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Full Length Research Paper

Dating of first emergence of human epidemics

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Abstract

This article presents initial results of the attempt to date the conditions, terms and places of the first emergence of some actual human infections. The investigation was based on the integration of relevant achievements of evolutionary immunology, epidemiology and anthropology. Nutritional infections associated with food of animal origin (anthrax, botulism, brucellosis, salmonelloses) as well as the launch of hereditary immunity against them first emerged on the territory of the African Savannah 5.3 mya among ape ancestors of *Australopithecus* (4.5 – 1.8 mya), and were then inherited by *Homo sapiens* (1.8 – 0.2 mya). Rabies infection appeared among the earliest humans over the same period of time. Infections whose existence depends on regular transmission could have been got by early humans over their wanderings out of Africa (60K-70K ya) in ecologically varied parts of the World especially on the Eurasian territories. It was here that human tuberculosis and influenza infection (between 50K ya and 15K ya), smallpox (between 15K ya and 8K ya), measles (not earlier than 15K ya), and HIV infection (between 12K ya and 14K ya) emerged. After their origin, both groups of infectious epidemics and the phenomenon of hereditary immunity against them continued to exist among humankind up to now.

Keywords: Anthropogenesis, epidemiology, evolution, hereditary immunity, infectious diseases, public health.

INTRODUCTION

Integrated results of both current and retrospective observations on epidemic processes indicate that the threat of infectious diseases has begun to diminish toward the end of the 20th century of the second millennium. The majority (over 90%) of the world's population remains uninfected. Most infected individuals (far over 90%) are in abridged progress to full-blown disease, being able to 'wall off' infectious agents inside restricted patches of affected tissue.

The Spanish influenza H1N1 (1918–1919) was the deadliest human pandemic in the recent history of humankind. It spread across the globe and killed more people than any other disease of similar duration. The pandemic annihilated close to 2% of the global population of the time (Ungchusak et al., 2005). At the same time, a significant proportion of humans were saved from the disease by their hereditary immunity to influenza (Rumyantsev, 2006). The recent 2009 pandemics of H1N1 influenza had a hundred times fewer victims (Lipsitch et al., 2009). The cases of *Salmonella typhi* infection killed about 0.009% of the worldwide population annually (Pang et al., 1998). Tuberculosis, one of the world's most pernicious diseases, currently kills approximately 0.02% of the world's population each year (WHO, 2009).

Analogous decreases are currently characteristic of any known infectious disease. Although over 30 bacterial and viral agents are included in the list of most dangerous

infectious agents (Centers for Disease Control and Prevention, 2010), only a small portion of the world's population currently suffers from infectious diseases (Rumyantsev, 2008). Epidemics of infectious diseases have, it seems, entered their dark age (Tibayrenc M, 2001).

This considerable decrease in the intensity of epidemics has resulted from the complex of epidemiological, hygienic, immunological, and pharmacological efforts made during the 20th century as well as by natural evolution of epidemic processes (Rumyantsev, 2008; Rumyantsev, 1997). Nevertheless, complete eradication of epidemics continues to be elusive. Many questions about the nature of infectious diseases and their variegated pandemic spread have not received the answers they deserve. One of the principal uncertainties surrounding human pandemics is related to the initial source of their origin: how, where and when each of the number of infectious diseases emerged for the first time and began its epidemic spread. These questions are of great theoretical and practical interest to both scientists and non-scientists.

Although humankind's confrontation with the existing set of life-threatening microbes has a long history (Khor and Hibberd, 2011), the dating of ancient pandemics can currently make reference only to the recent past. The attempt to obtain appropriate answers has been made by various researchers. According to the first hypothesis to be proposed, infectious diseases first occurred in the relatively recent history of mankind, i.e. over the last 5,000 years (Haldane, 1949). The hypothesis induced first series of discoveries of the matter based on epidemiological extrapolations.

Paleo-epidemiological extrapolation studies attempted to reconstruct the possible patterns of initial affliction of ancient humans with various infectious diseases. Such reconstructions has been undertaken through ethnic analogy – that is, by examination of disease pattern in contemporary isolated hunter-gatherer populations – followed by extrapolation of the findings into the ancient ones (Black, 1975; Cockburn, 1971; Polunin, 1953). The investigations were based on serological testing of isolated populations for relevant antimicrobial immunoglobulines as the evidential traces of foregoing infectious diseases.

This approach allowed consent with the initial hypothesis (Haldane, 1949), that epidemics of transmissible infections could not exist among ancient Neolithic hunter-gatherers groups whose smallness, high mobility, and isolation did not favor the transmission of infectious agents between them. Diseases that are infectious only in the acute phase die out quickly after introduction in a population (Black, 1975), and they thus require a larger population for their maintenance than existed in any coherent group in Neolithic times. It has been suggested that the latter diseases could not perpetuate themselves before the advent of advanced cultures and did not affect humans until relatively recently (Black, 1966). According to commonly accepted archeological accounts, the Neolithic period began 10,000 ya in SW Asia. Between 8,000 ya and 4,000 ya it spread through Europe, Egypt, India, and north China. By 3,500 ya Neolithic cultures were present in Mexico and South America.

The current publication develops these early discoveries on the basis of a new approach: the search for, integration and analysis of appropriate evolutionary, epidemiological, immunological, anthropological and paleo-genetic data. Primary attention has been focused on identifying among current humans the traces of ancient epidemics formed by natural selection for hereditary immunity to infections. This kind of evidence has not been adequately taken into account in previous studies.

The objective of this paper is not to present final results but to outline the rationale of the study as well as to describe the methods used and to report baseline data. The paper presents the initial results of an attempt to use an integrative (bio-ecological, epidemiological, genetic, immunological, anthropological and evolutionary) approach to estimate the dates of first emergence of infectious diseases among humans.

MATERIALS AND METHODS

The present integrative discovery has been based first of all on the results of previous long-term investigations performed by the author together with his team as well as on a selection of various published data, derived mainly during observations not related to the matter and goals of our current search. The main emphasis was on the search for traces of ancient paleoselection for hereditary immunity and on the sensing of its origin in association with the ecology of *Homo sapiens* on key stages of human descent and further development. In the present discovery, the integration of both epidemiological and evolutionary anthropological data and their integrative analysis has been taken into account for the first time in relation to consecutive periods of human evolution from its beginnings to the modern age.

The search for the traces of ancient infectious selections has been performed according to (Rumyantsev, 2008) on most known levels of infectious pathology, including species, population, inter-individual, individual, intra-individual, cellular, molecular and genomic. The revealed set of appropriate data of relevant observations, experiments and cumulative sensing of their hookup has been united using the approach of maximal bio-ecological and evolutionary integration. The efficiency of such approaches has been iteratively approved, beginning from (Darwin, 1888; Darwin, 1859)

and (Haldane, 1949) as well as in our previous investigations (Burgasov and Rumyantsev, 1974; Burgasov and Rumyantsev, 1985; Rumyantsev, 2011a; Rumyantsev, 2010; Rumyantsev, 2008; Rumyantsev, 2011b).

RESULTS AND DISCUSSION

Sensing evolutionary ecology of infectious diseases

Any infectious disease arises and exists as a result of natural ecological relations between two species in which the microbial one (the consumer) obtains the energy for its life at the expense of substances composed of the consumed organism (the victim). The action of parasite microbes restricts the vitality of the victim, thus provoking a loss of its viability. Microbial consumption differs from other marauding forms of symbiosis in many of its characteristics that are in sharp contrast to predatism.

Infectious consumption is realized by a large population of microbes and functions inside the victim body where it goes through a very intensive self-reproduction increasing the total population from some dozen of microbes to many billions. Being fulfilled with infectious agents, the body of the affected victim serves as a source of microbial invasion into new victims.

The intrusion 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 (as an alimentary intrusion), breathing (respiratory intrusion), and self-reproduction. Of the three, the alimentary transfer of infectious agents functions most widely and effectively (Burgasov and Rumyantsev, 1974). All steps of microbial consumption are performed by means of specific microbial molecular ecological agents (either by adhesins, toxins, enzymes, cytolysins, or polynucleotide, etc.) each of which is peculiar for separate microbial species. Each of the agents acts on its relevant molecular targets in the victim's body.

The success of microbial aggression depends strongly on the mutual chemical complementarity between relevant molecular structures of both the parasite and involved victim. In a case of intermolecular incongruence, the attacked organism appears to be constitutionally unsusceptible and thus cannot be affected (Rumyantsev, 1977, Rumyantsev, 1997). The incongruence created by mutant modification of target molecules makes mutant individuals constitutionally immune to the disease. They give rise to immune progeny, while susceptible individuals of the same species become affected and die without reproducing (Haldane, 1949). On repeated exposure of many generations to a given pathogen, the progeny of immune variants eventually predominate in a population (Figure 1) and, finally, among the majority of the species. In addition, the state of homozygosis launches full protection, whereas heterozygosis abridges progress to full-blown disease by means of the 'wall off' of infectious agents inside restricted patches of affected tissue (O'Brien and Dean, 1997; Paxton et al., 1996; Rumyantsev, 2002).

Every infectious epidemic leaves its specific hereditary immunological marks on the structure of both genotype and phenotype of individuals, populations and species involved in the co-existence with relevant infectious agent. Examination of these remains allows researchers to describe the disease patterns of ancient populations and establish relative chronologies. The relicts of ancient infectious epidemics have survived from earlier periods and can now be detected in various levels of the human bodily architecture. Extensive presence of relevant traits of hereditary immunity among contemporary human populations is now evidenced by many approaches including epidemiological and clinical observations, controlled experimental infections, cytological investigations, molecular biological investigations and by discovery of genome make-up (Rumyantsev, 2010, Rumyantsev, 2008). All the revealed traits can be considered in retrospect to be evidence or traces of previous infectious selection performed by ancient epidemics. Currently, the methods of evolutionary ecological analysis allow us to estimate how and when the traces appeared over well-estimated stages of human evolution.

Infections amongst human forebears

African apes, the nearest ancestors of humankind, began to evolve around 65 mya when tropical forest had covered all of the continents for a long time. The apes were plant eaters fed mainly by ripe fruits (rich in easily digested forms of carbohydrates) and tiny, young leaves (more rich 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 (Milton, 1999). The tropical forest provided its inhabitants with vegetarian food of a quality and quantity necessary for their intensive self-reproduction. Multiple random mutagenesis and genetic admixture continued to form regular levels 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 could also not exist among herbivorous settlers of tropical

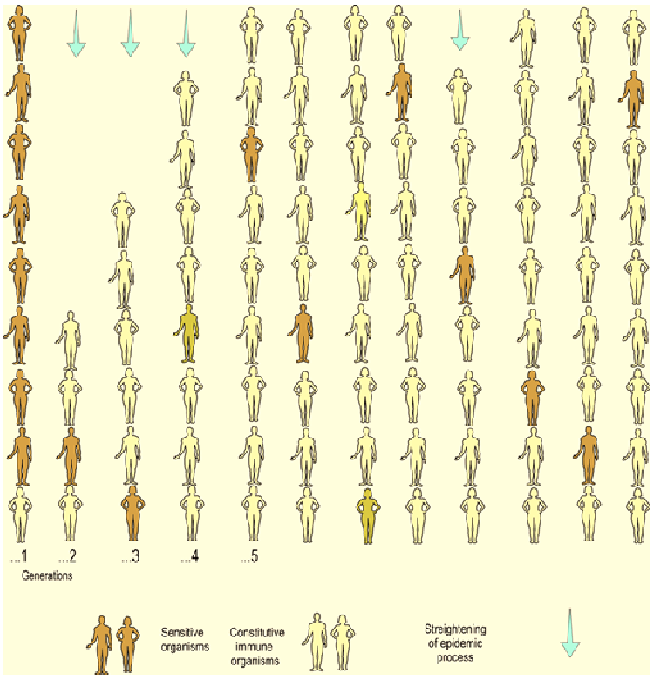

Figure 1. Hereditary immune state of a human population transformed over the emergence (1) and further evolution (2, 3 , 4 …) of epidemic process (Rumyantsev S.N., 2002, Rumyantsev SN, 1984) updated.

forest because the smallness, high mobility, and disunity of their groups. The same factors impeded the transmission of sex-dependent diseases. More likely was the existence of infectious diseases transmitted by bloodsuckers (malaria, tick-borne encephalitis, duple fever, and some others). Millions of generations of apes have changed, one after another, during this long period of primate evolution until nearly 100 species of herbivorous apes have evolved, including the predecessors of modern chimps emerged at 23.8–5.3 mya, with which humans shared a common ancestor from 5–7 mya (Brunet et al., 2002; Chen and Li, 2001).

Infections emerged during the human descent

This paradisiacal life changed dramatically toward the end of the Pliocene (5.3 mya), when global cooling dried out the tropical forests. These shrank and were replaced by woodlands and then by savannah grasslands. The existing primates (over 100 species of herbivorous apes) lost their tropical forest homes and had to adapt to life in the grasslands. The primates in the expanding savannah areas must have faced very difficult challenges, especially dietary ones. New ecological conditions forced the Pliocene apes to eat whatever was at hand. Instead of the plethora of moist tropical products, they had to resort to feeding either on dry grass, which provided little energy for the former tropical feeders, or on the remains of animals that had either died of disease or been killed by other species. Forage of this kind is extraordinary rich in easily digested proteins, carbohydrates, vitamins and minerals. The former fruit-eaters were forced either to become carrion eaters and predators, or die of famine. Beside very nourishing food they were forced to adopt, they were exposed to the many infectious diseases associated with it, which are very dangerous for any species that meet them for the first time (Burgasov and Rumyantsev, 1974; Burgasov and Rumyantsev, 1985; Rumyantsev, 2008).

Most vegetarian apes were unable to survive in these new conditions and went extinct. The fauna of the Earth lost 90% of its vegetarian apes within this period of time, but a few other species of apes became carnivores. They developed the abilities for meat-eating and could thus withstand the savannah environment that appears to have been deadly for most of their herbivorous primate predecessors (Rumyantsev, 2010; Rumyantsev, 2008).

Undoubtedly, a new way of foraging provided the adapting primates with food enriched by various proteins, lipids, carbohydrates, vitamins and so on that could lead to both intensive self-reproduction and the accumulation of pertinent genetic diversity that is very necessary for further evolution. However, this way of foraging provided the new primates with more than just abundant food. Untreated meat food is usually inseminated with deadly

microbes. In contrast to plant-based, a carnivorous diet is associated with a sharp increase in the possibility of catching various life-threatening infections (Rumyantsev, 2008). Thus, infectious diseases become the mightiest agents of natural selection, having played a role in the evolution of humankind since 5.3 mya (Rumyantsev, 2010, Rumyantsev, 2008, Rumyantsev, 1984, Rumyantsev, 1997), not only over the past 5000 years as was previously thought to be the case (Inhorn and Brown, 1992).

Adoption of nutritional infections

The forced transition from a safe herbivorous diet to a potentially dangerous carnivorous one inevitably brought former fruit eaters to multiple devastating epidemics associated with meat-eating (anthrax, botulism, tetanus, typhoid fever, other salmonelloses, brucellosis and so on). All the diseases existed as infections of carnivorous and omnivorous animals and birds far before the descent of *Homo sapiens*. Most carnivores currently possess hereditary immunity against named infections due to their million year long symbiosis with relevant infectious agents.

The involvement in relevant microbe-victim ecological systems should perform terrible devastation among populations of initially highly susceptible primates and hominids. The few survivors could have escaped the deadly infections by being the descendants of either mutant or heterozygous individuals whose constitutive molecular make-up provided them and their offspring with a hereditary defense against alimentary infections. The processes of infectious selection and accumulation of appropriate new special protective traits, the traces of emerged epidemics, have continued throughout a long succession of generations.

The mandatory transition of primates from an herbivorous to carnivorous diet led to the disappearance of most (90%) apes, and resulted in the descent of *Homo* genus (1.8 mya) and then *Homo sapiens* species (0.2 mya) (White et al., 2003). It should be noted that the factors that created this punishing environment impacted various species very differently. The situation became dangerous only for former tropical herbivorous animals, especially the primates. The environment did not change the principles of nutritional ecology for the traditionally carnivorous animals such as cats, dogs, bears, hyenas, weasels, civets, raccoons, mongooses and snakes, which continued their regular mode of carnivorous feeding. The forebears of modern herbivorous chimps, gorillas, and macaques avoided the worst influences of global cooling because they inhabited the remaining tropical areas at that time.

In contrast to most ape species, some mutant *Australopithecus*, the immediate ape predecessor of *Homo* genus, appeared to make the better of the two nutritive choices, and began to eat the corpses of dead animals (Rumyantsev SN, 2010). Most of them perished, being unable to counteract the cruel selection, and were replaced by first the representatives of *Homo* genus. In the beginning of the Pleistocene, 1.8 million years before the present, the last of consecutive species of the *Australopithecus* genus went extinct. But some of its mutant representatives appeared to become constitutionally immune to alimentary infections and were thus be able to counteract all these life-threatening alimentary challenges of infectious origin. The survivors became the founders of the *Homo* genus.

The processes of infectious selection and accumulation of appropriate new specialized protective features, the traces of emerged epidemics have continued to disperse throughout a long succession of many thousands of generations. During the subsequent 1.7 my period of humankind's establishment in the restricted territory of the region of genesis, most principal genes flowed between the different human populations by mixing together.

Early *Homo sapiens*, anatomically, physiologically and immunologically analogous to modern humans, emerged on the African savannah (Novembre J and Stephens M, 2008). The time of its appearance is currently dated from around 0.195 mya according to the age of its earliest known fossil (White et al., 2003). Except for the bipedality inherited from *Ardipithecus* through *Australopithecus*, 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, and also had a crude ability for conscious thought and speech. The analysis performed above allows this list to be updated with the traits of hereditary immunity against anthrax, botulism, brucellosis, typhoid fever, other salmonelloses, and so on. In addition, mutual evolution of antagonistic species inevitably led 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 (Burgasov and Rumyantsev, 1974) 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.

The features are now traced up to cellular and molecular architecture levels, including within the genome. The possession of all 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

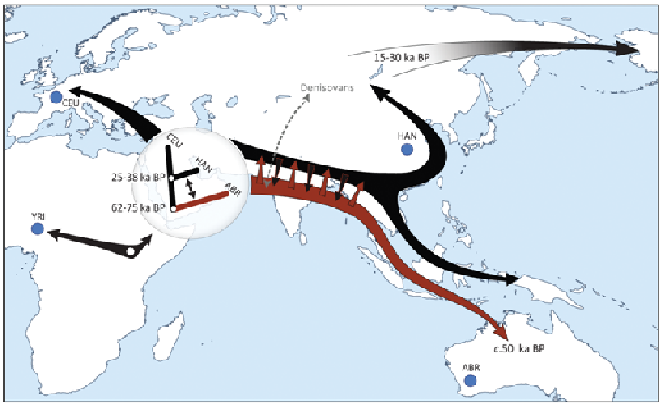

Figure 2. Reconstruction of early spread of modern humans outside Africa (Rasmussen M, Wang Y, Guo X, and et al, 2012).

by physical, chemical, and bio-ecological agents.

Adoption of rabies infection

The traits of hereditary immunity against rabies are now traced mainly on epidemiological, clinical and cytological levels (Halonen et al., 1968, Rumyantsev, 2008). Worldwide, more than 55,000 people die of rabies every year (about less than 0.001% of the world population). Nevertheless, there exist some differences between individuals, ages and ethnicities. In India, 0.002% of the population are estimated die annually, while in Africa, the corresponding figure is 0.004% of the population (WHO Media Centre, 2011).

Ecologically, rabies infection is mainly associated with both raptorial mammals (bats, bears, cats, civets, dogs, hyenas, mongooses, raccoons, weasels, and so on) and their mammalian consuments 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 (CDC, 1999). 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 humankind to the adoption of rabies infection and to the cruel selection for hereditary immunity against the disease. Far later (over 0.2 mya), the newborn species of the *Homo* genus appeared to have inherited from their evolutionary ancestors both their place in the relevant ecological system and the immunity to rabies. They could improve inherited immunity through natural selection continuously performed by relevant epidemic process.

Infections obtained in wandering around the World

Nearly 0.1 - 0.06 mya, some groups of early *Homo sapiens* began to sweep out of the African territory where their descent and initial establishment has been accomplished. This initiated the dispersion of humankind around the world (Figure 2). Some groups of migrants moved from the savannah's "Eden" back into the remnant of tropical forest that was the homeland of their faraway ape predecessors. The migrations to South Asia (62-75 kya), Europe (25-38 kya), and North Asia (25-38 kya) were more distant. The South Asian migration continued toward Australia and eventually reached this continent ~50.000 ya. The North Asian dispersal continued toward Melanesia and New Guinea as well as the American continent (15-30 kya). All currently living non-African populations probably derived from a single dispersal of modern humans out of Africa (Rasmussen M *et al*., 2012).

The wandering of human groups around the world substantially expanded both the quantity and quality of microbe species they encountered on their way. Different wandering generations were subjected to various infectious pressures. Most of these events occurred on the vastest and ecologically very diverse territories of the Eurasian continent. That is why humankind is currently not a single randomly mating population: over its wanderings it has been subdivided into bands, tribes, clans, ethnic groups, nations and races.

The encounter with new infectious diseases continued during the subsequent dispersal of humans around ecologically different parts of Earth. The intrinsic trait of humans to find a better place for life together with their widely practiced interbreeding created the unification of most Eurasian inhabitants concerning both the diseases and the inherent protective features. Nevertheless, some

groups of wanderers remained excluded from this process because of either geographical or ethnic isolation.

The great geographical discoveries and consequent intensive colonization of the American and Australian continents disrupted the isolation. Since the beginning of the 16th century, the new settlers of opened territories brought to indigenous peoples many infections they had not encountered before. They consequently had a devastating impact on many aboriginal populations, originally a highly susceptible. They did not have the traits of foregoing selection for hereditary immunity against these infections. Many historians say these invasions did more to decimate native populations than warfare or enslavement, especially through epidemics of new diseases such as smallpox, influenza, and measles by as much as 90% (Balter, 2011; Rumyantsev, 2004; Stearn and Stearn, 1945; Thornton, 1987).

Adoption of influenza

According to a WHO estimate (Stohr, 2002), 0.008% of the current world population dies of influenza per year. The majority escape the death thanks to their intrinsic traits of hereditary immunity (Rumyantsev , 2008; Rumyantsev, 2006), the result of cruel selection that has been performed beginning from the first appearance of influenza virus among ancient humans that were initially extremely susceptible to the infection. The natural selection for heritable immunity to influenza transformed cardinally the immune state of ancient humankind. But the indigenous populations of American and Australian continents did not possess such protective traits. They were extremely susceptible to influenza.

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 ya (Figure 2), this very ancient branch of *Homo sapiens* has been in almost total isolation from the main population of the species (Rasmussen et al., 2012). Colonization of the continent by Europeans began in 1780. The first colonists brought in to 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 appear among the Eurasian part of humankind earlier than 50,000 ya.

The indigenous peoples of North and South America had began to settle these continents nearly 15,000 years before the present and since then had them only to themselves. The sizes of their populations have remained essentially constant for many centuries. But that all changed when Columbus's discovery of the New World launched relentless waves of European colonization. The newly arrived infection effect on the Amerindians, originally a highly susceptible, non-immune race, was devastating. It was a weapon so powerful that Native Americans feared it more than bullets and swords (Stearn and Stearn, 1945; Thornton, 1987). At the same time, the infections were not as dangerous for Europeans as for Native Americans and the populations of European conquistadors and colonists increased sharply over the same period. This is evidence that most Europeans had acquired genetic immunity against influenza long before the time of the great geographical discoveries.

Both archaeological and historical records indicate that European contact and colonialism initiated a significant reduction in the indigenous population through warfare, enslavement, societal disruption, and especially widespread epidemic disease (Stearn and Stearn, 1945; Thornton, 1987). Crucial epidemics, warfare, enslavement, and famines resulted in significant population declines among Native Americans during the 16th century. Additionally, the scale of the contraction suggests that the 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 (O'Fallon and Fehren-Schmitz, 2011). The integration of these facts allows for the conclusion that influenza infection has not been met by indigenous Australians and Americans before European colonization of these continents to be drawn. In contrast, the Eurasian population of humans adopted the disease after the exodus out of Africa (60K ya) and after isolations of Australians (50K ya) but not earlier then 15K years before the present. Thus, final estimation of the first emergence of influenza among humans is between 50K ya and 15K ya.

Emergence of smallpox

Aboriginal settlers reached Australia ~50,000 years ago (Rasmussen et al, 2012). In 1788, Australia had probably between 750,000 and one million people. During the European colonization of Australia, the health of the aboriginal population declined rapidly in the face of highly infectious diseases including smallpox, which occurred as early as 1789 at Sidney Cove. With the introduction of smallpox, a Sydney aboriginal population of 1500 peoples was reduced dramatically in the first years of European contact. 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. Smallpox was thus a major catalyst for the decline of traditional aboriginal society during 19th century (Webb, 1995). The integration of this historical fact with the absence of hereditary immunity against smallpox among aboriginal Australians evidences that the adoption of smallpox by humankind could not have occurred before 50,000 years ago.

European colonization 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 (Foster, 1973). Recent comparative researches of genome's ancient and contemporary mitochondrial sequences confirmed that Native American populations suffered a significant, although transient, contraction in population size some 500 years before the present (O'Fallon and Fehren-Schmitz, 2011).

Because the isolation of indigenous Americans from the Eurasian population occurred 15,000 years ago, the adoption of smallpox and the selection for hereditary immunity against the disease could not have occurred before this date. In the case that Eurasians accepted smallpox from cattle, the adoption could be performed 8,000 ya after the domestication of cattle by inhabitants of the Middle East. Final estimation of the first emergence of smallpox among humans can be present as >8Kya<15Kya.

Emergence of measles

Before widespread global use of measles vaccination, the disease killed 0.4% of the worldwide population in 1980 (Wolfson et al., 2007) and nearly 0.1% in 2000 (CDC, 2009). Epidemics of measles are currently a major cause of childhood mortality in West Africa. Most currently living people are inherently immune to measles infection. 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 the ancestors of whom did not confront this specific infectious agent. This happened to the primary settlers of Australia (Rasmussen et al, 2012). European newcomers wrecked their 50,000 year-long isolation and brought to indigenous Australians aborigines a set of viral infections including measles, which had devastating effects on the population (Webb, 1995).

The same occurred with the primary settlers of America, whose isolation occurred nearly 15,000 ya. The integration of these 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 15,000 ya.

Emergence of HIV infection

Initially, the date of the first appearance HIV epidemics was identified as being 12,000 years before the present (Rumyantsev SN, 1992). Later, the emergence of HIV as a human pathogen was identified as being between 700 and 2900 years ago (Gaggiotti, 2006; Lucotte and Dieterlen, 2003). This statement has been based on the supposition that the Vikings had genetic immunity against the infection. Now, the integration of current observations on HIV epidemics with the dates of evolutionary immunology, epidemiology and anthropology can provide us with a more fundamental basis for the answer on the question. Further observations have confirmed the efficacy of the integrative approach.

During 2005, 3.1 million people (0,048% of the world population) died of HIV-related illnesses (UNAIDS, 2006). The epidemic of HIV infection remains present everywhere in the world, but with different levels of intensity (Figure 3).

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 (Centers for Disease Control and Prevention, 2007). For instance, among 15,135 American patients with HIV, 53.6% were black. The first attempts to understand the genetic and evolutionary reasons for this racial susceptibility were published at the beginning of 1990 (Rumyantsev, 1992, Rumyantsev, 1993a, Rumyantsev, 1993b). Although their conclusions have been confirmed recently (O'Brien and Nelson, 2004; O'Brien and Dean, 1997), there has been little advancement in this direction (Powe, 2003).

According to data presented in Figure 3, the rate of HIV/AIDS diagnosis is 0.07% for Asians and Pacific Islanders, 0.09% for White Americans, 01% for East Asians, American Indians and Alaska Natives, 0.2% for North Africa/Middle Eastern inhabitants, and 0.3% for Western/Central Europeans, in sharp contrast to Afro-Americans (7.13%) and sub-Saharan Africans (7.2%). The data indicates that many native inhabitants of the sub-Saharan tropical region and even their far later relati-

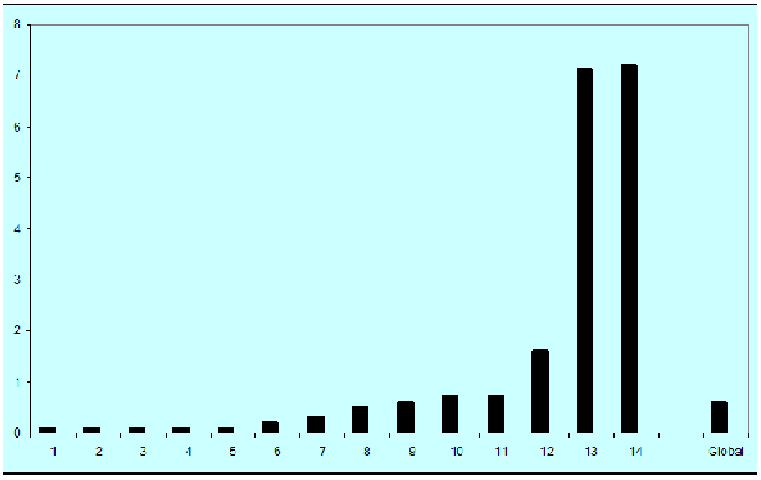

Figure 3. HIV prevalence by ethnicity* (CDC, 2008) or region (UNAIDS, 2006): Asians and Pacific Islanders* (1), White Americans*(2), East Asia (3), American Indians*(4), Alaska Natives*(5), North Africa/Middle East (6), Western/Central Europe (7), Oceania (8), Latin America (9), South/South-East Asia (10), North America (11), Caribbean (12), Afro-American* (13), Sub-Saharan Africa (14).

ves 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. The intercourse of the sub-Saharan African branch of *Homo sapiens* species with their Eurasian relatives was interrupted 60,000 ya when their ancestors 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 ya. This could also not have been accomplished before 12,000 ya, when the Sahara desert formed a geographical barrier between indigenous Africans and other parts of the populated world. The infection could also not have emerged after 14,000 ya, otherwise indigenous Americans would not demonstrate very expressive immunity against HIV. The beginning of HIV epidemics among humans should thus be dated between 12K and 14K ya 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 50,000 ya. They concluded their wanderings 50,000 ya (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 (Wrigh et al., 2005). 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 (Guthrie et al., 2000). Indigenous Australians did not show the decline in HIV that occurred among non-indigenous Australians (Wright et al., 2005). 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 (Bowden FJ, 2005). 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 hundreds years ago by European colonization.

Adoption of tuberculosis

Until recently, it was hypothesized that the inducer of tuberculosis, the *M. tuberculosis*, evolved from *Mycobacterium bovis* and was acquired by humans during the development of agriculture around 9,000 years ago (Sreevatsan et al., 1997). According to this hypothesis, TB would have been introduced into a subpopulation of mankind after their emergence from

Africa and one would have predicted, unless other infectious diseases provided comparable selective pressures on fitness and reproduction, that the current human populations would exhibit extreme traits of susceptibility (Russell DG, 2007). Such is not the case.

Many of our contemporaries do not suffer from tuberculosis (TB) even though in big crowded cities they are inevitably are affected with TB bacilli. Tuberculosis kills ~0.02% of the worldwide population annually, i.e. 20 per 100,000 (WHO, 2009). 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 red Indians and Africans when Europeans brought in with them this infection during the colonization of America and Africa (Thornton R, 1987). After European occupation of Australia, tuberculosis also became a major cause of mortality among aborigines, as did influenza, smallpox and measles (Webb SG, 1995). According to our estimation, this might indicate that humankind could not have been exposed to tuberculosis-mediated selection for hereditary immunity before geographical isolation of the settlers of sub-Saharan Africa (50K ya) as well as the aboriginal Australians (50K ya) and American Indians (15K ya). It should be located on the territory of Eurasian continent.

CONCLUSION

The present analytical research was based on integration and consequent sensing of appropriate recent achievements of evolutionary sections of epidemiology, immunology and anthropology. The results of the investigation allow us to conclude that origins of most of today epidemic processes have roots in the very distant past.

Many nutritional infections associated with food of animal origin (anthrax, botulism, brucellosis, salmonelloses and so on) as well as the launch of hereditary immunity against them began to emerge on the African Savannah 5.3 mya among the chimpanzee-like ape ancestors of *Australopithecus* (4.5 – 1.8 mya) and then been inherited by the descended *Homo sapiens* (1,8-0,2 mya). Rabies infection appeared among the earliest humans and their ape-like ancestors over the same period of time thanks to inevitable intercourse with traditional predators.

The infections the existence of which depends on regular transmission from one organism to another may have been adopted by early humans over their wanderings out of Africa (60K-70K ya) along different geographical directions and ecologically various parts of the world. The wanderings substantially expanded both the quantity and quality of infectious agents they encountered on their way. In addition, over the dispersion of humankind most infectious agents and principal protective genes flowed between different human populations by mixing together. This was most likely to have been realized mainly on the Eurasian territory. Some populations appeared to be excluded from this process at different times of their history. The African sub-Saharan population was isolated 60,000 ya, the Australian population 50,000 ya, and the American population 14,000 ya. Integration of these anthropological data with recent achievements of evolutionary immunology and epidemiology allows us to state that the emergence of all the considered infections among humans occurred on the Eurasian territories. Human tuberculosis and influenza infection emerged between 50,000 and 15,000 ya, smallpox between 15,000 and 8,000 ya, measles not earlier than 15,000 ya, and HIV infection between 14,000 and 12,000.

After their emergence, both groups of infectious epidemics and the phenomenon of hereditary immunity against them continue to exist among humankind up to now, supported by mitigated forms of relevant infections. The strategy and tactics of infectious prophylactic should be oriented on the identification and defense of both homozygous and heterozygous susceptible individuals.

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