

Title	Elderly of the Tibetan Highlands and Impaired Glucose Tolerance
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Citation	ヒマラヤ学誌 : Himalayan Study Monographs (2013), 14: 3-8
Issue Date	2013-03-20
URL	http://dx.doi.org/10.14989/HSM.14.3
Right	
Type	Departmental Bulletin Paper
Textversion	publisher

Elderly of the Tibetan Highlands and Impaired Glucose Tolerance

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The spread of diabetes in Asia

Diabetes is characterized by reduced secretion of insulin, a molecule that monitors blood sugar levels, or reduced sensitivity of cells to insulin. Considered a lifestyle disease, it is often seen in well-off individuals in developed countries. This view is beginning to change, as in recent years, diabetes is spreading throughout Asia, which our own studies corroborate.¹⁾ Indeed, while diabetes was originally seen predominantly among the rich, we found that diabetes is also prevalent among the poor in even in Japan, leading to a J-shaped curve.²⁾ Infectious diseases spread at three levels: endemic (within a region), epidemic (within a country or countries), and pandemic (worldwide). Although not infectious, diabetes is often referred to as a pandemic in Asia. One can speculate that the poor, whose bodies adapted to the limited calories available over their lifespan, could not adapt to the sudden abundance of food and lack of exercise brought about by globalism. This phenomenon apparently holds true in highland regions as well, where residents had lead traditional lifestyles. Before such a discussion, however, a brief survey of the natural history of mankind is warranted.

The natural history of mankind

Mankind's ancestors emerged about 7 million years ago in the African plains, and by about 2 million years ago, acquired an increased brain size and ability to use tools. About 1.8 million years ago, one group of *homo erectus* crossed a land bridge connecting Africa and Eurasia and spread into Asia. Those who ended up in East Asia are referred to as the Peking man or Jawa man. While a sizable group of *homo erectus* stayed in Africa for a few million years, mankind is thought to have spread

around the world by about 100,000 years ago. The amazing speed of this spread is evidenced by the presence within tens of thousands of years of mankind in Europe, Asia, North and South Africa, and Australia. Up to this point, mankind formed small groups of tens of people and led a nomadic lifestyle as hunter-gatherers. Population bursts were not observed at this stage.

About 10,000 years ago, mankind invented agriculture and domesticated wild plants and animals. This marked a major turning point in mankind's history. Agriculture made possible increased production and storage of food. Those not involved in food production became soldiers, bureaucrats, and technicians, and brought about an evolution of social structure, the byproducts of which were social and gender inequalities. Increased food production led to denser populations, which was accompanied by diseases. Farmlands became a breeding ground for mosquitoes, disease vectors for pathogenic microorganisms such as malaria, Japanese encephalitis, and filaria. Agriculture increased mankind's spread throughout the world, and humans began to penetrate different environments. They conquered many terrains, such as grasslands, mountainous regions, and deserts, and learned to live in tropical, temperate, and arctic climates. This is exemplified by the Eskimos of the far north, Kungs of the deserts, and pigmies living deep in tropical forests. Mankind's advance into the hypoxic highlands is thought to have occurred after the advent of agriculture. The main reason for mankind's move to the precipitous highlands was not only based on demographic pressures (which led to the search for new arable land and pastures), but also the advantageous ecological mechanisms such environments provided — protection

from diseases due to sparse populations and low temperatures. Touching on the relationship between the evolution of mankind and diseases will provide adequate background for a discussion of how humans adapted to highland environments.

Diseases and the evolution of mankind

Charles Darwin's theory of evolution is highly related to disease theory, as exemplified by the immune system (which adapts to fight pathogens), pathogens adapting to overcome the immune system, mismatches between the human body and environment, and adaptation by natural selection. From a single cell, life evolved over several hundreds of millions of years to achieve our current complex body structure. The human body is more complex and sophisticated than anything developed by the hands of mankind. Natural selection, over an extended period, exerts its influence by acting to maximize gene propagation. This not only applies to human genes, but to other organisms as well. Nowhere, however, is the generational shift of viruses and germs more pronounced and rapid than mankind. The evolutionary adaptation undergone by our bodies through genes reflects a history of battles and compromises with microbes, viruses, and various plant and animal genes. In addition to infections, modern lifestyle diseases such as high blood pressure and high cholesterol can be understood within the evolutionary context.

Using the body as a vehicle, our genes, for about several million years, designed the body to hunt and gather in small groups. Genes designed an immune system to fight infectious diseases, hemostatic mechanisms to minimize blood loss from injuries, energy storage mechanisms to stave off starvation, and a system for withstanding strenuous activity through nervous and muscular activity. Indeed, genes designed the body to maximally adapt to the environment and living conditions of the Stone Age. Since life expectancy during the Stone Age was about less than 30 years, this "maximal adaptation" was likely designed to last 30 years. The hunter-gatherer life gradually transitioned to an agriculture-based one about 10,000 years ago, leading to denser populations,

but did not markedly reduce the amount of physical labor or danger of starvation, nor did it increase life expectancy.

The most astounding physiological changes in mankind's 7 million year history were brought about in the past 50 years. With a stabilized food supply in developed countries, mankind was relieved of starvation and acquired a plentiful food supply. Food composition also shifted from a carbohydrate-based diet to more expensive protein and fat-based diets. Changes in industrial structure shifted the agricultural lifestyle of physical labor to a sedentary one, which was accompanied by constant lack of exercise. While it conventionally took tens of years, or even hundreds of years of changes in social structure for diseases to spread to different regions, advances in transportation made it possible for one individual to spread a disease to a different region within a few hours.

Possibly the greatest change brought about by medicine was the pronounced increase in human life expectancy. Changes in human physiology over the past 100 years also led to a concomitant major shift in disease structure. For the first time, the Stone Age-adapted body would experience a lifespan of 80-90 years. For most of human evolutionary history, fat, sugar, and salt were constantly scarce. Most people adapted by consuming as much as these substances as possible, and it was considered healthy to do so. Yet, sufficient intake of salt, which only recently became possible, leads to hypertension and stroke once past the age of 40. Similarly, the physiological mechanism of storing energy to overcome starvation brought about diabetes once food became plentiful. The cholesterol metabolism system, which effectively uses stored fat sources in times of food shortage, causes deposits in arterial walls after the age of 40, leading to atherosclerosis and myocardial infarction. The body's mechanism of incorporating calcium into bone during the growth years, causes accumulation of calcium in arteries in the middle years, also leading to atherosclerosis. By no means is it an exaggeration to say that the various chronic illnesses faced in current developed countries resulted from Stone Age-adapted physiological mechanisms being subjected to

conditions far exceeding the level of adaptation brought about by rapid changes in the environment and life expectancy. The past 100 years that induced marked changes in lifestyle is much too short a period for genes to evolve and adapt the body's regulatory mechanisms.

Biological adaptation refers to the process by which animal species alter their physical structure to make possible life in a particular environment and preservation of the species. People living in mountainous regions had genetically adapted to hypoxia and, until recently, maintained an effective lifestyle of exercise and although simple, a balanced diet. This lifestyle had been long lost by those in developed countries. Yet, pronounced changes are also becoming apparent among highlanders.

Adaptation to hypoxia by genetic mutation

In low oxygen environments, the hypoxia inducible factor (HIF) system becomes activated. HIF is a transcription factor induced when cells are faced with a deficient oxygen supply. For instance, nutritional deficiency, decreased extracellular pH, and hypoxia due to insufficient blood flow are observed in cancer lesions. For cancer cells to continue thriving, they need to establish new vascular networks to increase blood flow to the lesion and rectify the hypoxic condition. HIF is induced under hypoxic conditions and drives the expression of various downstream target genes. While one might assume that marked changes are occurring in the HIF system among Tibetan highlanders adapted to hypoxic environments, how this works overall remains unclear. Nonetheless, Tibetan highlanders have recently been shown to harbor various mutations in the HIF-related genes such as endothelial PAS domain-containing protein 1 (EPAS1), Egl nine homolog 1 (EGLN1), and peroxisome proliferator-activated receptor alpha (PPARA).^{3,4)}

Famous highland regions include the Andes in South America, Tibet and the Himalayas in Asia, and Ethiopia in Africa. Andean, Tibetan, and Ethiopian highlanders each underwent unique physiological adaptations to their respective hypoxic environments.⁵⁾

While Andeans adapted to hypoxia by increasing their hemoglobin levels, Tibetans instead increased their blood flow. It remains unclear how Ethiopian highlanders adapted to their hypoxic environment. EPAS1, EGLN1, and PPARA mutations observed in Tibetan highlanders appear to inhibit increases in hemoglobin.

Diabetes in the elderly of the Tibetan highlands

Our previous survey of highland residents of China's Qinghai-Tibet Plateau revealed that diabetes is increasing among the resident elderly.⁶⁾ Similar findings were observed in India's mountainous Ladakh region. Changes in lifestyle and life expectancy have not spared even highland residents who adhere to their traditional livelihood, and this may explain the emergence of diabetes. Exercise has decreased even among Tibetan highlanders, and this is particularly pronounced in urban regions, where overeating seems to be the trend. Thus, the phenomenon observed in Asian lowlands is also becoming apparent in the Tibetan highlands.

Notably, however, the type of diabetes observed seems to markedly differ from that in the Asian lowlands. Indeed, diabetics among the Tibetan highlanders often have concomitant polycythemia (Table 1).^{7,8)} This phenomenon is not observed among diabetics in Japan or the Asian lowlands. What does it mean that Tibetan elderly, who do not have increased hemoglobin, often have concomitant polycythemia? One must first consider that the hypoxia-related genes (i.e., EPAS1, EGLN1, and PPARA) mutated in some Tibetan highlanders are not only involved in hemoglobin synthesis, but also play key roles in fat and sugar metabolism.⁴⁾

Two hypotheses can explain why Tibetan elderly diabetics have a high frequency of concomitant polycythemia. First, as a strategy to adapt to hypoxic conditions, Tibetan highlanders acquired mutations in HIF-related genes, thereby selectively increasing blood flow, rather than hemoglobin. While effective until the late middle ages, the effectiveness of this mechanism begins to wane with further aging. Compounded with

Table 1 Close Association of Polycythemia with Glucose Intolerance in Elderly Highlanders in Asia (Ref.8).

	YuShu in Qinghai		Ladakh in India	
	Without Polycythemia	With Polycythemia	Without Polycythemia	With Polycythemia
N (%)	114 (55)	95 (45)	81 (69)	36 (31)
Male (%)	48	34*	44	33
Age (years)	65.7±5.8	66.6±6.1	69.0±6.5	70.1±7.3
Hb (g/dl)	15.3±1.6	17.6±1.7***	14.1±1.9	17.6±1.7***
SpO ₂ (%)	89.5±3.1	88.8±3.6	89.6±4.8	87.1±6.5*
BMI	26.2±4.3	28.8±4.4***	22.0±3.2	22.4±2.7
% BMI>25	54	82***	15	14
% HT	49	73***	51	58
% DM	10	18	3	19**
% DM or IGT	41	56*	36	58*
Odds Ratio for DM or I (CI for DM or IGT)	1.0	2.3* (1.2-4.3)	1.0	3.0* (1.2-7.1)

*: p<0.05, **: p<0.01, ***: p<0.001; Normocythemia versus polycythemia
Chi square test, Student's t test, Logistic regression

@: Odds ratio (95% CI) of polycythemia group for DM or IGT after the adjustment for age, sex, obesity(BMI<90) and SpO₂<90 by multiple logistic regression.

Hb: Hemoglobin

BMI: Body mass index

HT: Hypertension

DM: Diabetes

IGT: Impaired glucose tolerance

CI: Confidential interval

other lifestyle changes, this leads to diabetes. At the same time, the hemoglobin-reducing effect also begins to wane with age, leading to polycythemia. The other hypothesis purports that those unable to acquire mutations in HIF-related genes adapted to hypoxia by increasing hemoglobin levels. With age, this mechanism leads to glucose intolerance. Future studies will be needed to determine which, if any, of these possibilities is correct.

Conclusion

Mankind's history is marked by two principles: biological factors that allowed environmental adaptation via genes for the preservation of individual organisms and species, and the non-biological self-propagation of culture built and passed on through tradition and learning. Given that both genes and culture have self-propagating properties, Richard Dawkins referred to the former principle as "gene" and the latter as "meme."⁹⁾ Diabetes can be considered a phenomenon reflecting a blend of biological genes and cultural memes.

From the perspective of evolutionary medicine,

insulin, which monitors blood sugar levels, instructs cells to take in glucose when blood glucose levels are high, and instructs fat cells to save glucose as fat to prepare for unforeseen starvation. In one sense, diabetes can be considered the consequence of humans adapted to starvation conditions being thrown into an age of satiation. During the long course of evolution, our physiology, adapted to shortages and scarcity, was not sufficiently prepared for overabundance. Insulin represents one of few bodily mechanisms for signalling excess.

This article touched on elderly diabetics living in Tibetan highlands from the evolutionary perspective and cultural and disease aspects. Various biological adaptation hurdles exist for lowlanders to venture into the highlands, including high altitude sickness. Such hurdles further isolated these highland civilizations. The Tibetan highlands represent an environment that embodies the extremes of human habitability. Even in these environments, which push the limits of hypoxic adaptation, humans met these challenges by adapting to and developing vast civilizations.

The blue skies observed on a daily basis by



Figure 1 Holy Mountain, Amunemachin, in Qinghai Plateau in China.

highland residents are populated by pure white peaks, the source of pure water necessary for life. These peaks also serve the purpose of “holy mountains,” which concretizes the concept of high religion and acts as a rallying point for the beliefs of the people (Figure 1). Tibetan civilization has even developed a unique field of medicine influenced by its particular ecosystem and civilization.

The keywords agricultural production, population problems, and diseases explain why people moved to mountainous regions. In addition to the aforementioned criteria for real adaptation, just as Pytheas of Greece set out to the North pole at around 300 BC, exploratory activities carved into history by 20th century humans most likely existed in prehistorical times as well. Highland residents, even if poor, likely led healthy and psychologically fulfilling lives. However, globalism, which centers on industrialism, market economy, and the information revolution, has finally reached the highlands. Globalism necessarily alters the environment, as well as the physical and psychological nature of humans. Our medical survey of highland residents taught us that mankind should reflect back on the origins of, and reconsider the difficult issues of, globalism and regionalism. Only then does it become evident that mankind requires abilities that lie in a dimension different from either the biological adaptations acquired for survival during mankind's evolutionary history or the cultural adaptations in the

form of politics and economics, i.e. the spirit of exploring the unknown and courage.

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