wide variety of the new environments they encountered in their different directions. In the process, they experienced a vast range of new environments, climates, diets, ecosystems, including the abundance of various infectious pathogens [6;14]. Most of their features could be successfully improved over the dispersion stage. The details of this very fruitful period of humankind evolution deserve special investigation. Nevertheless, some initial remarks can already be made.

Some of the early sapiens tribes migrated out of the savannah’s? Eden? back into the remnants of African tropical wood, the homeland of their ape predecessors. Here, the ?returners? did not meet new infectious agent but became the subject of some selective agents and experienced remarkable transformations. The replacement of an initial (brownish) skin color with black is probably one of the most understandable of them. The skin melanism of tropical African ethnoses can be considered the result of a defensive camouflage adaptation to habitation in the tropical forest [14]. Some types of malaria resistance, with relevant transformations of molecular make-up, serve

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as examples of immune adaptation to coexistence with aboriginal African malaria plasmodium. In contrast, they did not experience the selection for hereditary immunity to HIV infection (AIDS). The absence of hereditary immunity to HIV-infection among inhabitants of African tropical woods also evidences different evolutionary influences of environmental conditions [14:86]. In addition, in contrast with the travelers in the Euro-Asian and South Asian directions, the earliest sapiens in the African tropical environment did not interbreed with Neanderthals [87]. Most other differences between current human races and ethnoses are due to events that occurred outside of Africa, and are accounted for as most first appeared in East Asia [88]. Before and after the dispersion, most principal genes flowed between the different human populations by mixing together. At this stage, early Eurasian sapiens interbred with Neanderthals, and since that time modern people from France to Papua New Guinea have carried about 1 to 4% Neanderthal DNA [87]. Adaptive functions of the admixed Neanderthal genes deserve special investigation. The wandering of human groups around other parts of the world substantially expanded both the quantity and quality of evolution's driving forces. These forces acted mutually on both the early predecessors of modern humans and on the multiple microbe species that the migrants encountered in their ways. The subsequent genetic admixture between distinct human populations increased the number of new features of the human molecular constitution because thousands of wandering generations were subjected to various selective infectious pressures. This process resulted in the establishment of Homo sapiens, a species with a plethora of unprecedented structural and physiological features that made it unique in comparison to any other species, including the earliest sapiens and their primate predecessors. The unique set of human differences included not only multiple physical traits (such as a cranial vault with vertical forehead, rounded occipital, reduced brow ridge, reduced facial skeleton lacking a projecting mid-face, alower jaw sporting a chin, short stature with a height of near 4?4.5 feet [similar to modern pygmies], a less-robustly built skeleton, and a specifically naked body [69] among others) but also innumerable physiological and cognitive traits (such as the ability to run; elaborate tools; thought and speech; control of thoughts, emotions, and actions; planning for future events; self-reflection and self-consciousness; creation and use of language; imitation and learning socially in particular ways; use of episodic memory; imagination and creativity; cooperation and altruism; and many others) [70].

This evolutionary process continues to function even today [4;14] and thus promotes the preservation of the traces—that is, the relics of archaic molecular selection—that created the highest living being on the Earth. The uniqueness of some features' origin is now traced to the levels of cellular and molecular architecture, including within the genome. The possession of all these features was initiated by a relevant change in a genome molecule, followed by subsequent transformation of the molecular phenotype through natural selection and acted on by physical, chemical, and especially bio-ecological agents.

**Conclusion(s)**

This integrative analytical investigation was based mainly on four scientific principles. According to first of them, the initial stage of evolution of any species takes place on the molecular level of its organization. The second principle states that evolution is initiated thanks to molecular selection that took place during antagonistic interrelations propelled by means of molecular ecological agents innately peculiar to the involved co-actors. The third principle certifies that most diverse and intensive interactions of such kind take place in microbe-victim ecological systems. Lastly, according to the fourth principle, the interactions have resulted in the formation of hereditary immunity against relevant infections by means of extraordinary specific changes of the victims? molecular constitution. The possessing of these phenotypic traits and relevant genome structures provides evidence of the past performances of infectious selection. On the basis of these principles, the role of infectious selection in human evolution has been analyzed and interpreted, beginning from the earliest insect-eating mammals to the descent and extinction of the apes (the tropical forest stage) and subsequent descent of the Homo genus (during the savannah stage). It has been accentuated that the proper descent of Homo genus took nearly 1.8 my about 35 times shorter than the evolution of all its primate predecessors (which occurred over a period of 63.2 my).

The swift evolutionary spurt in the human lineage was associated with global cooling and subsequent dramatic change of the typical place that human predecessors occupied in the biosphere food chain. The apes were forcibly moved from vegetarianism to carrion eating. On the one hand, this new way of foraging provided them with wide possibilities for intensive reproduction and diversification. On the other hand, this change inevitably led them to contract
unprecedented and various life-threatening infections and to abrupt intensification and diversification of their selection. The proper quantity and quality of these selective agents have been provided by repeated infectious epidemics induced by evolving infectious agents. The seldom survivors reached life-saving victory, being descendants of mutant individuals whose molecular constitution provided both them and their offspring with constitutional genetic immunity to infections met at this time. Subsequent migrations substantially expanded both the circle and the quality of microbe species that human predecessors inevitably met on their journeys. In addition, the number of new protective features may have arisen by means of genetic admixture through interbreeding with relative subspecies and species. In spite of this high tempo, this evolution resulted in the formation of a countless number of unique human features that are different from any other living beings, including the nearest primate relatives. Such very fast, but extraordinary, productive evolution could be initiated only by uncompromisingly cruel, but highly intensive, molecular selection. Harmful microbes performed very cruel selection among primates for inherent immunity and thus guided some herbivorous apes to become the Homo species. Amazingly, during the first two-thirds of the savannah stage, over 100 species of herbivorous apes became extinct. In contrast, representatives of the Homo genus continued their move around the world. Only the youngest of them, Homo sapiens, appeared to be able to counteract the plethora of new threats they met in their path. Others were eliminated by cruel natural selection.

Finally, as a result of multiple repetitions of such suffering events, the human forebears had constitutional genetic immunity against any infectious disease that exists today. Modern humankind continues to possess these genes. The achievements so favorable for routine life led to the weakening of human selection by means of infectious diseases, thus slowing down its further evolution. The study of hereditary immunity to infections is going to be a remarkable window, a time machine of anthropogenesis. The existing ethnic and geographical differences in susceptibility to infections today reflect the differences in phylogeography of both archaic and prehistoric migrations of different human groups. Human ethnic and racial polymorphisms of constitutional genetic immunity to various infectious diseases reflect the variation in traditional environmental conditions of relevant human populations or groups. These traits can be considered as a highly informative paleontological, historical, and geographic components of genetic diversity in humans. The evolutionary process slowly continues to function even today and thus promotes the preservation of the traces?that is, the relics of archaic molecular selection?that created the highest living being on Earth.

Now the evolutionary created features of human hereditary immunity to infections determine both epidemiological parameters and clinical manifestations of any infectious disease first the level of its prevalence and its severity. Only a minority of humankind does not possess hereditary immunity and needs to be defended. Individuals in need must be revealed by specific diagnostic tests. In contrast, the majority of the population who are hereditary immune should be relived of these procedures. Consequently, genetically motivated personalized actions should replace the existed system of total compulsory prophylaxis.

Hereditary immunity has played a major role in the history of mankind over the centuries and millennia. Today its protective capability continues to defend humanity from mass annihilation by epidemics and bioweapons. Given these circumstances, the main goal of modern medicine is to identify and defend the defenseless ones. The best way to counteract either epidemics or bioterrorists attacks is to identify and defend the defenseless minority. The tests for a population genetic immunity can provide public health institutions with information about the real danger of both emerged and re-emerged infections - that is their epidemic ferocity and how they can spread around the world via intercontinental travelers in the search of susceptible individuals and groups. The principles of testing for hereditary allow for the assessment of the grade of natural resistance to any infectious agents on the level of both individuals and populations.

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Illustrations

Illustration 1

Main principles of immunogenesis.
Illustration 2

Evolutionary transformation of a human population initiated by an epidemic process.
Illustration 3

The worthiest Spanish influenza H1N1 (1918?1919) was able to kill only 2% of the current population.
Illustration 4

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smallpox reveals the coexistence in affected body of both immune and susceptible components
Illustration 9

Infection of humans with abdominal typhoid

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<th>Dose</th>
<th>Number of microbes in a dose</th>
<th>Number of injurious doses</th>
<th>Number of unaffected persons (%)</th>
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<td>0,01</td>
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<td>0</td>
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<tr>
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<td>100</td>
<td>50</td>
<td>50</td>
<td></td>
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<tr>
<td>10,000,000,000</td>
<td>10,000</td>
<td>5</td>
<td>95</td>
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</tr>
</tbody>
</table>
Illustration 10

Immunity/susceptibility to anthrax infection in a selection of vertebrata species

<table>
<thead>
<tr>
<th>Species</th>
<th>The grade of ecological interaction with B. anthracis</th>
<th>LD$_{50}$ (number of spores)</th>
</tr>
</thead>
<tbody>
<tr>
<td>White mice</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Guinea pigs</td>
<td>2</td>
<td>50</td>
</tr>
<tr>
<td>Macaca rhesus</td>
<td>3</td>
<td>3,000</td>
</tr>
<tr>
<td>Rabbits</td>
<td>3</td>
<td>6,000</td>
</tr>
<tr>
<td>Rats Fisher</td>
<td>4</td>
<td>700,000</td>
</tr>
<tr>
<td>Black rats</td>
<td>4</td>
<td>1,500,000</td>
</tr>
<tr>
<td>Pigs</td>
<td>5</td>
<td>1,000,000,000</td>
</tr>
<tr>
<td>Dogs</td>
<td>5</td>
<td>10,000,000,000</td>
</tr>
</tbody>
</table>
Illustration 11

Hereditary immunity/sensitivity to botulinum toxins

Illustration 11. Levels of hereditary immunity/sensitivity to botulinum toxins types A, B, C, D, E, and F in a selection of vertebrata species

<table>
<thead>
<tr>
<th>Animal species</th>
<th>Minimal lethal doses of toxins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>A</td>
</tr>
<tr>
<td>Herbivorous animals</td>
<td></td>
</tr>
<tr>
<td>Guinea pig</td>
<td>1.0</td>
</tr>
<tr>
<td>Rabbit</td>
<td>1.0</td>
</tr>
<tr>
<td>Horse</td>
<td>0.4</td>
</tr>
<tr>
<td>Omnivorous animals</td>
<td></td>
</tr>
<tr>
<td>Mouse</td>
<td>5.0</td>
</tr>
<tr>
<td>Macaca rhesus</td>
<td>4.0</td>
</tr>
<tr>
<td>Dove</td>
<td>200.</td>
</tr>
<tr>
<td>Carnivorous animals</td>
<td></td>
</tr>
<tr>
<td>Mink</td>
<td>10.0</td>
</tr>
<tr>
<td>Dog</td>
<td>500.</td>
</tr>
<tr>
<td>Cat</td>
<td>500.</td>
</tr>
<tr>
<td>Hen</td>
<td>10.</td>
</tr>
</tbody>
</table>
Illustration 12

Vulnerability to microbial agents is dependent on the presence in cell membranes of gandliosides (1-7) congruent either to choleraic (a), botulinum (b), or tetanic (c) toxins.
Illustration 13

Evolution of microbe-victim ecological system
Illustration 14

Duration of principal stages of human evolution
Illustration 15

Investment of interbreeding in the descent of humankind
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