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Hereditary Immunity in Evolution of Humankind

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ABSTRACT

Modern anthropology successfully states the stages of human evolution by the comparing prehistoric genomes to current ones. But much remains a mystery as to how *Homo sapiens* emerged suddenly over African Pleistocene (1.8–0.2 mya, million years ago) and then evolved into *Homo sapientibus* over 0.1 my further dispersion around the world. The moving forces of the processes that have acted on decisive stages of human evolution remain uncovered. The present analytic publication is devoted to the try to integrate recent results in the revealing original ecological causes of anthropogenesis at the time of it decisive stages. Special attention is paid to the discovering of exceptional forces of natural contra-infectious selection that arose in the ecology of human predecessors at the time and to the evaluation of hereditary immune traits of modern humans that can be considered, retrospectively, as specific relicts of this selection. The achieved results, present supporting evidence on exclusive role of alimentary meat associated infectious epidemics, have played in driving the descent of humankind. The most intensive time these moving-forces have functioned was 5.3–1.8 mya, during the African savannah stage of anthropogenesis. The selection of this kind continued during the 1.8 my (million years) establishment of humankind both in the region of genesis and over subsequent 0.1 my dispersion of some wandering tribes around ecologically different parts of the earth where they were forced to oppose new cruel causative epidemic agents (influenza, measles, HIV, smallpox tuberculosis and so on). The dates and places of these counteractions are estimated.

Immune Movers of Evolution; 5. Bio-ecological Chronology of Anthropogenesis [In the Way from Earliest Mammals to the Apes, In the Spurt Descent of Earliest Humans, Over out of Africa Dispersion (Opposition to Influenza, Measles, HIV, Tuberculosis, Smallpox)] 6. Conclusion.

KEYWORDS: Anthropology; Human evolution; Molecular ecology; Molecular evolution; Moving forces of evolution; Natural selection against infections

INTRODUCTION

The great achievements of classic paleo-anthropology, the routine study of human evolution, have been resulted chiefly by the investigations of the remains of prehistoric bones and tools [1]. Recently the modern anthropology successfully enriched the investigations by the discovery of prehistoric genomes that can now be compared to modern ones [2].

The new tool of paleo-anthropological investigations impelled the appearance of extraordinary important discoveries. It was stated that early *Homo sapiens,* anatomically, physiologically and immunologically analogous to modern humans, emerged on the African savannah [3]. The ways of early spread of modern humans outside Africa was reconstructed (Figure 1). The evidence has been derived that all currently living non-African populations probably derived from a single dispersal of modern humans out of Africa [4]. Three ancestral genetic roots of current European population were evidenced [5]. Anthropology begins to move toward a new history and geography of human genes informed by ancient DNA [6].

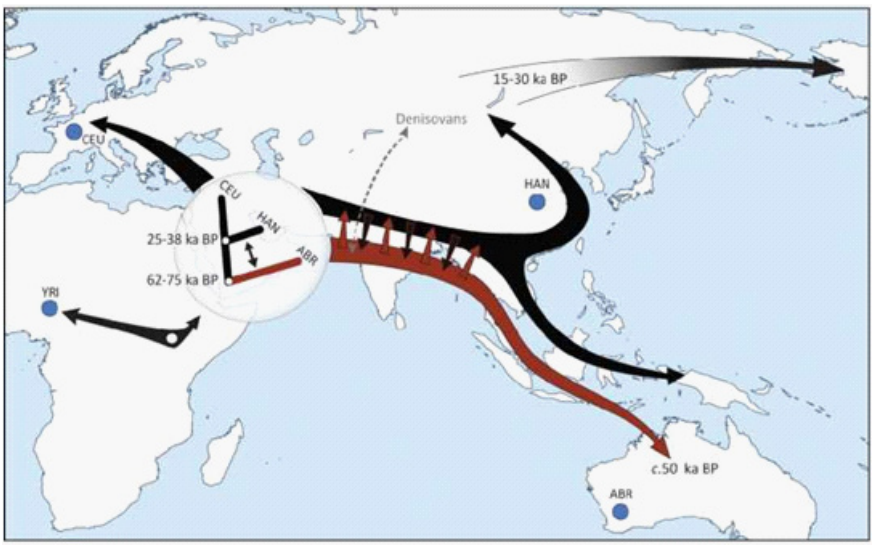

Figure 1: Reconstruction of early spread of modern humans outside Africa [4].

However, even the investigations of the genomes molecular architecture alone can only verify the results of evolutionary processes, but are unable to decipher the working forces and mechanisms that drove the evolution. The current inability to decipher the specific causes and

forces of human descent and further development may be interpreted as a result of a current shortfall of attention to the ecological agents of natural selection that were the movers of anthropogenesis. The history of humankind has been explored with tools from several disciplines including linguistics, archaeology, physical anthropology, and genetics [6]. The methods of evolutionary ecology have not been included in the ensemble. As a result the neglect, the creators of human evolution, the executers of natural selection remains unknown.

Modern anthropology still knows relatively little about the selection pressures that were important over the past 0.1 million years [7] but knows also very little about the selection pressures acting in the crucial stage of human evolutionary descent that have began in Paleocene (5.3–1.8 mya) and resulted in the appearance of early *Homo sapiens* in Pleistocene (1.8–0.1 mya). The signs of ancient bioecological selection should be searched for in the architecture of human phenome.

Much remains a mystery as to how *Homo sapiens* emerged suddenly over African Pleistocene (1.8–0.2 mya) after that some subdivisions of the species evolved into *Homo sapientibus* over 0.2 my further out of Africa dispersion around the world. The moving forces of the processes that have acted on relevant stages of human evolution remain uncovered.

The ecological approach should be used to reveal human evolutionary past at both the phenome and genome level. Mutual achievements in biology and medicine, and the identification of specific inherent traits of modern humans, allow us to verify what the constitutive relicts of precedent ecological selection were among these traits, and thus initiate filling in the information gap.

This chapter presents the united results of recently performed attempts to use integrative (bioecological, anthropological, epidemiological, immunological and evolutionary) approaches to decipher the causes and driving forces of anthropogenesis during its decisive stages. The study was based on integrative analyses of relevant data that have published mainly over the first decade of 21st century [8-14]

PREPARATIVE AND SELECTIVE STAGES OF EVOLUTION

Any evolutionary act is performed by an ensemble of preparative and selective processes. Preparative stage of evolution forms genetic diversity, the building materials for future transformations. The preparation consists of constant but very infrequent episodes of spontaneous mutagenesis. It can be supplemented by genetic admixture through heterozygous mating which enriches intra-species diversity and thus provides evolution with additional selectable building materials [12,15]. The process of diversification can be intensified by greater reproduction rates of the transformed population. But the proper driving of any evolutionary transformation is performed only by natural selection. In contrast to 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 [12,16].

MOLECULAR STARTS OF EVOLUTIONARY DEVELOPMENT

The living nature consists of colossal variety of biological species; each of them is being unique and original not only by its outward appearance but also by the features of its molecular anatomy, by the structure of the biomolecules peculiar to it - polynucleotides, proteins, lipids, polysaccharides etc. The sequence of amino acids in dog or hen haemoglobin, for example, differs from that of human haemoglobin. Most of all there is a great number of various distinctions in molecular anatomy of subspecies, populations and individuals. Still more surprising and still less intelligible is a phenomenon of intraspecific polymorphism of those same kind of molecules which have a common origin, perform the same functions but differ by some or other details of their structure.

The human hemoglobin is now well known as an example of diversity at the molecular level. It occurs in over 100 different forms of human hemoglobin, each differing in its details amino acid composition [17]. Within *Homo sapiens* species about 500 different versions of molecular structure of erythrocytes have been found [18]. Some of them are widely met, others are very seldom. So, among the Red Indians - aborigines of Argentina there is met blood group 1(O) only. On the contrary, the features of the molecular constitution responsible for their belonging to group II(A) are peculiar to the erythrocytes of the majority of the Europeans; blood group III(B) prevails among the Mongoloids [18].

The biomolecular heterogeneity of living beings has been known in principle for a long time. However, science has failed to give an exhaustive explanation to the origin of the majority of interspecies distinctions of molecular constitution. The origin and biological significance of these molecular-anatomic features as well as reasons of their so peculiar spreading remains unknown. One could have thought that the similar distinctions have sense in realizing the physiological functions of the adequate biomolecules. And such a supposition is really right in respect of a number of distinctions between biological species. But why and for what do the distinctions exist, for instance, in the structures of blood cells among the various populations of one and the same species? How did these distinctions between populations arise? What does the availability of some isoferments in one and the same body stipulate when some cells of the given organism contain one of the versions of the same ferment, for instance, glucose-6-phosphate-dehydrogenase, whereas other cells of the same type contain another version of the same biocatalyst and the third ones contain neither this nor that [19].

It is argued that, although molecular diversity, for instance, various histocompatibility antigens were first recognized through tissue grafting experiments, such grafting does not normally occur

in nature. Thus, MHC polymorphism could not have evolved in response to a selection pressure generated by the need to reject foreign grafts. So we must look elsewhere for an explanation for the origin of MHC polymorphism. This view is widely disseminated in textbooks and popular science journals [20].

So far as the victims of microbial parasitism are the representatives of all forms of the living matter, such conjugated processes of the evolutive transformation of the molecular constitution are realized in the majority of the ecological microbe-victim systems within the whole period of their existence on the Earth; great varieties of reacting molecules and innumerable amounts of competing organisms are being involved. According to Forsdyk, 1991 [20], MHC proteins could have evolved as a defense against viruses before the evolution of multicellular organisms. A cell which had evolved prototypic MHC proteins with some degree of polymorphism would be better prepared to maintain the integrity of its own nucleic acid by preventing invasion by a foreign nucleic acid.

IMMUNE MOVERS OF EVOLUTION

All the existing-in-nature colossal variety of biotic molecules arose as a result of biomolecular evolution. But not until recently there was no opinion as to the mechanism of this process and its moving forces. Boisterous discussions were developed on this problem [21-23]. In the course of this discussion two opposite viewpoints were revealed. As the alternative to the Darwinian evolutionary theory there arose and developed a theory of the non-Darwinian neutral evolution [24-26].

At the center of Charles Darwin's theory of evolution, is the principle of natural selection of variants that arose spontaneously among populations of living beings before the selection? A variant with a new inherent trait making it better adapted to a particular environment was more likely to survive and leave progeny than one that was less well adapted. Its progeny would tend to compete with and supplant, in that environment, those of less well-adapted parents. The evolution of living matter is taking place when three biological phenomena participate without fail - heredity, inherent variability and natural selection through biotic interactions between living beings, i.e. bioecological factors of natural selection are being the most significant motive force.

The theory of neutral evolution was based upon the notion on the non-participation of natural selection in evolutionary transformations of biomolecular structures. According to the neutral theory, the overwhelming majority of evolutionary changes at the molecular level are caused not by Darwinian natural selection but by random fixation of selectively neutral mutants under continued mutation pressure. The creators and supporters of this theory believe that under the natural conditions no factors exist which can distinguish the organisms by their molecular features and the more so - by the details of their molecular structure [27]. "The belief in the truth of the Darwinian theory of evolution appeared to be shaken when one tried to interpret its theses

according to the statements of molecular biology. Up to now no one has reached this aim" [28].

However, far before the neutral theory arose, it was stated that molecular level of evolution is a basic one and should be also performed under control of natural selection [29]. The support of the role of natural selection in the processes of molecular evolution [21,30-32] and subsequent correction [25] of the neutral theory confirm that molecular changes in the course of evolution are also crafted by natural selection. It became clear that any level of evolutionary transformations of individuals, populations and species should be initially based on the processes of biomolecular evolution. The evolution of cells, tissues and organs, as well as of the entire body, populations and species is secondary to the evolution of biomolecules of which they are composed [33].

This crisis of evolutionary biology has been solved by synthesizing the Darwinian evolutionary theory and basic conceptions of molecular biology, a science on the chemical aspects of the structure, functioning and developing of the living matter. Its main parts are molecular anatomy, molecular physiology, molecular (chemical) ecology and the discovery on biomolecular evolution primarily on the level of molecular ecological interactions [31].

Molecular ecology acknowledges the interactions of organisms by means of chemical substances synthesized by them [34]. Such chemical ecological interactions play a part at any level of life organization and functions. Most diverse and intensive molecular ecological interrelations take place when living beings are confronted with parasitic microbes. The discovery of the origin of hereditary immunity made it possible to make the clue contribution to solve the above considered gnostic crisis of biological science. Such interactions are widely spread in living nature in the form of molecular biological contradiction [35]. The infectious origin of selective forces and movers of evolution has been accentuated too (Figure 2).

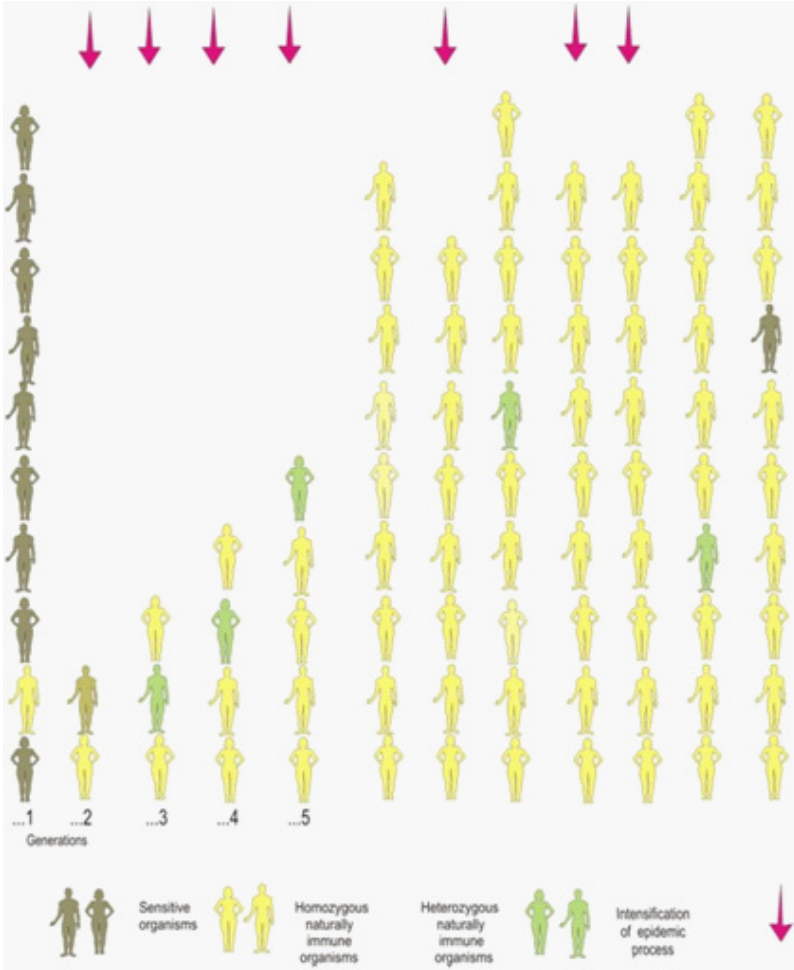

Figure 2: Hereditary immune state of a human population transformed by contra-infectious natural selection over the emergence (1) and further evolution (2, 3 , 4 ...) of epidemic process [36,37] updated.

The discovery of chemical ecology now plays a leading part in solving the problem under consideration. The roles which such chemical-ecological factors are playing in the selective stages of biomolecular evolution of humankind will be considered below. This sense of theirs is relevant especially brightly at analyzing those biotic interrelations in which the role of intermolecular interactions is the dominating one. The investigations of molecular anatomical structures should be considered as a prelude to understanding how they may act in health life and disease.

The promise of constitutional immunity that brought in widespread attention at the time, however, was its apparent ability to compare molecular constitution among different species populations and individuals. The comparative investigations of molecular anatomical structures should be considered as a prelude to understanding how infectious agents and molecular make-

up of hereditary immunity may act not only as the simultaneous movers of human descent and further evolution but also both in health life and in the disease state. What is more, their assemblage and combination with the data of molecular physiology are necessary to discover and elucidate the physiological aspects of molecular biology.

The discussed primary molecular ecological mechanism is not the sole driving force and regulator of molecular evolution. Other types of ecological interactions should also be mentioned as well. One may also suppose [33] that in the processes of molecular evolution, there may act a regularity similar to the correlation rule by J. Cuvier [38], according to which any change of one organ entails a change in all other organs connected to it. Molecular components of anybody 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 [33]. These secondary changes also play very important part in the fitness of organisms, thus additionally improving the efficiency of natural selection, which creates new forms trait by trait.

BIO-ECOLOGICAL CHRONOLOGY OF ANTHROPOGENESIS

The descent of first humans and further evolution of humankind had been initiated nearly 100 million years ago (mya). The myriad steps of anthropogenesis are currently divided into three principal ecological stages: the tropical forest stage; the savannah stage; and the stage of dispersion, when humankind migrated from the region of descent toward other parts of the Earth (Figure 3).

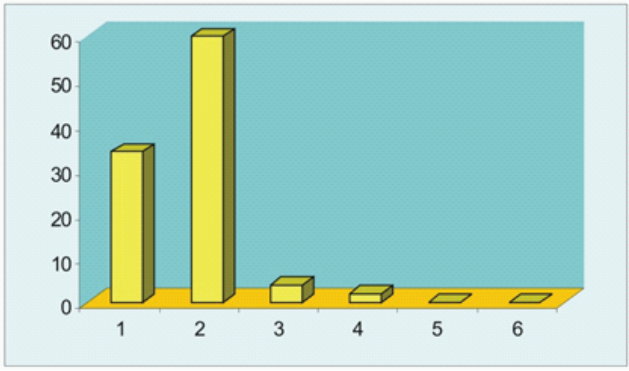

Figure 3: The duration of principal stages of evolution from earliest mammals to ancient humans (According to [12], updated):

*1. The tropical forest stage (*93.5 my*):*

a) The descent of insect-eating mammals, 33.8 my (1),

b) The descent of apes, 59.7 my (2);

2. The savanna stage 3.5 my:

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

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).

3. The dispersion stage:

a) The exodus of ancient humans out of African savannah and their further evolution over dispersion around the world, 0.06 my (6).

The data present in Figure 3 illustrate sharp differences in the dynamic of mammalian evolution toward the human descent and further evolution of humankind. However, the data do not explain the causes of differences. To fill in the gap, all the consequent stages will be considered below at the analysis of planetary and bio-ecological forces which moved the evolution of humankind.

From Earliest Mammals to Modern Humans

In the way from earliest mammals to the apes

The tropical forest stage has begun at Late Cretaceous geological epoch characterized by global warming of the Earth. The stage lasted 93.5 my and included period when the earliest human predecessors (insect-eating mammals) evolved over 33.8 my (Figure 1a, 3). The tropical forest provided the earliest mammals with numerous insects to feed on and perform intensive self-reproduction whereas stochastic mutagenesis and interbreeding formed the regular level of their inherent variability. These parts of preparative forces of evolution functioned with regularity and provided very wide biodiversity. However, the forces that could drove natural selection among earliest insect eaters were restricted by few avian and insect predators that could act on their evolutionary transformation very slow and with low intensity.

The influence of microbe/victim relationships was also restricted by their scarcity. 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, for example, through feeding, breathing and self-reproduction. Among these three, the alimentary transfer of infectious agents functions most widely and effectively. The intrusion of infectious agents inside the bodies of insect eating mammals through feeding could not be performed with appropriate efficiency. However some infections could exist even among earliest mammalian insect eaters (Box 1), for instance some nutritional infections as well as viral and protozoan infections transmitted by insects (malaria, tick borne infections), and avian or mammalian bloodsuckers (rabies). Such infections might be saved from holocaust through planetary disaster induced by asteroid impact that killed most forms of earth life including the dinosaurs and became a turning point in biotic evolution around the Cretaceous-Paleogene boundary [39].

Box 1

Supposed movers of evolution from earliest mammals to apes

Nutritional infections

Unknown
Trasmissive infections:

Malaria,
Tick borne infections,
Rabies

Nutritional infections could exist among earliest mammalian insect eaters but in very restricted forms. Food of insect origin could not serve as a major source of infectious agents dangerous for insects-consuming animals and thus did not execute intensive natural selection among them. Respiratory infections could not exist among insect eaters because the smallness of their populations, high mobility, and disunity. The same factors did not favor the transmission of sex-dependent diseases. More likely was the existence of infectious diseases (the ancestors of future malaria, tick-borne encephalitis, duple fever, and some others) transmitted by insect, and by avian or mammalian bloodsuckers (rabies) [11,12,16].

The rate and intensity of evolution of the insect eating mammals was restricted mainly by the sluggishness of selective agents that existed at the time. The selective power of life-threatening challenges was too weak to perform rapid evolutionary changes. However some of the insect eaters became able to climb into the trees. This achievement formed an important step toward the appearance of earliest apes. This initial process was continued and improved in the evolution of higher mammalian species, the ancestors of apes, and in consecutive descent of apes, that was performed over 59.7 my. Besides, it should be especially noted that successive progression of evolutionary development does not annihilate their initial executors which also continue to evolve over together with next generations of their prays [12,40,41].

The emergence of apes began around 65 mya when tropical forests spread all over the Earth's continents. The later descendants of earliest insect-eaters came to rely on a plethora of edible plants from the forest, and this change in diet set the stage for the initial emergence of herbivorous primates. The apes were plant eaters fed mainly by ripe fruits (rich in easily digested forms of carbohydrates) and tiny, young leaves (richer in protein) drawn from relevant plants. They obtained an estimated 94% of their annual diet from plants, primarily ripe leaves and fruits, which was supplemented with insects [42]. The tropical forest provided its inhabitants with vegetarian food of quality and quantity necessary for their intensive self-reproduction. Multiple random mutagenesis and genetic admixture continued to form regular level of their inherent variability.

Fresh vegetarian food could not serve as a source of infectious agents dangerous for plant-consuming animals. Vegetarian foraging restricted the interrelation of apes with infectious agents.

Thus the intrusion of infectious agents inside the apes' bodies could not be carried out through feeding. Respiratory infections also could not exist among herbivorous settlers of tropical forest because the smallness, high mobility, and disunity of their groups. The same factors did not favor the transmission of sex-dependent diseases. More likely was the existence of infectious diseases transmitted by bloodsuckers inherited from their insect eating ancestors. As plant-foods assumed increasing importance, selection gradually gave slow rise to the suite of traits that facilitated movement and foraging in trees [42].

Million generations of apes have changed, one after another, during this 59.7 my long period of very slow primate evolution until nearly 100 species of herbivorous apes have evolved including the predecessors of modern chimps, gorillas and Macaques emerged at 23.8-5.3 mya. Future humans shared a common ancestor with them 5–7 mya [43,44]. The tropical forest environment provided apes with very wide diversity of species and thus favored the preparation for future evolutionary transformations. In contrast, the scarcity of forces of natural selection that existed at that time was unable to exploit the achieved lot of selectable building materials [11,12,16]. Among these species only one, the predecessor of Australopithecus has been prepared to be accounted as the most probable ancestor of future hominids.

In the spurt descent of earliest humans

Toward the end of Pliocene (5.3 mya), the climate of the Earth changed dramatically. The global cooling dried out tropical woodland. The tropical forests shrank and were replaced by savannah grasslands. These sharp shifts transformed both flora and fauna in very large geographical areas. The existed herbivorous primates (over 100 species of apes) have forcedly lost the forest and appeared in the expanding grasslands. The changes of climate induced sharp transformation of environmental selective conditions for all primate species [11,12,16]. Absolute majority of vegetarian apes appeared to be unable to survive at these new conditions. The fauna of the Earth lost 90% of its vegetarian apes within this period of time. Meanwhile, the predecessors of modern chimps, gorillas and Macaques have avoided the worst influence of global cooling as well as subsequent holocaust and selection induced by the savannah environment. They escaped at the remnants of the tropical forest.

Beside, the new conditions induced the appearance of *Ardipithecines* (4.4 mya) and *Australopithecines* ("Lucy", 3.2 mya), the earliest members of human family. *Ardipithecus* had a brain and body the size of a chimpanzee, it did not knuckle-walk or swing through the trees like an ape. Instead, "Ardi" walked upright reveals the first ancient anatomical changes that laid the foundation for upright walking. However "Ardi" still must have spent a lot of time in the trees [45]. Following a supposition, it should be noted that unlike herbivorous chimpanzee and other apes of tropical forest "Ardi" likely fed both in trees and on the ground and probably was more omnivorous than chimpanzees (ripe fruit specialists). It apparently consumed only small amounts of open-environment resources, arguing against the idea that an inhabitation of grasslands was the driving force in the origin of upright walking [46].

Like modern chimpanzees, monkeys and prosimians as well as other apes, contemporary to it, Australopithecus was small-bodied, small-brained bipedal vegetarian hominid, but its brain was not appreciably larger than those of today's apes. It was well adapted to find food products that have been provided by tropical forests and thus obtained adequate nutrition with a certain amount of energy, vitamins and amino acids. Like 'Ardi" *Australopithecus* had a brain and body the size of a chimpanzee but walked upright and did not need to live in the trees [47]. Probably it was more omnivorous than chimpanzees and even *Ardipithecus.*

The primates in the expanding savannah areas must have faced many new dietary challenges. New ecological conditions forced them to eat whatever was at hand. Instead the plethora of ripe fruit and other moist tropical products they get the choice to eat either dry grass that provided low energy for former tropical feeder or the bodies of hunted and dead animals that were extraordinary rich both in easily digested forms of proteins and carbohydrates as well as in vitamins and minerals. The former fruits eaters have been forced to become the meat-eaters, either as predators or the consumers of carrion.

Extraordinary importance of the meat-eating for human evolution has been accentuated by numerous anthropologists. The data of recent investigations continues to confirm the paradigm [48]. But the intimate forces of this influence were discovered only just recently [11,12,16,49]. It was integrated that on the one hand, the proper and diverse savannah's food provided newcomer apes with a capacity to probably intensive self-reproduction, i.e. with relatively large quantity of various mutations.

But on the other hand, the new way of nutrition brings the new omnivorous feeders in contact with a lot of various animal sources of new food and a plethora of very harmful infectious agents inhabiting the bodies of hunted or died animals. Among the new infectious agents to be named (Box 2), include the broad set of bacterial nutritional infections associated with the forage of animal origin (anthrax, botulism, salmonelloses, brucellosis, enteral clostridioses and many others). Beside, the necessity of movement and foraging on the ground as well as confrontation with various predators inevitable led to the rise of traumatism and dangerous traumatic infections (tetanus, has gangrene).

Box 2

Supposed movers of evolution from apes to ancient humans

Trasmissive infections:

Malaria,
Tick borne infections,
Rabies

Enteral infections:

Anthrax,
Botulism,
Salmonelloses,
Brucellosis,
Clostridioses

Traumatic infections

Tetanus
Has gangrene

Most of the infections were absolutely new for yesterday's eaters of tropical fruits. They did not meet the infections before and thus were not subjected to the transformation of their molecular constitution through the selection by infectious movers of evolution. Because most known infectious agents are able to kill modern herbivorous animals [50], one can approve its ability to affect their archaic predecessors too. Besides, the savannah's new settlers were not able to avoid and reject infected exemplars among the herds of hundreds healthy animal or birds. On the contrary, it is well known that the diseased animals are caught by hunters more easily than the healthy ones.

The set of the above considered data implies that not climate change itself but infectious epidemics which have been conditional upon it, could be primarily responsible for wiping out most vegetarian apes including the *Ardipithecus* and *Australopithecus*, the most acknowledged ancestors of future hominids. The descent and subsequent extinction of Australopithecus lasted 2.7 my (between 4.5 mya and 1.8 mya).

The *Australopithecus* predecessors of human chose the last of the two nutritive choices and began to eat the corpses of died animals including relatives. On the next step they could begin to hunt. Though by inheritance a vegetarian primate, the nearest predecessor of future humans began to become a predator and carrion eater. Most Australopithecines perished being unable to counteract the cruel selection and were replaced by first representatives of *Homo* genus. In the beginning of Pleistocene that has gone 1.8 million years before present time; the last of consecutive species of *Australopithecus genus* went extinct. But some of its mutant descendants appeared to become constitutionally immune and thus were able to counteract all these life-threatening challenges of infectious origin. The survivors got larger brains and became the founders of Homo genus. The infections could improve inherited immunity through natural selection continuously performed by relevant epidemic processes. Modern science is able to

observe numerous of immunological traces of archaic epidemics (Section 2) that give evidence of this statement [12,16,51].

In addition to infectious and immune movers of evolution, the small-bodied hominids may become the catches of many savannah's predators, including wild cats (tigers, lions, leopards, hepards), dogs, wolfs, hyenas, foxes, snakes, crocodiles and birds (hawks, raptors, toucans, owls) [52]. In contrast with analogous tropical challenges selective influence of predators on the savannah stage became too far stronger. For instance, although the rabies infection could emerge over the evolution of insect eaters and apes, the environment of savannah could lead to the intensification of its impact on the evolution of apes toward *Homo sapiens*.

Ecologically, distribution of rabies infection is mainly associated with both raptorial birds (eagle, hawk, owls) and mammals (bats, bears, cats, civets, dogs, hyenas, mongooses, raccoons, weasels and so on) as well as with their victims that mainly inhabit the open areas such as the savannah. The transmission of rabies virus between raptors and their victims is usually performed by bite, scratch, salivation, and by gobbling of untreated flesh including milk [53]. Undoubtedly, this association arose long before the appearance of humans forebears. The forced settling of human predecessors (*Ardipithecines* and *Australopithecines*) on the very open spaciousness of savannah grassland (5.3 mya) inevitably brought them into a state of intensive confrontation with many predatory species that led to the adoption of rabies infection by humankind and to the selection for hereditary immunity against the disease. The traits of hereditary immunity of human against rabies are now traced on epidemiological, clinical and cytological levels [12,54]. About less than 0.001% of current world population die of rabies every year [55]. Over 99.9% of current humans resisted rabies thanks to the legacy inherited from their very ancient predecessors.

The mutual impact of infectious agents and immunogenic selection began in the savannah stage of human evolution (3.5 mya) and led to the appearance of *Homo sapiens* (1.8 mya). The newborn species of the *Homo* genus appeared to have been inherited from their evolutionary ancestors both their place in the relevant ecological system and the immunity to rabies, malaria and tickborn encephalitis. The infections could improve inherited immunity through natural selection continuously performed by relevant epidemic processes. However the impact of new infection (anthrax, botulism, salmonelloses, brucellosis,alimentary clostridioses, tetanus, has gangrene and so on) must be counted as fare more vigorous.

The new challenges gained paramount importance for the intensity of subsequent humankind evolution. The duration of the savannah stage of human evolution was extraordinary short and successful, it lasted less than 5.3 my but included the descent not only of *Australopithecus* genus but also the many subsequent species of Homo genus, a highest achievement of evolution with the known plethora of its unprecedented features. The high speed of Australopithecus stage of human evolution confirms the efficiency of creative agents acted at that time, their extraordinary high intensity and unusual quality of natural selection toward principally new features which

were able to perform the life-saving functions at the face of life-threatening challenges functioned at this ecological environment.

The *Australopithecus* predecessors of human chose forcedly the last of the two nutritive choices and began to eat the corpses of died animals including relatives. On the next step they could begin to hunt. Thus the nearest predecessor of future humans began to become a predator and carrion eater. Most Australopithecines perished being unable to counteract the cruel immune selection and were replaced by first representatives of Homo genus. In the beginning of Pleistocene that have gone 1.8 million years before the present time, the last of consecutive species of *Australopithecus genus* went extinct. But some of its mutant representatives appeared to become constitutionally immune and thus be able to counteract all these life-threatening challenges of infectious origin. The survivors got larger brains and became the founders of Homo genus.

The *Homo* genus began to emerge over the end of Pliocene under the influence of the same selective agents. Early species of *Homo* were similar in body size and shape to *Australopithecus* but had notably larger brains and relevant skills. These species were replaced by even larger-brained *H. erectus* and then by *H. sapiens,* which has the biggest brain of all. In parallel with the increases in brain size, many other amazing anatomic changes were also occurring in the *Homo* genus.

The meat-eating strategy was forcedly adopted by primates to cope with the dietary challenges of the savannah's environment. It influenced profoundly the evolutionary trajectory of the primates order, particularly that of the anthropoids. This kind of food put them in contact with wide 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 a couple with other selective agents of the savannah's environment, the newly met agents have performed very important role on the way from apes to modern humankind.

In response to this challenge, natural selection gradually gave rise to the suite of traits most of which facilitate the surviving in the fight against the infectious agents. Now the traits first of all the constitutive (i.e. genetic) immunity to a plethora of harmful microbes are regarded as characteristic of both modern humans and their carnivorous predecessors. The molecular selection and subsequent evolution of molecular constitution became far more intensive and extensive. It was a most significant event that moulded the human history. As the relicts of such intensive selection, that began 1.8 my ago, most modern people as well as their evolutionary ecological omnivorous satellites are characteristic of very strong inherent immunity to many known infectious diseases. As a secondary result of this process the relevant macro-anatomical transformations appeared to be performed, for instance, the stature increased, and finally unprecedented mind arose.

Over out of africa dispersion

According to the generally accepted Out of Africa Theory and its latest development, early *Homo*

sapiens, the species of anatomically, physiologically and immunologically analogous to modern humans emerged in the Africa's savannah [3]. The time of it first appearance is currently dated from around 0.195 mya according to the age of its earliest known fossil [45]. This stage of human evolution led to the establishment of *Homo sapiens*, a species with a plethora of unprecedented structural, physiological and technological features that make it unique in comparison with any other animal species, including its chimpanzee-like predecessors, and other African apes.

Except for the bipedality inherited from *Ardipithecus* through *Australopithecus*, the early *Homo sapiens* differed from ape ancestors in that they had a far bigger brain, naked body, the ability to run, could use primitive tools and elaborate on them. It also had a crude ability for conscious thought and speech. The unique set of human differences included not only multiple physical traits such as a cranial vault with a vertical forehead, a rounded occipital and reduced brow ridge, a reduced facial skeleton lacking a projecting mid-face, a lower jaw sporting a chin, a short stature with a height of near 1.2-1.4 m, similar to modern pygmies and bushmen, a less robustly built skeleton, and a specifically naked body [56] among others. Thus early *Homo sapiens* possessed an anatomical make-up essentially like modern human. Its technological features were characteristic of the Middle Paleolithic period that lasted between 100,000 and 40,000 years ago [57].

Besides, they possessed the ability to control thoughts, emotions, and actions; plan for future events; self-reflect and be self-conscious; create and use primitive language; imitate and learn socially in particular ways; use episodic memory; imagine and use creativity; cooperate and show altruism; develop theory of mind; and many others. The uniqueness of some features is now traced to cellular and molecular architecture levels, including those within the genome [58]. The possession of any of these features was initiated by a relevant change in a genome molecule, followed by the subsequent transformation of the molecular phenotype through natural selection acted on by physical, chemical, and bioecological agents.

The analysis performed above allows the update of this list with the traits of hereditary immunity against anthrax, botulism, brucellosis, typhoid fever, other salmonelloses, and so on. Besides, mutual evolution of antagonistic infectious species inevitably resulted to the emergence of microbial subspecies among which the *Clostridium botulinum* types A, B, C, D, E, F, G as well as innumerable variants of other alimentary *Clostridium* [41] and *Salmonella* genus can be named, for instance. The traits for inherent protection against enumerated alimentary infections today belong to the majority of current members of *Homo sapiens* species too.

But the driving of humankind evolution forced by natural selection for hereditary immunity was not finished at that time. Nearly 75,000 - 62,000 ya, some small (20-60 persons) groups of early *Homo sapiens* began to sweep out of the African Savannah territory where their descent and initial establishment had been accomplished [4]. This initiated the dispersion of humankind around the world (Figures 1 and 3). Over the dispersion, different groups of middle paleolithic humankind appeared in epidemiologically various ecological environments but in some cases

even in strong geographical isolation of subpopulations from one another. These circumstances performed very deep impact on the differences in the rates and quality of their consequent evolution.

Some groups of migrants moved out of the former savannah's "Eden" back into the remnant of tropical forest that was the homeland of their faraway vegetarian ape predecessors. In the reawaken tropical environment this branch of ancient humankind met the same agents of natural selection that induced evolutionary transformation of insect eating mammals into herbivorous hominid apes (Box 1). This part of ancient humankind became inaccessible for other movers of human evolution (Boxes 2 and 3) up to the Epoch of Great Geographical Discoveries i.e. over 50,000 years.

Other groups began migrations along either South Asian or North Eurasian directions. All non-African populations of humankind currently living in the world were probably derived from a single small (20-60 persons) dispersal of early humans out of Africa [4]. The south branch of Asian migration has continued toward Australia. Over this period of time (nearly 20,000 years) the ancestors of current Aboriginal Australians performed the change of genes between the carriers of Neanderthal and Denisovian genomes segments. Then they split from the ancestral Eurasian population and eventually reached Australia ~50,000 ya. Since then, the first settlers of Australian continent lost any interrelations with other parts of humankind. For 50 millennia this branch of *Homo sapiens* has been in almost total isolation from other subpopulations of the species [4] as well as from the set of new immune drivers of human evolution (Box 3) that have born later among Eurasians. In contrast to Australians, American subdivision of humankind has split from Eurasians by geographical barriers fare later, nearly 15,000 ya [59].

Box 3

Supposed movers of human evolution over dispersion around the world

Trasmissive infections:

Ancient malaria,
Tick borne infections,
Rabies

Enteral infections:

Anthrax,
Botulism,
Salmonelloses,
Brucellosis,
clostridioses
and many others

Traumatic infections

Tetanus
Has gangrene

Infections of social intercourses:

Influenza
Measles
HIV/AIDS
Tuberculosis
Smallpox

The new immune/infectious movers emerged among the Eurasian branch of humankind after African, Australian and American subdivision of the species were physically separated from Eurasian by geographical barriers. Consequently, influenza, measles, HIV, tuberculosis, smallpox could impact only on the evolution of the Eurasians. The named movers could include in the evolution of Indigenous Americans, Africans and Australians only under the impact of Grate Geographical discoveries, i.e. about 600 ya.

Opposition to influenza

Influenza viruses make up three of the five genera of the family Orthomyxoviridae: Influenza virus type A, Influenza virus type B and Influenza virus type C. Influenza virus type A has one species subdivided into many different subspecies (H1N1, H2N2, H3N2, H5N1, H7N7, H1N2, H9N2, H7N2, H7N3, H10N7, H7N9). These subspecies are perpetuated in aquatic birds, particularly in waterfowl seasonally migrating from South East Asia to North Asia and back. Possible cooperation of influenza viruses with other aquatic inhabitants including invertebrata and protozoa should be investigated too [60].

All of the registered human pandemics were induced by just three of these viruses (H1N1, H2N2 and H3N2). Other subtypes of influenza A virus, as well as types B and C, induced neither pandemics nor epidemics among humans – only small outbreaks. According to a WHO estimate [61] only 0.008% of the current world population dies of influenza per year. The majority (99.992%) escape the death thanks to their intrinsic traits of hereditary immunity [12,62]. That

means the result of cruel selection that has been performed beginning from the first appearance of influenza virus among ancient humans which should initially be extremely susceptible to the infection. But the indigenous populations of American and Australian continents did not possess such protective traits. Before European colonization of these continents they were extremely susceptible to influenza. Originally they were highly susceptible non-immune races.

The indigenous peoples of North and South America had entered these continents nearly 15,000 years before the present. The sizes of their populations have remained essentially constant for many millenniums. But that all changed when Columbus's discovery of the New World launched relentless waves of European colonization that brought to the continent some new infections including influenza. The newly arrived infection effect on the Amerindians was devastating. It was a weapon so powerful that Native Americans feared it more than bullets and swords [63,64].

Crucial epidemics resulted in significant population declines among Native Americans during even the 16th century i.e. more than 10,000 years after they entered American continent. The performed depopulation was not localized to particular regions or communities, but was instead likely to have been widespread or to have had an especially severe impact on the most populous regions [64]. At the same time, the infection was not as dangerous for Europeans as for Native Americans. The populations of European conquistadors and colonists increased sharply over the same period. Most Europeans had acquired heritable immunity against influenza long before the time of the great geographical discoveries.

Aboriginal Australians are the direct descendents of the first people who left Africa and arrived on the Australian continent some 50,000 years ago. Since reaching Australia ~50,000 years (Figure 1), this very ancient branch of *Homo sapiens* has been in almost total isolation from the main population of the species [4]. Colonization of the continent by Europeans began in 1780. The first colonists brought into the aboriginal population viral infections including influenza. The consequent epidemics laid waste to the indigenous populations of the entire continent.

Thus, the integration of historical and epidemiological data about the first intrusion in the aboriginal Australian population of influenza reveals very high susceptibility of aborigines to influenza in contrast to the inhabitants of the Eurasian continent. These facts evidence the virginity of the Australian branch of *Homo sapiens* in relation to influenza that existed over ~50,000 years and was only broken near 200 years ago. This can be taken as evidence that influenza could not impact the Eurasian part of humankind between 50,000 years and 15,000 years.

These facts allow for conclusion to be drawn that influenza infection has not impact the evolution of indigenous Americans and Australians before the European colonization of these continents. In contrast, the Eurasian population of humans adopted the disease after the exodus out of Africa (60,000 years) but after isolations of Australians (50,000 years) and indigenous

Americans (15,000 years before the present). Thus, final estimation of the first impact of influenza on the evolution of human is <14,000 years. This anthropological and historical event should be located on the Eurasian territories.

Opposition to measles

Most currently living people are inherently immune to measles infection. Before the widespread global use of measles vaccination in 2001, the disease killed 0.4% of the worldwide population in 1980 [65] and nearly 0.1% in 2000 [66]. Epidemics of measles are currently a major cause of very high childhood mortality in equatorial West Africa. This evidences the performance among ancient humankind of very strong natural selection for saving traits of hereditary immunity against the disease.

Meanwhile, infection with the same virus may be extremely disastrous for people whom ancestors did not confront this specific infectious agent. Such disastrous effect of firstly arose measles epidemics happened to the primary settlers of Australia when European newcomers wrecked 50,000 year-long isolation and brought to indigenous Australians aborigines a set of viral infections including measles (Webb, 1995). The same occurred with the primary settlers of America, whose isolation was broken nearly 500 years.

The integration of the above considered epidemiological, immunological and anthropological data and their sensing from the position of evolutionary ecology of infectious diseases allow for the estimation of the emergence of human measles in the territory of Eurasia not earlier than 14,000 years ago.

Opposition to HIV

The date of the first appearance of HIV epidemics among humans was initially identified as being 12,000 years before the present [10]. Later, the emergence of HIV as a human pathogen was identified as being between 700 and 2900 years ago [67,68]. This statement was based on the supposition that the Vikings had genetic immunity against the infection. In contrast, more later discoveries have pointed out that HIV originated in west-central Africa near the beginning of the twentieth century i.e. near 100 years ago [69].

Recently, the integration of current observations on HIV epidemics with the dates of evolutionary immunology, epidemiology and anthropology provide us with a more fundamental basis for the answer on the question [70]. The research was performed over the series of consecutive stages [8-10,12-14,70,71]. Firstly, the data of current worldwide epidemics of HIV was summarized and re-sensed from the viewpoint of evolutionary immunology.

The 30 years of worldwide testing of various human populations for the presence HIV infection created more than exhaustive and very informative picture of the prevalence of relevant epidemics among different parts of current humankind. The achieved data were extracted from the plethora

of scientific publications and united in official documents of the Joint United Nations Programme on HIV/AIDS [72] and the USA Centers for Disease Control and Prevention. For the goals of our investigation the lots of selected data were used. The populations of territories characterized by opposite levels of HIV prevalence were selected and used for further analyses.

The first result achieved by evolutionary immunology evidenced that most of current humankind possess heritable immunity against HIV/AIDS infection. During 2005, 3.1 million people (0.048% of the world population) died of HIV-related illnesses (UNAIDS, 2006) whereas more than 99.9% of currently existing population appear to be able to resist the epidemics. The remains of ancient HIV epidemics are now present everywhere in the world, but with different levels of intensity (Figure 4).

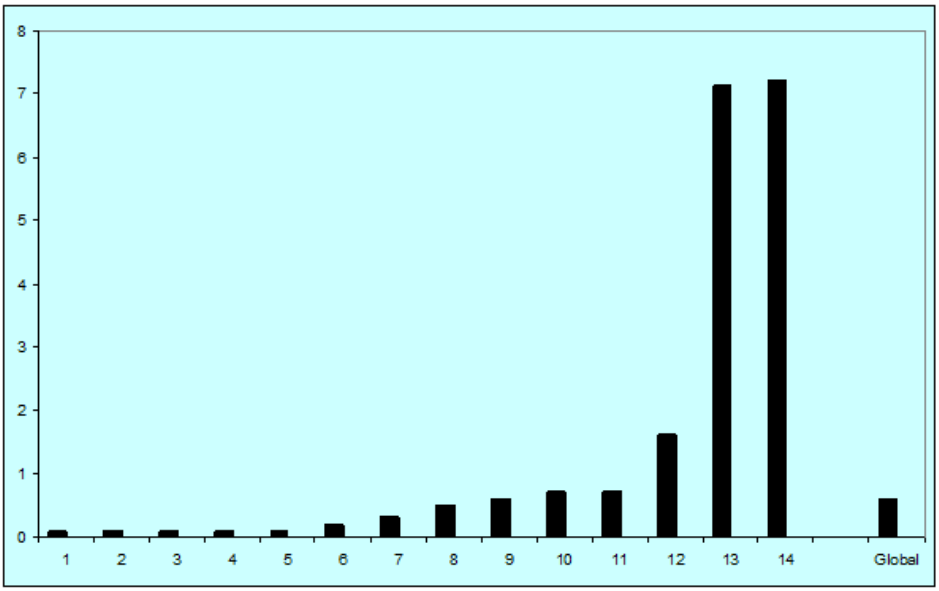

Figure 4: Difference in HIV prevalence among worldwide human population: Asians and Pacific Islanders (1), White Americans (2), East Asians (3), American Indians (4), Alaska Natives (5), North Africa/Middle East (6), Western/Central Europe (7), Oceania (8), Latin America (9), South/South-East Asia (10), North America (11), Caribbean (12), Afro-Americans (13), Sub-Saharan Africans (14). According to [14].

The populations of Sub-Saharan Africa are the worst affected. The region is home to about 10% of the world's population, but is home to 63% of all people living with HIV (UNAIDS, 2006). In contrast, the populations of North Africa are characterized by the lowest levels of the HIV-epidemics intensity. Half of all new HIV infections in the United States are among black individuals, who represent only 15% of its overall population [73]. For instance, among 15,135 American patients with HIV, 53.6% were black.

The most opposite levels of HIV prevalence revealed and grouped among African countries are

present in Table 1. One group of 10 countries had highest prevalence of HIV. The opposite group included 10 countries of lowest prevalence.

Table 1: Opposite levels of HIV prevalence among African countries.

The levels of HIV prevalence (%) in 2009			
The countries of highest prevalence [H]		The countries of lowest prevalence [L]	
Countries	Levels	Countries	Levels
H1.Swaziland	25.9	L1. Sudan	1.0
H2. Botswana	24.8	L2. Mali	1.0
H3. Lesotho	23.6	L3. Senegal	0.9
H4. South Africa	17.8	L4. Niger	0.8
H5. Zimbabwe	14.3	L5. Mauritania	0.7
H6. Zambia	13.5	L6. Somalia	0.7
H7. Namibia	13.1	L7.Madagascar	0.2
H8. Mozambique	11.5	L8. Algeria	0.1
H9. Malawi	11.0	L9. Morocco	0.1
H10. Kenia	6.3	L10. Egypt	0.1

The differences are extraordinary sharp. For instance, in contrast to population of Swaziland [H1], the populations of Algeria [L8], Morocco [L9] and Egypt [L10] reveals ~260 fold resistance to HIV. The population of Mozambique (H8) is more than 100 fold less immune in contrast to geographically neighboring Madagascar (L7). The level of HIV prevalence in Kenia (6.3) is nine fold higher in the contrast to territorially neighboring Somalia (0.7).

The results of the attempt to understand the genetic and evolutionary reasons for this racial susceptibility were published at the beginning of 1990 [8-10,71] according to which the indigenous Africans were subjected to evolutionary impact of discussed infection incomparably later then indigenous Eurasians. The Sahara desert formed a geographical barrier between indigenous Africans and other parts of the populated world. Indigenous Africans could not be subjected to evolutionary impact by HIV infection and begin to elaborate heritable immunity against it. These conclusions were confirmed very soon [74,75]. The isolation of Indigenous Africans from the pandemic could probably begin to be broken only after oceanic voyages of Vasco da Gama (1497) and other Portugal sailors.

The data stated above indicates that many native inhabitants of the sub-Saharan tropical region and even their far later relatives who were transplanted to America are in sharp deficit of hereditary immunity against HIV infection. That means that their ancestors did not face this kind of virus in their ancient evolutionary history, and were thus not exposed to natural selection for hereditary immunity against HIV infection as well as to appropriate evolutionary process.

The intercourse of the sub-Saharan African branch of *Homo sapiens* species with their Eurasian relatives was interrupted 60,000-70,000 years ago when the ancestors of Eurasians moved east. This means that the emergence of human HIV infection, as well as the launch of hereditary immunity of Eurasians against HIV, cannot have occurred earlier than 60,000 -70,000 years ago.

The HIV infection could also not have emerged and involved in human evolution after 14,000

years ago otherwise indigenous Americans would not demonstrate so very expressive immunity against HIV. The beginning of HIV epidemics among humans should thus be dated between 12,000 and 14,000 years ago and located on the Eurasian continent, since the HIV epidemics exist without interruption thanks to unbroken transmission of the virus from a susceptible people to another one.

The ancestors of Australian aborigines also left Africa 60,000-70,000 years ago. They concluded their wanderings 50,000 years ago (Figure 2) and since then lost intercourse with the main part of humankind. Now, indigenous Australians are at greater risk of HIV transmission than non-indigenous inhabitants of the same country. There are similarities between the epidemiology of HIV infection in indigenous Australians and that observed in sub-Saharan Africa [76]. For instance, in contrast to Eurasians, heterosexual intercourse is the main route for HIV transmission among aboriginal Australians, and women have a greater vulnerability of acquiring HIV.

Indigenous females were 18 times more likely to be infected than non-indigenous females, and three times more likely than non-indigenous males. Notification rates for HIV infection in indigenous people have been higher than in non-indigenous people. Indigenous males were twice as likely as non-indigenous males to be infected with HIV [77]. Indigenous Australians did not show the decline in HIV that occurred among non-indigenous Australians [78]. Nevertheless, the Australian HIV epidemic situation is complicated by very specific ethnic peculiarities: the aboriginal sexual network strongly identifies who is having sex with whom, how often and where. What is more, the beginning of HIV epidemics among aboriginal Australians and the launch of appropriate selection for hereditary immunity can be induced over two hundred years ago by European colonization. But before then, they were discussing epidemic process and relevant evolutionary influence.

Opposition to tuberculosis

Until recently, it was hypothesized that tuberculosis was acquired by humankind over the development of agriculture around 9,000 years ago [79]. According to this hypothesis, TB would have been introduced into a human subpopulation over dispersion of humankind around the world but far after their exodus from Africa and one would have predicted, unless other infectious diseases provided comparable selective pressures on human fitness and reproduction, that the current human populations would exhibit extreme traits of susceptibility [80], such is not the case. In contrast, most of the current worldwide populations do not suffer from Tuberculosis (TB) even though in big crowded cities they are inevitably meet with TB bacilli.

Tuberculosis kills ~0.02% of the worldwide population annually [81] whereas other 99.98% are resistant. Acute tuberculosis, which can kill a patient in two or three weeks, has practically been done away with. Meanwhile, such a galloping form of TB prevailed in 16-19th centuries among indigenous Indians and Africans when Europeans brought in with them this infection during the colonization of America and Africa [64]. After European occupation of Australia,

tuberculosis also became a major cause of mortality among aborigines, as did influenza, smallpox and measles [82]. According to our estimation, this might indicate that humankind could not have been exposed to tuberculosis-mediated evolution by means of selection for hereditary immunity before geographical isolation of the settlers of sub-Saharan Africa (60,000-70,000 years ago) as well as the aboriginal Australians (50,000 years ago) and American Indians (15,000 years ago). The emergence of tuberculosis mover of human evolution should be referred to between 9,000 and 14,000 years ago and located on the territory of Eurasian continent.

Opposition to smallpox

In the beginning of European colonization (1788), Australia had probably between 750,000 and 1000,000 people. During the European colonization of Australia, the health of the aboriginal population declined rapidly in the face of highly infectious diseases that emerged at the time. The first smallpox epidemics emerged as early as 1789 at Sidney Cove. The bodies of aborigines were reported floating in the Sydney harbor and found in foreshore rock shelters. Two years later, almost half of the entire indigenous population died in the smallpox epidemic of 1789 and it is said that only three people were left by 1791. As a result a Sydney aboriginal population of 1500 peoples was reduced dramatically just over the first years of European contact [82]. The integration of this historical fact with the absence of hereditary immunity against smallpox among aboriginal Australians evidences that the intrusion of smallpox in the process of humankind evolution could not have occurred before 50,000 years ago.

The smallpox epidemics brought in America by European colonist induced widespread mortality among indigenous Americans too. For instance, according to the records of Franciscan friar Fray Toribio de Benavente, during the 16th century the Mexican territory was extremely full of people. But when the smallpox began to attack the Indians it became so great a pestilence among them that in most provinces more than half the population died [83]. Recent comparative researches of genome's ancient and contemporary mitochondrial sequences confirmed that Native American populations suffered a significant contraction in population size some 500 years before the present i.e. just at the beginning of the conquest [84]. Because the isolation of indigenous Americans from the Eurasian population occurred 15,000 years ago [59], the emergence of smallpox and the selection for hereditary immunity against the disease could not have occurred before this date. Thus the estimation of first inclusion of smallpox in the evolution of Eurasian part of humankind can be present as <15,000 years ago. American, Australian, and African branches of humankind were implicated in the epidemics incomparably later.

Two kind of evolutionary ecological movers play the leading part during the triggering events and further progression of biotic evolution. The first ones is the life threatening impact on a population of the agents of cruel molecular ecological relations between species. This kind of evolutionary movers includes mainly infectious agents, animal venoms, plant and fungal poisons. The second kind of evolutionary movers includes the agents of hereditary immune defense of

attacked population against the impacts of the first kind. The movers of both kinds function mutually and perform conjugated selective impact on the biotic evolution. Infectious and immune anti-infectious movers perform most influential impact on the discovered process.

The first revolutionizing impact of recently emerged infections and immunity on human evolution was performed during the evolution from apes to earliest *Homo sapiens* on the territory of African Savannah. Second revolutionary impact was processed over the dispersion of humankind out of Africa around other parts of the world. It was associated with the emergence of influenza, HIV/AIDS smallpox, measles, tuberculosis on the Eurasian territories between 50,000 and 15,000 years ago. It resulted in colossal improvement of intellectual capabilities of Eurasians. Australian, African and partially American branches of Humankind did not participate in this part of the process up to the epoch of the Great Geographical Discoveries.

CONCLUSION

The evolution of Humankind has resulted long-term development of mammalians from earliest insect eaters to vegetarian apes (33.8 my) and then from apes to the first Hominids (59.7 my). The way from the last ones to *Homo sapiens* has continued 3.5 my. Modern anthropology successfully states these stages of human evolution through the investigation of prehistoric bones and by comparing prehistoric genomes to current ones. But much remains a mystery as to how *Homo sapiens* emerged so suddenly over African Pleistocene (1.8–0.2 mya) and then evolved into *Homo sapientibus* over 0.1 my further dispersion around the world.

The moving forces of the processes that have acted on the stages of human evolution remain uncovered. The present analytic investigation is devoted to the try to integrate recent results in the revealing original ecological causes of anthropogenesis at the time of it decisive stages. Special attention is paid to the discovering of exceptional forces of natural contra-infectious selection that arose in the ecology of human predecessors at the time and to the evaluation of hereditary immune traits of modern humans that can be considered, retrospectively, as specific relicts of this selection (Table 2).

Table 2: Consecutive intervention of most probable movers in human evolution.

Main stages humankind evolution of	Conditions		
	Climate	Duration (my)	Most probable executors of contra infectious natural selection
Evolution of insect eating mammals	Subtropical and tropical forest	33.8	Nutritional infections of ancient insect eaters Viral and protozoan infections transmitted by bloodsuckers (Malaria, Tick borne encephalitis, Rabies
Evolution of apes		59.7	Nutritional infections of Herbivores
Evolution from apes to Homo genus	African Savannah	3.5	Nutritional infections of Meat eaters and Euryphages (Anthrax, Botulism, Salmonelloses, Tetanus Brucellosis, Has gangrene, Enteral clostridioses)
The descent of *Homo sapiens*	African Savannah	1.8	
Variations of the quality of natural selection over wandering of different folks around the Earth	Ancient Eurasian (South-Asian, Near East and European Territories)	0.06	Influenza (<14,000 ya) HIV (12,000-14,000 ya) Smallpox (<14,000 ya) Measles (<14,000 ya) Tuberculosis (9,000-14,000 ya)

The achieved results, present supporting evidence on exclusive role of alimentary meat associated infectious epidemics, have played in driving the descent of humankind. The most intensive time these moving-forces have functioned was 5.3–1.8 mya, during the African savannah stage of anthropogenesis. The selection of this kind continued during the 1.8 my establishment of humankind both in the region of genesis and over subsequent 0.1 my dispersion of some wandering tribes around ecologically different parts of the earth where they were forced to oppose new cruel causative epidemic agents (influenza, measles, HIV, smallpox tuberculosis and so on). The dates and geography of these counteractions were estimated through the integration of relevant data of anthropology, ecology of contra-infectious natural selection, immunology, genetics and epidemiology of infectious diseases.

The integral approach used for the present discovery provides innovative framework and landmarks for existed ancient DNA studies of the history and evolutionary geography of both humankind and its different ethnic populations. It affords major opportunities at least in two areas: studies of population history and studies of natural selection. Bio-ecological aspects of human subsistence and further evolution should be among main sources of the studies of the history of humankind. The signs of ancient bioecological selection should be searched for in the architecture of human genome and phenome. They can form new promising directions for future research of many undiscovered mysteries of ancient evolution, current persistence and future development of humankind.

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