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Global Environmental Issues from the Viewpoints of Medical Surveys on Non-Caucasian Highlanders in the World

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Introduction

A big project entitled " Human Life, Aging, and Diseases in High-Altitude Environments: Physio-Medical, Ecological and Cultural Adaptation in Highland Civilizations" lead by Kiyohito Okumiya in Research Institute for Humanity Nature in Kyoto, Japan has carried out during 8 years and finished in 2013. The achievements of this projects included 201 original articles and 3 books until now.

The contemporary brief summaries were reported in the Editorial of *Himalayan Study Monographs* volume *12, 13, 14,* respectively.[1,2,3] And medical summary of the project will be published by the project leader Kiyohito Okimiya elsewhere.

At the end of the project, Editors try to view the points of the global environmental issues in the world from the standpoints of long-term evolutionary timespan based on the findings and discussions we obtained throughout the project.

Non-Caucasian Highlander's Lifestyle and Environments

As researchers who study highlanders living in hypoxic environments, we ourselves, of course, need to adapt to the highland environment. Most members of our team suffer from the symptoms of high altitude sickness when moving from sea level to the highlands, but gradually acclimate to the low oxygen. Even after adapting to the new environment, our breathing becomes labored when handling heavy loads. We cannot help but feel intrigued by the mystery of hypoxic adaptation achieved through evolution over a vast period, as well as the deep religious faith, of Tibetans who travel tens of kilometers, while repeatedly prostrating themselves, as they make pilgrimages to the holy mountains.

Compared to the fleeting human lifespan of less than a hundred years, the silver peaks of the Himalayas visible far away, which have surely been in existence for the past several million years, appear unchanging in their eternal form. Highlanders have continued to look to the Himalayan peaks for generations, revering and passing on to future generations their holy existence.

Migrating birds forming a full arc, leisurely flying above the Himalayas and taking a lengthy lakeside rest at an altitude of 4000 meters, prompt the following question: "How did they manage to adapt to this hypoxic environment?"

Highlanders who farm and herd morning to evening, sheep and yac herds that freely graze, Himalayan peaks that shine brightly in the blue sky and form the distant scenery of highland villages, gulls that dance in the firmament-these are all part of the typical highland scenery. Only here does it seem that time flows slowly. Life-of humans, animals, and plants-and the ecological and cultural environments that form the Earth come together, linked by the keyword "hypoxia," as a single archetype within the global frontier known as the highlands.

We have touched on the fact that a vast period of time was needed for highlanders to genetically adapt to the hypoxic highland environment and, at the same time, establish the sphere of daily living. They exercised ingenuity toward their livelihood and brought about cultural adaptations, such as the sharing of religion as a spiritual entity. Over the past several thousands of years, highlanders have led a stable existence in this harsh ecological environment. These highlanders are all non-Caucasian people. Yet, recent years have brought marked changes to their lives, changes that have been discussed primarily in terms of medical findings. Changes in nature-human interactions brought about by mutual influences between the global environment and human action, are thought to arise in most radical form at the Earth's ecological frontiers, which are characterized by unique natural ecosystems. It is now clear that the genetic adaptations that allowed highlanders to the adapt to the hypoxic environment throughout life (over the course of birth, development, and middle age) act to advance the pace of developing lifestyle-related diseases, such as diabetes, particularly in view of longer lifespans.

Biological trade-offs are phenomena in which genetic factors that worked to one's benefit in youth become detrimental at older ages. Relationships between hypoxic adaptation, older age, and lifestyle-related diseases become much clearer in the highlands. The most important issue, however, is that once discovered, lifestyle improvements allow for the management or prevention of lifestyle-related diseases attributed to genetic factors implicated in biological adaptation. It is never too late.

By construing genetic adaptation to the global environment and its result as "the global environment etched onto the human body," we have found alterations in the interplay between the global environment, the anthroposphere and animal/plant life, reflected in the aging of highlanders. If we assert that alterations in the interrelationship between the three spheres forming the global system (anthroposphere, biosphere, and geosphere) are reflected in human diseases and aging in the form of 'global environmental issues,' the study of highlanders has provided us with an important awareness of these issues.

While global environmental problems are important issues to be faced by mankind in the next 50 years or so, they must be considered on both spatial (from the microscopic gene level to the unit/group level) and temporal (the 4.6 billion years of Earth's history, 4 billion years of biological evolution, and mankind's 7 million year history) scales when contemplating their essence.

Construing "global environmental issues"

Although global environmental issues are regarded as problems of the compounded and complex sort that must be studied on multiple levels, the preface of the Encyclopedia of Global Environmental Studies simply lays them out as, "in the context of Earth-anthroposphere interactions, a group of 'problems' in which environmental changes that carry the risk of drastically stressing the environment to the extent of threatening the realm of life are seen as problematic, and for which an agreement to take preventative measures based on scientific prediction is in the process of being developed." Such an understanding places strong focus on the reality that global environmental changes brought about by humans alter the Earth's physical factors and ecosystems, and this change threatens the conditions for mankind's existence. These are urgent issues that have instilled fear in the human race over the past few decades.

For the time being, we classify global environmental issues based on the three spheres of geosphere, biosphere, and anthroposphere. When considering these issues in the context of adaptation, maladaptation, over-adaptation, and discord resulting from the interaction between these three spheres, various broader aspects of global environmental issues come to light.

Geosphere-anthroposphere interactions

Our awareness regarding global environmental issues begins, for the most part, from concerns about various problems arising from geosphere-anthroposphere interactions. The damage attributed to and influence of global environmental issues, first of all, are not limited to a single country of origin, but rather spread past national borders, expanding to the global scale. Addressing global environmental issues originating in developing countries requires concerted global efforts involving advanced countries as well. Recent noteworthy issues include destruction of the ozone layer, global warming, acid rain, transboundary movement of hazardous waste, water pollution, rain forest deforestation, desertification, exhaustion of fossil fuels, and pollution in developing countries. These issues have become more severe due to the social structure of mass production, mass consumption, and mass disposal in advanced countries, and population increases and the associated stress on environmental resource use in developing countries. Since these issues have the potential to greatly influence the survival and prosperity of mankind, they have been raised as issues of utmost importance in international politics. All of these factors are alterations to the global environment resulting from human production activities and consumption behavior, and their impact is beginning to be felt around the world.

In order to consider global environmental issues at the most fundamental level, as symbolized by biodiversity, a discussion of the 4 billion year history of the biosphere from a multilayered and wide angled perspective is warranted.

Geosphere-biosphere interactions

The signs of primitive life can be seen from about 4 billion years ago, and the biosphere existed throughout this period as a presence that tirelessly altered cells and genes to facilitate the adaptation to physical and chemical changes in the global environment. This process is called evolution. Only those species that adapted to the global environment were allowed to survive and propagate, and those that failed to adapt or overadapted went extinct.

We are inclined to think that this world was always as we see it now. When considering global environmental issues, we are prone to the mistaken impression that the global environment is invariable. While it is common knowledge that the Earth was covered in magma 4.6 billion years ago, it is difficult for us to grasp the subsequent environmental changes that occurred.

For example, it was thought until the 19th century that the positioning of Earth's landmasses was unchanged since the beginning of life history. The German geophysicist Alfred Wegener realized that continents far apart, such as South America and Africa, had land shapes that could be fit together like jigsaw puzzle pieces. When he proposed the continental drift theory in 1912, many scholars dismissed his views. We now know that when dinosaurs came into existence about 250 million years ago, the continents were part of one massive supercontinent called Pangaea. Dinosaurs went extinct about 65 million years ago, and our ancestors, the prosimians, emerged about 63 million years ago. At about this time, the continents of Asia, Africa, Europe, North and South America, and Australia took on the form that we know today. The theory of plate tectonics, developed in the 1950s, made it clear that mountainous regions such as the Himalayas came into being over the course of tens of millions of years. The photograph shows a rock found in the Himalayas. A fossil of a shell can be seen in the rock, providing evidence that in the ancient times, the Himalayas were under the ocean.

When mammals replaced dinosaurs as the rulers of Earth about 65 million years ago, the concentrations of oxygen and carbon dioxide in the atmosphere and sea were completely different from what they are now. We earlier posed the question of how migrating birds flying over the Himalayan peaks at ease have adapted to hypoxia. Although the current atmosphere is 21% oxygen, it was only 15% when birds evolved. Thus, the ancestors of birds likely evolved to adapt sufficiently to hypoxic conditions.

The biosphere also faced the challenge of changing temperatures. Glacial periods are relatively rare in history, with three such periods that occurred about 400 million years ago, 275 million years ago, and 2.5 million years ago. In midst of the cycling temperature changes, there were also periods of extreme changes in heat. This is evidenced by the existence of insects, such as the wooly aphid that lives in glaciers, as well as microbes that live in hot springs, sulfur vents, volcanos, and undersea hydrothermal vents at temperatures as high as 120° F.

As discussed above, dramatic physical changes occurred in the global environment during Earth's 4.6 billion year history, and the biosphere constantly adapted to these changes and evolved.

Biosphere-anthroposphere interactions

Although humans are an integral part of the biosphere, a specific relationship exists between food and illness when considering biosphere-anthroposphere interactions.

With the mass extinction of dinosaurs about 65 million years ago came the dawn of mammals. Having lived nocturnally as small animals until then, mammals came out in the open during the day. The accidental extinction of dinosaurs allowed these mammals to take over as main actors. This KT boundary served as a junction for mammals. Our ancestors, the prosimians, evolved from these mammals and eventually branched off into anthropoids, a subset of which evolved into humans. Although early mankind was high up on the food chain, they were not at the apex. For a few million years after mankind's ancestors came into existence, they had no choice but to co-exist with large carnivores that also preyed on human species in the African savanna. One can say that when mankind was hunting and gathering in the early stages of the anthroposphere, humans were still an integral part of the global food chain and abided by nature's laws.

The agricultural revolution brought about a breakthrough in human diet about 10,000 years ago. At this time, mankind learned to domesticate wild plants and animals and invented farming. Agriculture made increased food production and storage possible. Those not engaged in agriculture became soldiers, bureaucrats, and technicians, further spurring the evolution of society. At the same time, this brought about social and gender inequalities. The increase in human diversity and divide between tribes arose in the past 10,000 years or so.

Agriculture not only brought about groundbreaking advances in the anthroposphere, but also presented new threats to the foundation of human survival. While it was likely difficult to secure daily meals when humans were hunting and gathering, they were nonetheless able to maintain adequate variety in meals from the perspective of protein, mineral, and vitamin intake. With the advent of agriculture, however, the main energy source shifted to carbohydrates, leading to the biased intake of nutrients and increase in malnutrition. When comparing nutritional intake between hunters and gatherers and farmers, paleopathology reveals that hunters and gatherers likely led a healthier lifestyle.

Agriculture relies on a limited number of crops. As a result, in addition to nutritional balance issues, poor harvest years brought about famine due to difficulties in securing sufficient food to feed groups with large populations. Since the agricultural revolution, the threats of malnutrition and famine increased substantially more than experienced during the period of hunting and gathering.

Disease epidemics, the greatest misfortune in human history, form a byproduct of the agricultural revolution. Although increased food production made denser populations possible, it also brought about epidemics. Infectious diseases were rampant among highly populated, malnourished groups, and were transmitted from animal to humans and from human to human. Epidemics resulting from the concentration of populations were not a problem for hunters and gatherers, who kept in small-sized groups and constantly traveled. The emergence of bacterial infectious diseases that transmit from human to human, such as tuberculosis, leprosy, and cholera, became particularly pronounced after the advent of agriculture. Viral infections such as smallpox, the bubonic plague, and measles are thought to have arisen in the past several thousands of years since cities began to form and concentrated populations became possible. Since the beginning of agriculture until recent times, about one-fifth of the human population is estimated to have died before the age of 5 years due to infectious diseases or malnutrition during infancy. Even now, an arms race ensues between the biosphere (pathogenic microbes) and anthroposphere in the form of the development of new antibiotics and evolution of drug-resistant microbes.

Anthroposphere-anthroposphere interactions

Struggles within the anthroposphere, i.e., wars, represent a phenomenon that became pronounced after the advent of agriculture. Several human species are thought to have existed about 200,000 years ago.

While human species we know of today, such as *Australopithecus, Homo habilis, Homo erectus,* and Neanderthals, were all fated to extinction, no conclusive evidence exists that they fought each other.

While many human species remained in Africa, some moved to Eurasia about 1.8 million years ago. This is known as the first migration from Africa. These species, later to become known as the Peking man and Java man, are referred to as *Homo erectus*, along with their fellow species that remained in Africa. At least one group of *Homo erectus* began using fire, a monumental event in mankind's history. Homo erectus survived until 250,000 years ago.

The era of modern humans began about 200,000 years ago. This era is notable as the period during which symbols, such as language, and original forms of artistic expression, came into use. Coexisting with modern humans were the Neanderthals. In an event known as the second migration from Africa, one group of modern humans left Africa about 100,000 years ago and eventually adapted to all environments in the world. Mankind conquered various terrains, including grasslands, deserts, and mountains, and began living in various climates (tropical, temperate, and polar). They advanced into every environment, as exemplified by the Eskimos in polar regions, bushmen in the deserts, pygmies living deep in the rainforests, and Tibetans living in highlands. The speed of this expansion is particularly striking, as within tens of thousands of years, humans reached Europe, Asia, South and North America, and Australia.

This migration of early stage humans was likely prompted by a desire to avoid fighting over limited resources and search for a frontier that would serve as a new niche. However, the situation began to deteriorate after the agricultural revolution. Agriculture brought about repeated conflicts over limited land, resources and labor forces. This further exacerbated the stratification of social structure, as exemplified by the divide between people with power, aristocracy, soldiers, and farmers. The history of mankind, who began writing about the past in words, is rife with descriptions of war.

Up until 50 years ago when global environmental issues were laid out on the table as a topic for discussion among international society, humans, over the several thousands of years of their history, were engaged in an arms race linked to the destruction of the global environment. Even in current times, armed conflicts transform into fights over rights of possession of resources, economies, and information-no harmonious solution has been achieved on this front. Even when taking up the one issue of preserving the global environment, there is no hope for a quick solution or consensus, as developing and developed countries have their different interests and views. Indeed, global environmental issues are anthroposphere-anthroposphere-based social problems.

History of the "Global Environmental Disaster (GED)"

When considering global environmental issues, a broad, entangled, and multilayered phenomenon interpreted differently by region, it helps to view the historical shift of the subject at hand. It is possible to tentatively name the changes brought about by stresses to the environment as a result of human production and consumption activity since the 20^{th} century (e.g., pollution, global warming, water pollution, reduced rainforests, and desertification) as the "Global Environmental Disaster (GED)." Rather than the narrow sense of global environmental issues currently faced by mankind, this broadens our perspective to the enormous changes brought about by geosphere-biosphere-anthroposphere interactions, and makes clear that many GEDs have occurred over the course of Earth's history. It is most typical to approach questions about interactions between Earth, life, and humans, and the direction these interactions are headed, by exploring case histories.

Oxygen concentration in the atmosphere

Hypoxia is an absolute reality of highland environments. While the fact that the atmosphere consists of 21% oxygen does not change, given that atmospheric pressure is reduced in highlands, the concentration of oxygen in the atmosphere at an altitude of 5000 meters is one half that at sea level, and it becomes one third at an altitude of 8000 meters.

While we fear changes in the global environment, this is premised on our inclination to think that the world that we comfortably live in has existed in its current form for ages. We are prone to think that the oceans, mountains, and even the composition of air in the atmosphere are eternal. Until the theory of plate tectonics was developed in the latter half of the 20th century, Earth's continents were thought to have been fixed in their current position. This mistaken mindset is evident more so with respect to oxygen, which is required for life, as we are inclined to think that its levels have been maintained for ages.

According to Peter Ward, even 5 million years ago, which is only a brief moment on the geological time scale, the concentration of atmospheric oxygen may have been higher than current levels, while 60 million years ago, the concentration was clearly lower.

The planet known as Earth came into existence about 4.6 billion years ago in what we know as the Big Bang. With the expansion of the universe came hydrogen and helium, followed by the birth of stars and the formation of metals within the stars. The Earth was formed through the constant collision of dust and mineral particles orbiting the sun, and at the time of its birth was molten due to the flurry of collisions. Elements forming the dust particles of Earth mixed, and recombined to form new minerals. While there was essentially no oxygen in the atmosphere at the dawn of Earth, atmospheric carbon dioxide was more than 10,000-fold higher than current levels, and this is thought to have led to an extreme greenhouse effect. From at least 3.5 billion years ago, cyanobacteria, which use sunlight for photosynthesis, arose and began producing oxygen. A group of cyanobacteria transitioned to plant cells and became chloroplasts. Through extensive photosynthesis, they contributed to the accumulation of oxygen in the atmosphere. However, until 2.2 billion years ago, the concentration of oxygen in the atmosphere is thought to have been, at most, 2-3%.

According to the GEOCARBSULF model, which estimates the concentration of oxygen and carbon dioxide in the atmosphere of past geologic periods, the concentration of oxygen in the Cambrian age (about 550 million years ago), which was notable for the explosion of new species of life, was substantially lower than the present 21%, at about 15%. However, the ensuing 200 million years saw the concentration increase from 15% to 25%. About 380 million years ago, the concentration went back down to about 15%, but then again increased about 260 million years ago to the maximum value of near 30%. At around the beginning of the Jurassic period of the Mesozoic era (about 190 million years ago), the concentration of oxygen decreased below 15% to a record low, and since then, while vacillating up and down, reached the current 21%. It has also become apparent that the concentration of carbon dioxide and oxygen were inversely proportional, and this relationship differed by geologic period. As we know today, the concentration of carbon dioxide in the atmosphere influences Earth's temperature through the greenhouse effect, contributing to the formation of characteristic climates throughout the course of Earth's history.

Changes in the concentration of atmospheric carbon dioxide and oxygen are thought to have had an important and deep impact on the anthroposphere and its evolution. This is believed to have been involved in the mass extinction of life discussed below.

Mass extinction of life

The history of life is ridden with a sporadic, rapid series of mass extinctions. About 10 such extinction events have taken place within the last 500 million years, the most well-known of which are discussed below.

At the end of the Proterozoic era (Pre-Cambrian period), about 600 million years ago, soft-bodied organisms known as the Ediacara biota were prominent. They disappeared about 545 million years ago in what is known as the VC boundary (the first extinction). After their extinction, trilobites flourished, but a mass extinction that occurred during the Ordovician period of the Paleozoic era (about 435 million years ago) reduced the number of trilobite species by half. Trilobites were not the only victims, as about 85% of all living species are thought to have gone extinct. At the end of the Devonian period of the Paleozoic era (about 360 million years ago), placoderms, such as Dunkleosteus, and many marine organisms, such as armored fish, went extinct, as did about 82% of all living species.

During the Permian period at the end of the Paleozoic era (about 225 million years ago), the largest mass extinction known to date occurred, which is referred to as the PT boundary. Victims included all trilobites, all ancient corals, all ammonites with the exception of one strain, and most bryozoans, brachiopods, and crinoids. This mass extinction also saw the death of many synapsids (i.e., mammal-like reptiles) that flourished during the Paleozoic era. Among the archosaurs that survived this period and flourished in the Triassic period were dinosaurs that first adapted to the hypoxic environment by acquiring air sacs-these species formed the foundation for the following period of prosperity. Synapsids that developed diaphragms and acquired the ability of abdominal breathing also overcame the threat of the hypoxia to become the ancestors of mammals. Following the PT boundary, during the late Triassic period of the Mesozoic era (about 212 million years ago), many ammonite species, along with the lineage of many large reptiles and synapsids, were among the 76% of all living species that succumbed to mass extinction. This period saw the rapid expansion of dinosaurs, which at the time were relatively small in size.

Dinosaurs flourished from the late Triassic period to the Jurassic-Cretaceous period, but suddenly went extinct about 65 million years ago. This extinction event, which places second in scope in the evolutionary history of organisms, is known as the KT boundary. While many views exist, the leading view has it that the mass extinction was caused by an asteroid colliding with Earth near the Yucatan peninsula. The resulting fire and dust that blocked sunlight led to globally-reduced temperatures, paving the way to mass extinction. About 25% of living species went extinct, effectively cleaning out the dinosaurs which ruled the land up to that point. This was an important turning point for mammals, and the event that set the stage for human evolution.

The events discussed above are known as the "five mass extinctions," and a common factor shared by four of these is hypoxia. During the Ordovician, Devonian, and Triassic periods, the concentration of oxygen in the atmosphere decreased to below 15%, whereas the concentration decreased by 10% when the Permian mass extinction occurred. While these mass extinctions are events in geological history, some biologists take the view that a mass extinction is currently underway. For instance, Wilson estimates that mankind's destruction of the biosphere will kill off half of all species on Earth within 100 years.

History of mankind

Mankind is thought to have split from common ancestors with chimpanzees about 7 million years ago. At the time, the habitat of Africa's forests began to undergo desertification, leading one group to leave the treetops for the savanna. Many early stage human species are known to have walked erect, and walking erect was likely attempted many times by numerous groups. While many theories attempt to explain why mankind transitioned from walking on all fours to walking erect, this remains an unsettled question. Bipedalism clearly conferred the ability to carry food in hands, made it possible to see further distances, and eventually led to an expansion in brain volume. It took 4 million more years from the time our ancestors began walking erect for our brain volume to expand. One explanation for this evolutionary delay is climate change in Africa. The progressive drying of the climate led to a reduction of forests, and our ancestors living in the grasslands were subjected to a natural selection pressure unlike any known before-this is thought to have led to changes in body structure and behavior. One reason why orangutans, which were transported to Asia by continental drift, remained in the trees is probably because the rich forests in Asia's tropics were preserved about 2.5 million-30 million years ago, while the northern hemisphere and Africa progressively became cooler and dryer.

The development of glaciers about 2.5 million years ago and the resulting drastic change in climate likely instilled a potent selection pressure on the several thousand species living on Earth. This pressure prompted adaptations to the new conditions in order to facilitate specific organisms' success in propagation. Evidence exists for enlarged brains and the use of tools from about 2.5 million years ago. The concept of preadaptation in evolutionary biology refers to gradually changing body structure so that, when a particular environment is faced, the changes work to one's advantage. The advantages of bipedalism are thought to have played an important role in human evolution again 2.5 million years later. Armed with an expanded brain volume, mankind began using stone tools and brought about a revolution in food energy-the intake of high calorie meat rich in nutrition. Despite being "meat-eating" and hunting herbivorous animals on occasion, most of the food supply likely came from rotten meat left over by carnivorous animals. The expansion of brain volume led to improvements in meat eating efficiency, and was accompanied by acquiring the body structure of modern humans, increases in range of activity, and loss of body hair.

The genetic design acquired by mankind over 7 million years of evolution was designed to adapt to the African environment. When considering the entire span of human evolution, the achievement of bipedalism was a groundbreaking event. In order for bipedalism to be possible, it was necessary to undergo morphological changes to the pelvis and develop complex motor skills for body balance. Even from the standpoint of human ontogeny, achieving stable body balance takes infants many years. The stability of bipedalism, once achieved, declines later in life with advancing age. Genes probably did not foresee that, 7 million years later, bipedalism would cause falls and fractures, which are ranked third for reasons elderly are bedridden. Abilities that worked to one's advantage in youth have the opposite effect in old age, i.e., a biological trade-off. Bipedalism is considered a typical case of such a trade-off. From the perspective of evolutionary medicine, parallels are also seen between the evolution of intelligence resulting from the enlargement of the brain, and Alzheimer's disease in old age.

Mankind has continuously altered the global environment since the agricultural revolution. They increased the density of populations while living settled lives, but some also sought new farmlands or grazing lands, and developed livelihoods in all environments throughout the world. By taking advantage of a region's particular nature/ecosystem, humans developed cities, established trade networks between regions, created a human-specific social mechanism called "civilization," and even began to contemplate the well-being of their spiritual world.

The highlands, which served as the site for the Highland Project, are an example of such a frontier.

Research paradigm for global environmental issues

Thought experiment

The "global environment" can be considered a massive, complex system that takes sunlight as its source of energy in order to weave a grand tapestry of biochemical, biological, geological, economical, and political energy exchange.

Kauffman, a researcher of complex systems and the theory of evolution, states that "one way to underline our current ignorance is to ask, if evolution were to recur from the Precambrian when early eukaryotic cells had already been formed, what organisms in one or two billion years might be like." The main shortcoming of our current view of evolution is that it never led us to ask such questions, despite the fact that the answer may provide us with deep insight into the qualities that organisms are expected to develop.

Until the early 20th century, scientists believed that climate and the chemical composition of the atmosphere were fixed and a given. We now know that organisms were responsible for conditioning the atmosphere to have a particularly high oxygen and low carbon content. One view has it that atmospheric changes occurred under the influence of biological evolution. Life influences climate, at times, to the extent of influencing glacial periods and droughts.

Through Kauffman's thought experiment, one can confirm the products of nature's experiment with mammalian evolution over the long 65 million year period since the extinction of dinosaurs, for example, in lemurs in Madagascar, a region isolated from the rest of the world, ungulates of Australia, and even in places where mammals never existed, such as New Zealand. The continents had been shifting. Ancestors of new world monkeys, born in Africa, were carried, like lemurs, on continents to the Americas, and can be now found in both Central and South America.

Lenski experimentally validated Kauffman's views in a laboratory setting. About 10^{20} *Escherichia coli* exist in the world, and a human has about 1 billion *E. coli* in the large intestine. Over the course of 20 years, Lenski and colleagues serially passaged 12 populations of E. coli that divide every 20 minutes. After about 40,000 generations, they performed an evolutionary experiment by introducing a period of abundant nutrition followed by starvation. The results of this experiment can be used to explain why, no matter how fast new antibiotics are developed, microbes instantaneously acquire a resistance to them. This led to the view that, from an experimental perspective and based on results of evolutionary experiments, the strategy of developing new antibiotics is not the right approach.

In the context of infectious diseases, there are limits to engineered disinfecting methods. Indeed, the need for an evolutionary medicine-based approach is evident. One such strategy is to 'coexist with microbes.' That is, even if infected, an approach that delays the onset of disease or symptoms as much as possible-past the human lifespan, for example.

"If" is a taboo word in history. At the same time, we regularly use expressions like "history repeats itself," "the present-day significance of historical research lies in viewing and designing the future," and "the lessons of history apply to the future." In such cases, the historical "if" represents an important thought experiment.

When considering global environmental issues, a vast, evolutionary history-based thought experiment might offer the key. From the standpoint of a "thought experiment," the interpretation of history lends itself to various opinions that are not necessarily aligned along a single path. This process becomes possible only when mobilizing sciences, such as ecology, meteorology, geophysics, paleontology, and medicine, in addition to humanities-like historical studies that rely on documentary records.

Infectious diseases and the global environment

The landmark discovery of cholera by Koch at the end of the 19th century elegantly proved the hypothesis that diseases can be traced to single factors, such as viruses and bacteria. Following this, it was also discovered that mold, toxins, and vitamin deficiency can lead to illnesses. This established the model in medicine that one pathogen leads to one disease. This model contributed to the prevention of various diseases by avoiding, killing, or acquiring a resistance to specific bacteria and viruses.

From the 19th century to the first half of the 20th century, deaths due to infectious diseases markedly decreased. Public health methods based on the one pathogen-one disease model effectively severed the path to infection by specific bacteria. In 1910, Paul Elrich and Sahachiro Hata discovered the drug salvarsan which targeted syphilis, and in 1928, Fleming discovered penicillin. Since then, an enormous variety of antibiotics have been developed, allowing mankind to conquer most infectious diseases, which led in turn to the extension of lifespan. Human waste was completely removed from the water supply, and continuous efforts were made to remove pathogens from the food supply. By implementing vaccinations, developing drugs to treat diseases, and blocking the path of bacterial infection, it appeared that infectious diseases, for the most part, were eliminated.

A large number of antibiotics were developed since then, and it appeared that mankind had eradicated infectious diseases for good. In 1969, the U.S. Surgeon General William Stewart reported to Congress that it was time for developed countries to "close the book on infectious diseases." Yet, by the 1960s, methicillin-resistant *Staphylococcus aureus* was discovered, marking the rise of new and re-emerging infectious diseases.

The traditional strategy of attempting to eradicate pathogenic bacteria with pharmacological methods, such as antibiotics, only serves as a temporary solution. More basically, for example, there are currently searches for strategies of co-existing with these pathogens, while delaying the onset of diseases/symptoms to past a human's lifespan.

The spread of infectious diseases can be classified in the order of smallest to largest scale as follows: endemic (regional), epidemic (national and involving several countries), and pandemic (global). Global environmental issues, too, are initially considered endemic problems arising in various regions that threaten residents and crops. These eventually come to be considered in terms of common factors (epidemic) shared by problems across multiple regions, and when these problems go global (pandemic), they are considered "global environmental issues." The causes of global environmental issues are complex, and likely involve various factors. However, the issues initially take on a concrete form in "regions," and how the issues come to light likely differs by the mode of life or culture of the region. By combining science, which takes a universal approach in surveying the global environment, and regional research, which is well-acquainted with the workings of individual regions, the nature of global environmental issues becomes all the more apparent. When considering preventative measures to take against global environmental issues based on scientific predictions, it is necessary to carry them out in a way that comports with the current condition of the region.

Population increases, extension of lifespan, and lifestyle-related diseases

It is essentially a given that the actions of humans and the increase in global population are causes of global environmental issues.

Through the last stages of the hunting and gathering period, mankind formed groups of tens of people and repeatedly traveled as hunters and gatherers. The global population is thought to have been 100,000 about 1 million years ago, and grew to about 500,000 roughly 200,000 years ago when modern humans were born, and then to about 10 million when agriculture began about 10,000 years ago. After that, the population continued to increase, although it was less than 1 billion before the Industrial Revolution. It thus appeared that a delicate balance was stuck between the global population and environment. Only since entering the 20th century, more specifically the past 50 years or so, have global fears presented in the form of global environmental issues come to light. The 100 years of the 20th century were marked by technological breakthroughs, changes in disease structure, globalization of politics and economics, and last, but not least, an increase in global population. This last factor deserves special mention from the perspective of mankind's history. The global population within these 100 years may in fact be larger than the total number of humans that existed from mankind's birth 7 million years ago to the 19th century.

The 20th century is not only the century of huge population growth, but it is also the century of extended human lifespan. While concentrated populations began to form about 10,000 years ago with the advent of agriculture, human lifespan was largely unchanged. However, the latter half of the 20th century brought about phenomenal changes in mankind's 7 million year history. An extended lifespan, which was one such change, brought about marked changes in population structure.

Even in the highlands, average lifespan increased as the food supply stabilized, and relief from starvation is now giving way to satiation. Fat, sugar, and salt were essentially lacking in all of highland history. Most people, who lived for about 30-40 years, took as much of these substances as possible, thinking it healthy, and adapted to the environment.

However, the plentiful intake of salt, which only recently became possible, leads to hypertension and stroke once past the age of 40 or so. Bodily mechanisms for storing energy, which were meant for times of starvation, lead to diabetes due to a satiating diet. The cholesterol metabolism pathway, a system of storing fat and effectively utilizing it in times of food shortage, causes cholesterol to deposit in blood vessel walls once past the age of 40, leading to arteriosclerosis and myocardial infarction.

The possibility that the genetic system that adapted the body of highlanders to hypoxia may speed up the development of diabetes with old age, as discussed above, can in fact be understood as "the global environment etched onto the human body."

In a society faced with a growing elderly population, it is vital to consider how the elderly view life and death, as well as how they attribute meaning to their lives.

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