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Non-Caucasian Highlanders and Modern Globalization

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Adapting to high altitudes: historical, evolutionary, and physiological perspectives

The birth of civilization and society can be traced back to the flatlands near large river basins such as the Nile, Yellow, and Indus river valleys. These "River Valley Civilizations," and their fates, have been debated to a large degree. High-altitude civilizations, on the other hand, have been largely overlooked.

High altitude regions (highlands) might be defined as those at altitudes greater than 2,500 m. About a quarter of Earth's area constitutes highlands, and 10% of Earth's population lives in these regions. The most prominent highland societies are those that have settled in the Andes, Tibet/Himalayas, and Ethiopia where all indigenous residents have been non-Caucasians. Each of these regions is populated by a few million people, and traces of mankind can be found that date back to prehistoric times.

Living in the highlands requires genetic adaptations to low oxygen, or hypoxia. Moreover, each highland civilization has developed strategies for domesticating crops and livestock that are specifically tailored to different altitude conditions (e.g., frigid climate and arid soil). While being isolated from the outside world, highland societies have maintained strategic commerce with lowland regions. On the mental level, religion among highland populations serves as a symbol of unity and the will of the people to overcome the harsh living conditions.

Although highland societies share many similarities, including hypoxic adaptation and environmental utilization, particularly notable are their diverse features. Moreover, while the lifestyles of highland populations have been maintained over thousands of years, this is beginning to change with the spread of globalism.

In this report, we trace the process of adaptation to high-altitude environments. In particular, we focus on the physiological and cultural adaptations of highlanders to these environments, and how highland cultures came into existence.

The high-altitude challenge

For lowlanders, an excursion to high-altitude regions (i.e., altitude >2,500 m) is accompanied by acute mountain sickness symptoms, including headache, loss of appetite, nausea, fatigue, dizziness, difficulty sleeping, rapid pulse, and shortness of breath with exertion. High-altitude illnesses, such as high altitude pulmonary edema and high altitude cerebral edema, can be lethal.

Highland expeditions by Caucasian lowlanders have been popularized by historical accounts, such as Plutarch's depiction of Alexander the Great's India expedition in 326 B.C., Cortez' conquest of the Inca Empire in the 16th century, and hardships experienced by Jesuit priests on missions to the Andes and Tibet after the 16th century.

In 1865, the famous Edward Whymper, whose party was the first to reach the summit of the Matterhorn (Swiss Alps) and ended with a tragic descent, also detailed the symptoms of high mountain sickness and high altitude conditioning on an Andean expedition. Upon reaching the second camp (5,079 m) during a trek of Mt. Chimborazo (6,262 m), Whymper and his guide lost all mobility and experienced headaches, difficulty breathing, and a high fever of 38ºC, which continued for 24 to 36 hours. Two days later, Whymper's group arrived at the third camp (5,268 m), and although the headaches subsided, their health continued to deteriorate. Several days later, they reached the summit. After that, their symptoms subsided and they remained at an altitude greater than 5,000 m for the following 26 days. Whymper classified the effects of decreased barometric pressure as either acute or chronic. Acute symptoms include increases in heart rate, body temperature, and blood pressure, whereas chronic symptoms include increased breathing, decreased appetite, and muscle weakness. Even by current high altitude medicine standards, Whymper's descriptions are considered accurate. His keen sense of observation as an artist is reflected throughout these descriptions.[1)]

Such descriptions have provided an understanding of the severe physiological conditions that hypoxia exerts on the body. Yet, even under these inhospitable conditions, non-Caucasian people settled in these regions thousands of years ago and continue to do so to this day. Descendants of the original non-Caucasian colonizers include the present highlanders of the Andes, Tibet, and Ethiopia. In order to appreciate how these highlanders came to settle in these regions and adapt to their respective environments, we must first consider the spread of mankind throughout the world.

The natural history of mankind

Our ancestors diverged from chimpanzees about 7 million years ago and came into existence in the grasslands of Africa. They began walking on two legs as *homo erectus* about 1.5-2 million years ago. Some of this population migrated to Europe and Asia by crossing land bridges about one million years ago. Those who arrived in East Asia and Europe are referred to as the Peking man and Neanderthals, respectively. Yet, no evidence exists to suggest that *homo erectus* reached or settled in the highlands.

Orogenic activity in the Andes, Tibet/Himalayas, and Ethiopia was essentially complete about 65 million to 180 million years ago, i.e., the Tertiary period. Dinosaurs went extinct 65 million years ago, and mammals adapted and spread to various locations around the world. An ice age marked the several hundred million years during which *homo erectus* was active.

Modern mankind diverged from *homo erectus* about 200,000 years ago. After remaining in Africa for an extended period, they left Africa about 100,000 years ago and populated various regions of the world, including Europe, Asia, the Americas, and Australia.[2)] At this time, humans formed nomadic hunter-gatherer groups consisting of tens of people, and population density remained low. Yet, about 10,000 years ago, humans began to cultivate and domesticate wild plants and animals, marking a new era of agricultural development, allowing for increased food production and storage. Those not engaged in agriculture became soldiers, bureaucrats, and technicians, further spurring the evolution of society, but at the same time, bringing about social and gender inequalities. Agriculture made large populations possible, and as a byproduct, introduced epidemics. For instance, the advent of irrigation prompted the concentration of humans and livestock, as well as the spread of mosquito-borne illnesses. Humid conditions on farmlands allowed mosquitos to survive and exert their functions as disease vectors. Indeed, mosquitoes and schistosomes proliferated in farmlands producing important crops, introducing diseases such as malaria, encephalitis B, and filaria.

The agricultural revolution, while significantly contributing to human well-being and progress, was essentially the prelude to environmental manipulation, i.e., environmental intervention by humans. Agriculture not only amplified the spread of mankind throughout the world, it made possible the conquest of various terrains (e.g., grasslands, mountains, and deserts) and life under various climates (e.g., tropical, temperate, and polar). The existence of Eskimos in polar regions, bushmen in the desert, and pigmies deep in the tropical forests, attest to the increased adaptability of humans to various environmental conditions.

Although humans are thought to have settled in the highlands after the development of agriculture, human bones have been found in Peru at an altitude of 4,200 m, with radioactive isotope dating confirming the bones to be 9,000 years old. [2)] Other studies have dated the existence of humans in highlands much earlier—20,000 years ago for the Tibet, and 10,000 years ago for the Andes.

Among the likely reasons for settling in the highlands were demographic pressures which forced the search for new hunting/gathering grounds and farm/pasture lands. The sparse population and lower temperatures also offered protection from insect-born infectious diseases. Yet, the transition to the highlands likely involved many groups repeatedly adapting and failing, until they ultimately acquired their distinct highland niches. A brief overview of hypoxic adaptation will provide us with the background needed to discuss such adaptations.

Adaptation to high-altitude hypoxia

The human respiratory system evolved to make efficient use of the 21% oxygen in the atmosphere. Alveoli, separated from air and blood by a thin membrane, exchange oxygen for carbon dioxide, and the oxygen is subsequently distributed to all organs throughout the body. Generally speaking, oxygen concentration decreases at higher altitudes. For instance, the oxygen concentration at 3,000 m is two-thirds that at sea level, and one-half and one-third that at sea level at 5,000 m and 8,000 m, respectively. Yet, as shown in Table 1, the actual concentration of oxygen in human arteries is one-half that at sea level at the summit of Mt. Fuji, and one-third that at sea level at 5,000 m.[3)]

After 30 years of extensive effort, Great Britain in 1953 finally succeeded in reaching the summit of Mt. Everest. Among the contributing factors for this feat were hypoxic adaptation, an inexhaustible passion, being equipped for frigid conditions, climbing technique, and oxygen supply. Humans who colonized the highlands several thousand years ago obviously had no supplemental oxygen to rely on. Thus, as a first step in adapting to their new environment, they underwent genetic alterations to redesign and restructure their bodies to make the most efficient use of oxygen by maintaining bare minimal oxygen saturation in organs. Settling in the highlands required physical activity for survival. Moreover, oxygen not only functions to maintain the mental capacity, physical strength, and cardiopulmonary capacity required to carry out strenuous activities key to survival (e.g., hunting/gathering, agriculture, livestock farming), it also plays essential roles in fighting infections, hemostatic mechanisms, and stocking energy.

Genetic adaptations to hypoxia not only involved physiological modifications, but also those that ensured that descendants would survive (spanning the processes of pregnancy, delivery, and development). In other words, highland settlers were subjected to the same need for stability as lowlanders with respect to the four inevitables of human life (birth, aging, sickness, and death). When the City of Potosi (4,000 m) was founded in the Inca Empire, there were about 100,000 Indios and 20,000 Spanish people. While Indios continued to proliferate as before with a steady birth rate, the Spanish either became infertile or had children with growth defects. Given this situation, Spanish mothers would descend to sea level, give birth, and live at lower

Table 1　Altitude and Hypoxia (Source: Masuyama S [3)])

Altitude	Sea-Level 0m	Top of Mt Fuji 3776m	BC of Everest 5200m	Top of Everest 8848m
Atmospheric Pressure (mmHg))	760	480(2/3 AP)	380(1/2 AP)	250(1/3 AP)
Atmospheric Oxygen (mmHg)	159	101	80	52.5
Inspiratory Oxygen (mmHg)	149	91	70	43
Alveolar Oxygen (mmHg)	100	51	37	28
Arterial Oxygen (mmHg)	95	46	32	23
Arterial Oxygen ratio (vs.Sea-Level)		**1/2**	**1/3**	**1/4**

AP: Atmospheric Pressure

altitudes for one year. The first Spanish child was born in Potosi 53 years after its founding. The birth occurred on Christmas Eve of 1598, and was considered a miracle brought about by St. Nicholas.[4] Ever since, the Spanish began to intermingle with the Indios, allowing for hypoxic adaptation at the genetic level.

Genetic adaptations to high-altitude hypoxia

As mentioned above, Andean, Tibetan/Himalayan, and Ethiopian highlanders required genetic strategies to adapt to their respective hypoxic environments (Figure 1).

Growing evidence suggests that strategies for hypoxic adaptation differ by region. According to Beall et al.,[5] Andean and Tibetan highlanders both have lower oxygen saturation than their lowlander counterparts, and Andeans have higher hemoglobin levels. Hemoglobin is only slightly increased in Tibetans. Although the reasons are unclear, Ethiopian highlanders exhibit neither lower oxygen saturation nor increased hemoglobin (Table 2).

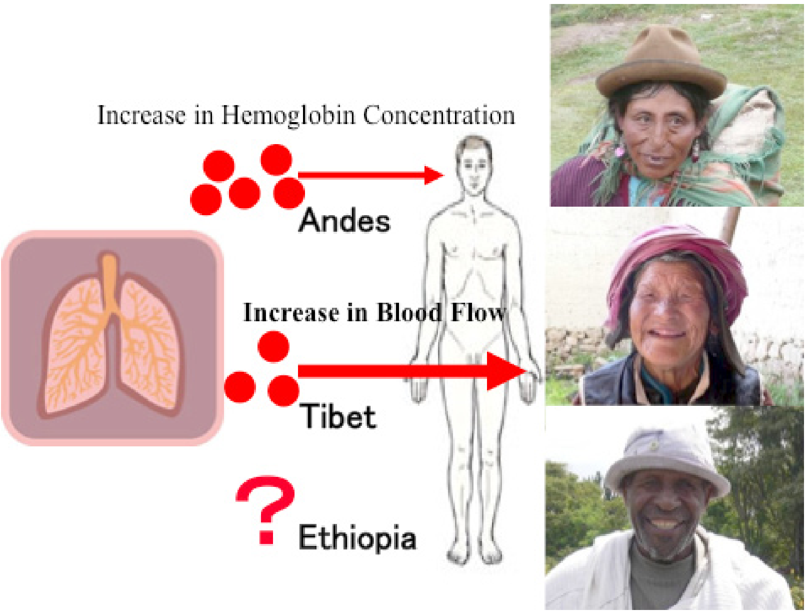

Fig. 1 Diversity of Hypoxic Adaptation

Table 2 Difference in Hypoxic Adaptation among Andean Tibetan and Ethiopian Highlanders (Source: Beall CM [5])

	Altitude (m)	Oxygen Saturation (%)	Hemoglobin Levels (g/dl)
Lowlanders	0	97	15.3
Andean Highlanders	4000	92	19.1
Tibetan Highlanders	4000	89	15.8
Ethiopian Highlanders	3500	95	15.6

The main form of hypoxic adaptation among Andeans highlanders is increased hemoglobin concentration, the molecule that carries oxygen throughout the body. A similar phenomenon is seen when lowlanders travel to high altitudes. Figure 2 depicts the changes in oxygen saturation and red blood cell counts of a Japanese expedition team as they climbed from Lhasa (3,650 m) to the base camp (5,000 m) and reached the 8,000 m summit (Shishapangma). As altitude increases and atmospheric oxygen decreases, oxygen saturation decreases and red blood cells increase.

This physiological phenomenon might be similar to that observed in Andeans, who colonized the highlands about 10,000 years ago. On the other hand, the strategy adopted by Tibetans, who colonized the highlands about 20,000 years ago, is pulmonary arterial dilation, which allows for increased blood flow. Hemoglobin levels are only mildly increased in this population. As will be discussed in the elsewhere,[6] Qinghai in China is populated by Tibetans and Han Chinese. Interestingly, the Hans have significantly higher hemoglobin levels than their counterpart Tibetans at the same altitude and region. Consistent with this, the Hans are also more susceptible to polycythemia.

Evolutionarily speaking, Tibetans have adopted an adaptive strategy that requires more time to achieve. They have little need for increased hemoglobin, given their increased blood flow via arterial dilation. With regard to the Ethiopians, who have lived in hypoxic environments for the longest (more than 50,000 years), their adaptive mechanisms remain a mystery. As mentioned above, Ethiopian highlanders neither have increased blood flow nor hemoglobin. Consistent with the ample evidence suggesting that mankind originated near Ethiopia, evidence points to mankind settling in the Ethiopian highlands much earlier than in the Andes or Tibet. Given the mystery surrounding the adaptive strategies of Ethiopian highlanders, they most likely have adopted strategies distinct from those of Andeans and Tibetans.

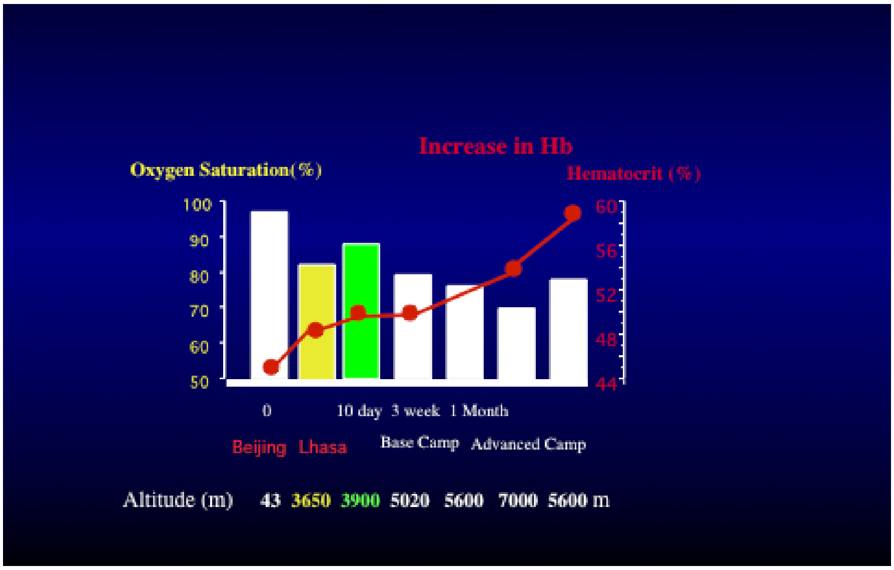

Fig. 2　Change in Oxygen Saturation and Hematocrit of Kyoto University Medical Ecpedition to Shishapamgma (0-7000 m) in 1990

Birth and illness at high altitudes

The birth rate in Indio society essentially mirrors that of their lowland counterparts. Similarly, the rate of population growth in Peru is essentially no different from lowland regions. Although infant mortality rate is somewhat higher in highland villages, fetal mortality and miscarriage rates are similar to that seen in the lowlands.[7] This suggests that unlike the situation when lowlanders visit highlands, those adapted to highland environments do so with respect to reproduction, delivery, and child-rearing as well. Thus, rather than a direct effect of hypoxia, the increased infant mortality rate likely reflects differences in nutritional and sanitary conditions.

Infectious diseases are rarer in the highlands. Indeed, Andeans hesitate to travel to the lowlands during the malaria season. Two forms of infectious diseases exist, those transmitted by animals and those transmitted directly among humans. One likely factor for settling in the highlands was to escape diseases brought about by densely populated lowland societies. In the highlands, disease-bearing vectors (e.g., mosquitos) have difficulty surviving, and given the sparsely populated communities, disease outbreaks are rare. Deep ravines and springs at high altitudes function as both water sources and sewers, inhibiting the proliferation of pathogenic microbes. Radiant heat from sunlight also prevents bacterial proliferation.

The harsh natural conditions that separate high altitude regions from the outside world also restrict the influx of human-transmitted diseases. While endemic diseases such as goiters exist, ecological, sociocultural, and lifestyle related factors have contributed to maintaining highlander health. Given their isolation from the outside world, both geographically and informationally, the experience and knowledge provided by elders were of particular importance. The few elders who existed were likely treated with great care and respect. Until about 30 years ago, spurred by the lack of tourism, trade routes, and market economies, as well as lack of contact with the outside world, legends suggestive of Shangri-La were abound in a number of highland societies.

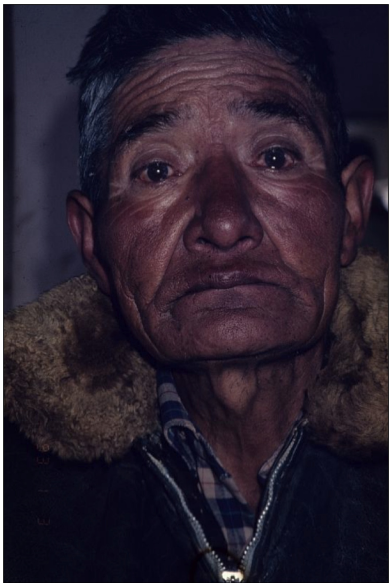

Fig. 3 An old male with chronic mountain sickness in Titicaca area (3800 m above sea-level) in Andes.

Despite these advantages, highlanders, probably due to their limited interactions with outsiders, had little immunological resistance to viruses, and were particularly susceptible to human-introduced viruses. Historically famous is the downfall of the Inca Empire in the 16th century upon invasion by the Spanish. While cavalry and iron weapons played a large part, the smallpox epidemic introduced by the mass migration of Spanish into Panama and Columbia is thought to have played a much larger role and foreshadowed the Spanish victory. Smallpox, typhus, bubonic plague, and influenza existed and have been documented since the Hellenistic Age, and thus most Europeans had some degree of immunity to these pathogens. Yet, the natives of the New World had no such exposure. Diseases introduced by European migrants spread faster among the natives than their rate of expansion, decimating 95% of the native population even before Columbus discovered the Americas.[8]

A number of highland-specific diseases exist that result from hypoxic adaptation. In the preceding section, we discussed increases in hemoglobin as an Andean strategy. Yet, excessive production of hemoglobin leads to Monge's disease, a chronic mountain sickness resulting from excessive adaptation to hypoxic environments. Monge's disease is often seen at altitudes greater than 3,000 m and is characterized by severe hypoxemia, marked polycythemia, and psychological symptoms (Fig 3).

Monge's disease has not been reported outside South America. Among Tibetans, the strategy of increasing blood flow can lead to chronic pulmonary hypertension, a chronic mountain sickness rarely seen in South America. Thus, chronic mountain sicknesses reflect the respective mechanisms of hypoxic adaptation, and are considered to be conditions brought about by excessive or insufficient adaptation.

Aging at high altitudes

While the average life expectancy in Japan is currently above 82 years, it was 42 years at the beginning of the 20th century. At that time, average life expectancy was 45 years even in England, the most advanced country. Life expectancy involves a complex interaction between genetic, environmental, and social factors. In Japan, living past 75 years is common. Yet, even with the most advanced medicine, only a few people live past 100 years, and living past 120 years is considered virtually impossible.

One hundred years ago, the average age of highlanders likely did not exceed 40 years. Yet, recent years have seen an increase in the ratio of elderly among highland residents. When we visited the Tibetan city of Tinley (altitude 4,000 m) for a medical survey in 1990, there were no elderly >75 years of age. In an elderly health survey conducted in 2008 and 2009 in China's Qinghai-Tibet Plateau, of the 398 (2008; Qinghai Prefecture; altitude 3,000 m) and 209 (2009; Yushu Prefecture; altitude 3,800 m) elderly, 10% of each population was >75 years. The oldest individual was 87 years in both populations.

Diseases and aging can be easily understood from the perspective of evolutionary medicine. When the ancestors of mankind diverged from those of chimpanzees 7 million years ago, our genes, using the body as a carrier, designed the body to hunt and gather in small groups. Genes also programmed the body to withstand diseases by establishing an immune system, keep damage from external injury minimal with a wound healing mechanism, stave off starvation with an energy storage system, and withstand strenuous physical activity with a system for nervous and muscular activity. That is, genes had programmed the body to maximally adapt to the environment and living conditions of the Stone Age. Life expectancy during the Stone Age was likely on the order of 20 to 30 years, and adaptation occurred so that the body would last for this duration. The transition from a hunting/gathering life to an agriculture-based one, in addition to increased population density, was accompanied by starvation, physical labor, and altered life expectancy. Yet, in all of mankind's 7 million year history, the most astounding changes to human physiology occurred in the 100 years following the 20th century. Stabilization of the food supply in developed countries relived people from starvation to obesity, changing food composition from carbohydrate-based to more expensive protein- and fat-based diets. Changes in industrial structure shifted manual labor to a more sedentary lifestyle, leading to a lack of exercise. With respect to diseases, although it conventionally took hundreds of years for diseases to spread to different regions, transportation made it possible for one individual to spread a disease within a few hours.

More than anything else, the medical revolution increased human life expectancy. Changes in human physiology also altered disease structure. The Stone Age-adapted body, for the first time, experienced an 80-year lifespan. The entire span of human evolution was marked by a constant shortage of fat, sugar, and salt, and most people adapted by taking as much of these substances as possible, and it was considered healthy to do so. Once salt became plentiful and readily available, it brought about hypertension and stroke. The body's energy storing mechanism, which was originally developed to overcome starvation, served to promote diabetes. Cholesterol metabolism, which functions to store fat as an effective energy source during times of food shortage, accelerates arteriosclerosis. By no means is it an exaggeration to say that many of the chronic diseases faced by developed countries today are a result of conditions far exceeding the level of adaptation, tailored to a 30-year lifespan during the Stone Ages, due to rapid changes in the social environment and life expectancy. One hundred years is obviously too short a period to genetically adapt and alter the body's regulatory mechanisms.

Biological adaptation is the process by which animal species alter their bodily structure based on the natural environment in order to ensure conservation of the species and allow for survival in a specific environment. Highlanders likely maintained, until recently, adaptation to ultraviolet rays with protective skin, the invaluable lifestyle of exercise habits, and, although simple, a balanced diet throughout life, which were lost long ago by those in developed countries. Social globalization is starting to change this, hypertension and diabetes are also beginning to increase among highlanders.

Genetic and cultural adaptation

In contrast to genetic adaptation, cultural adaptation involves minimizing physiological changes and adapting to the outside world by adopting a new culture. Highlanders have established a delicate balance tailored to each respective region. For instance, to ensure their survival and heritage, they selected for various region-specific resources capable of domestication and propagation in the highland environment, and established sustenance strategies tailored to the respective regions. For instance, the Andeans domesticated potatoes, llamas, and alpaca, whereas Tibetans domesticated barley and yaks. Ethiopians, on the other hand, cultivated indigenous grains such as teff and ensete. Also important to these highland societies was the spiritual world. For instance, Andeans worshiped the Sun God, Tibetans adhere to Tibetan Buddhism, and Ethiopians have the Ethiopian Orthodox Church.

If the consequences of cultural adaptation can be called "civilization," then one can say that many diseases have been brought about by civilizations. Culture-specific mindsets, religious ceremonies, and taboos greatly influence the use of technology, the search for resources, population control, and health and survival. Each individual civilization and society brings about particular diseases, and such diseases in turn have the power to reform civilization and society. According to McNeil, leprosy of 13th century Europe, pests of the 14th century, syphilis of the 16th century, typhus and smallpox of the 17-18th centuries, cholera and tuberculosis of the 19th century, and influenza of the 20th century are all diseases specific to particular civilizations and societies. Even recently, despite their biological underpinnings, kuru in Papua New Guinea, leprosy in Southeast Asia, AIDS in Africa, and cancer and cardiac diseases in Western countries are closely associated with the values specific to the respective societies. Infectious diseases such as tuberculosis and syphilis, and even acute communicable diseases such as cholera and typhus, do not cause a "sickness" because the pathogens "exist." Rather, only when conditions are optimal for the transmittal and propagation of the pathogen does a sickness arise. Such conditions have been brought about by human intervention, i.e., "society."

With the exception of the Americas in the 16th century, sparsely populated mountainous regions have been spared from major infectious diseases, and while poor, most highland residents likely lived life in health and with a sense of mental satisfaction. The wave of social globalism, however, with its associated industrialism, market economies, and information revolution, has not spared the highlands. Globalism necessarily alters the natural environment and the physical and mental state of people. Of particular interest is the "glocal" issue of how hypoxic adaptation, which developed over several thousands of years, will relate to recent lifestyle-related diseases.

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