HYPOXIA AND HEALTH: FROM FIRST HISTORICAL DOCUMENTS TO PREVENTION AND TREATMENT

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*Clinical Research Laboratory
of "Hypoxia Medical Academy",
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In ancient times, when the population of the Earth was no more than just several millions, people preferred to live where it was easier to survive. High mountains difficult to climb were regarded to be fit only for Gods, as Gods were almighty and immortal. Olympus, the highest mountain in Greece (2918 m) with numerous acute peaks and inaccessible canyons, which were covered with thick snow in winter, was considered by ancient Greeks as the place of residence of the twelve chief Gods. The sacred oath "By twelve Gods of Olympus" expressed deep respect to those who determined the destiny of the world [I, p. 20-23].

High altitude air was harmful for humans, and, as Alexander Humboldt noted, ancient people were much more afraid of the mountains than admired them [2, p. 10]. Only rarely people climbed the mountains.

However, they built cathedrals in honor of their gods in the mountains, on the slopes ilnd peaks accessible for humans. We can remember the famous Apollo Sanctuary in Delphi created in the YI th-IV th centuries I1C on the slope of the sacred Parnassus mountain (2458 m). One reason for this was human desire to reach the abode of gods. In addition pilgrimage to places difficult to access was considered as a manifestation of selflessness [2, p. 10]. However, one more reason is probable. Now we know that the majority of unprepared people suffer from acute mountain sickness starting from 250()-3500 m on the Elbrus and from 4500 m in the Andes, Himalayas, and in African mountains [3, p. 76]. Therefore repeated pilgrimage to cathedrals situated at an altitude of 1-2 km fortified the defense forces of the organism, making it resistant to stresses and diseases.

The first written report about the effect of high-altitude air on human organism dates back to the IV th century BC.

Francis Bacon (1561-1626) citing Titus Livius (59 BC to AD 19), the author of History of Ancient Rome, noted that Aristotle (384-322) knew that those climbing the Olympus had to breath through sponges wetted in water and vinegar, because high altitude air was very dry and not fit for breathing [4]. Robert Boyle (1627-1691) also referred to Aristotle in 1666 in his book *New Experiments Physico-Mechanical Touching the Spring of the Air* [5]. However authors of later times could not find relevant note in Aristotle's works (2, p. 8), as time and wars destroyed the greater part of precious texts.

There is indirect evidence that ancient Greek philosopher and physician Empedokles (490-430 BC) climbed Etna (3263 m) on Sicily, the highest volcano in Europe.

Several years later an ancient Greek historian Xenophon (43()355 BC) described how the soldiers of Kyrus Jr. crossed high Armenian mountains on their way to Byzantia; the ten-thousand army lost many soldiers during this crossing. The same happened to one hundred thousand army of celebrated Hannibal in the year 218 BC in the Pyrenees and Alps. Though he lost many soldiers

" and elephants in the mountains, he crossed the mountain ridges 8nd conquered the enemy by suddenly "falling" on the Romans from behind high inaccessible mount8ins [2, p. 9].

However the Chinese West Han Dynasty chronicles. dating back to the 30s BC, "remain the first historically reliable written evidence of the detrimenwi effect of high altitude air on humans and domestic animals.

The chronicler writes that the court counselor Too Kin advised Emperor Chung ti who governed in 37-32 BC not to send a C8ravan of a hundred people to Afghanistan across Tibetan mountains:

"Next, one comes to Big Headache and Little Headache Mountains, as well as Red Earth and Swelter Hills. They make a man so *hot that his face turns pale, his head aches, and he begins to vomit. Even the donkeys and swine react this way"* [6, p. 316]

'The walkers and riders hold on to each other and are led forward by ropes for some 2000 Ii [1000 km or 600 miles] *before they reach Hsientu* [Hindu Kush]. *By then, half of the animals have fallen to their death in the gorges. If a man falls, it is impossible to save him. It is so difficult and dangerous that words cannot describe it"* [6, p. 322J.

It is the very first reliable description of mountain or high-altitude sickness. Written two thousand years ago, it is acknowledged to be the first golden page in the history of high-altitude medicine and hypoxic states [4,7,8,9, 10].

American scientist Daniel Gilbert analyzed the possible ways le8ding from China to Afghanistan [6] and showed that this route could go across the K8rakoram Range in the Himalayas or across Pamir. The most difficult fragment of this route was the Kilik Pass at an altitude of 4827 m above the sea level. Based on L. Pugh's data who measured the pressure at various altitudes [II], D. Gilbert showed that " ... the barometric pressure at the Kilik Pass equ81s 8pproximately 430 Torr. Thus, the ambient barometric pressure is reduced 43 % from the sea level value. The corresponding oxygen pressure in the lung passages saturated with water vapor equals 80 Torr" [6, p. 323].

Four hundred years later, 8bout the year 403, Chinese monk Fa Hsien described his companion death from mountain sickness when they passed from Kashmir to Afghanistan across the high Karakoram Pass at an altitude of 5690 m [12]. The fellow died with foam on his lips, which might be a characteristic of acute lung edem8.

The first description of mountain sickness in Americ8 appeared much 18ter, in the XVlth century, and is associated with the conquest of Incas. The Inca civiliz8tion bloomed in the Andes between [100 and [532. From ancient times the aborigines well knew acute mountain sickness. Its local name was *soroche.* For centuries the Incas knew the means preventing it: COC8 leaves, which they chewed when climbing the mountains [13]. This plant was more precious than gold:

"... *in certain mountain valleys there grows a plant called coca, which the I nd ians prize higher than gold or silver. The unique property of this plant, as experience shows, is that whoever chews its leaves feels neither cold, nor hunger, nor thirst"* [13, p. 244].

This is how Spanish physician de Zarate described coca in 1555. However coca gave just a temporary effect, alleviating the manifestations of mountain sickness, such as headache, nausea, vomiting, loss of appetite, insomnia, and fatigue.

The Incas had no written language, and the first description of this sickness in America was made by a Spanish Jesuit, Father Jose de Acosta (1540-1600). He spent almost 20 years in Peru during the conquest (between [569 and [589). [n 1590 he wrote a book about the New World *Historia Natural y Moral de las Indies* [14], which was soon translated into many European languages. [n Chapter 9 Acosta describes the difficulties of crossing the Andes, which he experienced in [572, when he crossed Escaleras de Pariacaca, the highest pass (about 4800 m) in the mountains. D. Gilbert suggests that the modern name of this mountain is Tullujuto [15]:

'There is in Peru a very high mountain range that they call Pariacaca. I had heard tell of this, malady that it caused in one, and so I went prepared as best J could in accordance with the instructions that those whom they call guides or pathfinders provide thereabout; and with all my preparations, when I climbed the Escaleras [de Pariacaca], *as they are called, which is the highest part of that mountain range, almost suddenly I felt such a deadly pain that I was ready to hurl myself from the horse onto the ground; and, although there were many of us, each one hastened" his pace without waiting for his companion in order to leave quickly from that evil spot; I found myself alone with an Indian, whom I begged to help me stay on the beast. And immediately there followed so much retching and vomiting that J thought I would lose my soul, because after what I ate and the phlegm, there followed bile and more bile both yellow and green, so that J brought up blood from the violence that I felt in my stomach.*

Finally, J must say that if that had continued, I would have understood death to be certain, but it did not last more than about three or four hours, until we went a long way downward and arrived at a more agreeable atmosphere; where I found all my companions, about fourteen or fifteen, all extremely tired, some going about pleading for confession thinking that they were really going to die. Others cLismounted, vomiting and experiencing diarrhea, going completely astray: and J was told that some had lost their lives from that accident, J saw another who threw himself on the ground screaming from the ravaging pain that the passage of Pariacaca had caused him. Yet, ordinarily it does no injury of importance, besides that temporary fatigue and distressing grief' [14; 16, p. 329].

This is the first historically verified description of high-altitude sickness in America (1590).

Acosta took it for "sea sickness on earth".

Interestingly, that Acosta asked an Indian to stay with him to help him remain on horseback. It means that the Indian felt more or less well and was even 8ble to help others. Therefore, the aborigines were adapted to high-altitude conditions [17]. Moreover, 8ccording to Acosta's narration, we see that Europeans had different individual resistance to high-altitude conditions, which improved during repeated climbing:

"it is not only .... the Pariacaca mountain pass. which produces this effect [of altitude sickness], *but also ...... the entire mountain range ... and much more for those who ascend from the seacoast to the mountain, than for those who return from the mountain to the plains* [llanos]." [IS, p. 329].

In other words, Acosta wrote about high-altitude acclimatization and adaptation during repeated ascents (as was first noted by R. Kellogg [181 and D. Gilbert [9]) or, speaking in modern professional language, he described the phenomenon of natural hypoxic training in the mediaeval Andes.

One more observation made by Acosta is interesting:

"Pariacaca ... is one of the highest places in the Universe; it is a place totally deserted: neither animals nor birds are raised there except vicunas; there. the air is more subtle [thin] *than that which human respiration can stand"* [16, p. 332].

We may ask: why a 32 year old Spanish monk risked his life to climb a mountain more than 4800 meters high? The only explanation is the conquest. There were no tourists in the mountains at that time. Such risky travels were undertaken only with certain purposes. In Asia the motive power was commerce: the silk route across mountain passes. In America it was the conquest. Europeans who sailed to the New World, climbed the Andes with the only purpose of conquering the aborigines and their lands. This was the reason why in 1572 Father de Acosta conquered the peak of 4800 m, which was virtually equal to Mont Blanc (4807 m), the peak from which the history of modern alpinism started in 1786.

The first documented evidences of mountain sickness in ancient China (the *30s* BC) and mediaeval America (1572) are separated by 1600 years. These unique historical documents, thoroughly studied by D. Gilbert [6, 16], shed light on the initi81 empirical stage in the written history of hypoxia. As a true scientist, D. Gilbert repeated the climbing undertaken by Acosta from Lima to Cusco [16, p. 343]. This enabled him precisely determine the route, the pass altitude (up to 4800 m). and evaluate the conditions and difficulties of the travel.

Interestingly that during the first years of coloniz8tion of South America the conquistadors unexpectedly faced the problem of childbirth under conditions of high 81titudes [2, p. 14-15; 19, p. 320]. The course of childbirth and child's development were normal in 8borigines. Moreover, their children were strong and healthy; there were no domestic animals in the pre-Columbian America, and the children were breast-fed for 3-4 years [20, p. 140, 159]. By contrast, conquistadors' wives, who recently settled in the mountains, suffered from pregnancy complications and their babies died immediately after birth.

Europeans could not understand at that time that this was due to unfavorable effects of high altitudes on the reproductive function [21]. The problem had not been solved for many decades. We learn about it from A. Calancha [22], who wrote in 1639 the history of the city of Potosi, situated in modern Bolivia at the height of about 4000 m. Twenty thousand Spaniards and 100,000 aborigines lived in the city, and only Spanish neonates died within the first weeks. Then Spanish women started to descend to the planes before delivery, gave birth to children and reminded there until the babies were aged one year. This went on for more than 50 years, and only in 1584 the first Sp8nish baby born in Potosi survived [19, p. 320]. This once more confirms that adaptation to life in high altitudes is a long process, for which the life span of one generation may be insufficient [23].

Spanish reports of that time describe a "sterile" city Hauha" (former capital of ancient Peru) situated at an altitude of 3500 m above sea level. It was called "sterile city" because it was impossible to breed there poultry, domestic swine and horses, heretofore unknown in America. However the situation changed after a century, and the city become a flourishing stock breeding center, from which foodstuffs were imported even to better situated cities on the plane, including Lima [24].

High altitude lands remained a puzzle in ancient and mediaeval times. The level of knowledge was insufficient to help understand the phenomenon and the terrible sufferings caused by "thin" high mountain air. For example, in ancient China it was believed that fierce mountain dragons attack man high in the mountains, and there is no rescue from them [25, p. 76].

The true understanding of these phenomena became possible only after centuries, when two scientists independently discovered oxygen: a Swedish apothecary and chemist Carl Wilhelm Sheele (1771) and a British clergyman Joseph Priestley (1772), and after splendid experiments made by Antoine-Laurent Lavoisier with "acid-generating" gas (1774-1786), which he called oxygenium (1779) .

By the end of the XIXth century the structure of the respiratory system of a live organism was known, some aspects of tissue metabolism elucidated, and it was known that oxygen consumption and carbon dioxide production were determined by physiological requirements of the organism.

However the first scientific observation of the effect of rarefied air on the organism became possible only with the appearance of a decompression chamber. The first device that resembled a modern pressure chamber was "air vessel" designed by Robert Hooke (1635-1702) in 1677. However it was Paul Bert (1833-1886) who became the father of high-altitude physiology [25, p. 254]; In 18711874 he presented at the Academy of Sciences of France the results of experiments in a decompression chamber of his own modification. He studied the effects of pressure changes on the organism by "elevating" animals (sparrows, guinea pigs, frogs) and humans (starting from himself) to various "altitudes" almost to the height of Everest (up to 8800 m). Bert showed that acute altitude sickness was caused by decreased partial oxygen pressure, and inhalations of enriched oxygen cancelled the unfavorable effect. The results of his studies were presented in the fundamental' work La pression barometrique (1878), which laid the basis for modern airspace medicine, high altitude physiology, and underwater activities [26]. This was the first scientific analysis and an experimental research of the mountain climate effect on the organism. Like William Harvey, who proceeded from the ideas of ancient Chinese philosophers, Ibn an-Nafis and Michael Cervet, and created the theory of blood circulation (1628), Paul Bert, analyzing and developing the achievements of former scientists, laid the basis for modern hypoxic medicine.

The tragic death of two French aeronauts Croce-Spinelli and Sivel, who rose in 1875 on a "Zenite" balloon to the height of more than 8600 m [2, p. 32-33] struck P. Bert; he took part in the preparation of this flight and was the friend of aeronauts. Tissandier, the third aeronaut, who remained alive only by miracle, wrote later, "These heroes of science demonstrated the hazards of such travels by their death, so that others learn to foresee the danger and escape it" [27]. After the tragedy P. Bert completed his famous work (1878). But the last years of his life he spent in IndoChina as a governor general [25, p. 255].

The report about the dramatic flight of "Zenite" alarmed a Russian physiologist Ivan M. Setchenov (1829-1905) and stimulated him to investigate the causes of the disaster. The alveolar air composition was unknown at that time, and Setchenov wanted to understand how the changes in partial oxygen pressure in the lung air were related to changes in atmospheric pressure. His estimations showed that aeronauts reached the height at which partial oxygen pressure was so low (20 mm Hg) that it could no longer support life. Setchenov was the first to investigate in detail partial oxygen pressure in the alveoles in health and in "fluctuations of air pressure downwards". He revealed the law of permanent alveolar air composition under normal barometric pressure and partial oxygen pressure. He designed an absorptiometer, a device permitting to analys gas consumption by whole blood and plasma with high accuracy and to study gas tension in the blood [28-30]. These investigations laid the base for a new trend in airspace medicine in Russia.

In 1920 Joseph Barcroft (1872-1947) carried out an autoexperiment which stopped the speculations on the possibility of oxygen secretion by the lungs. He spent six days in a decompression chamber of his own design ("glass house") to study oxygen tension in samples of his own arterial blood and partial oxygen pressure in alveolar air. He was surprised by the *dark* color of the first blood portion under conditions of hypoxia and its *red* color in the samples collected after oxygen inhalations. Confirming his observations by results of analysis Barcroft established that oxygen tension in arterial blood was always lower than its partial pressure in the alveoles [31]. Hence, the diffuse theory proved to be the only true, and Barcroft's book *Lessons from. High Altitudes* [32] became one of the fundamental works in respiratory physiology.

Barcroft is the author of one of the first classifications of "anoxic states ,. (1920), based on oxyhemoglobin content in the blood [33-34] (the term "hypoxia" was introduced only in 1941 by C. Wiggers). Barcroft distinguished anoxic, anemic, and congestive anoxia (hypoxia). In 1932 J. P. Peters and D. D. van Slyke distinguished the fourth type of anoxia (hypoxia): histotoxic, caused by injury to oxidative mechanisms in tissues (blockade of cellular oxidative enzymes in cyanide poisoning) [35, p. 13].

The first hypoxic states classification, based on their etiology and pathogenesis, was suggested by Victor V. Pashutin (1881), I. M. Setchenov's disciple at the Department of Pathophysiology at the Military Medical Academy in St. Petersburg [36]; later it was supplemented by P. M. Albitsky (1884) and E. A. Kartashevsky (1906). The authors distinguish hypoxia which can develop in a healthy organism as a result of partial oxygen pressure drop in the environment, and hypoxic states as a result of some diseases (pulmonary, cardiovascular, hematological. disorders in tissue processes, etc.).

Classification created by Nikolay N. Sirotinin (1949) was widely used in the middle of the XXth century; later it was supplemented by A. Z. Kolchinskaya (1963, 1981) [37-38]. Kolchinskaya's classification is based on a systemic approach. taking into consideration both exogenous and endogenous factors at any of the stages of oxygen transport. According to this classification there are eight main types of hypoxia: hypoxic, hyperoxic, hyperbaric, respiratory, circulatory, hemic, cytotoxic, and exercise hypoxia [39, p. 34-35]. The most common is *hypoxic hypoxia* caused by decrease of partial oxygen pressure in inhaled air.

The adaptation to hypoxic hypoxia can form under the effects of various factors: (I) staying in the mountains, (2) hypobaric hypoxic training in a decompression chamber, and (3) normobaric hypoxic training.

The idea of repeated hypoxic training formed in close connection with the aviation progress.

Before the Second World War the pilots flied in open cabins and the aircrafts flied no higher that 5-6 km. It was believed that every healthy pilot can work at such altitudes. However under real conditions of oxygen deficiency the pilots sometimes inhaled oxygen through an oxygen respiratory device [40]. In order to elevate the "threshold altitude" and to improve the efficiency of pilot's work. hypoxic training in the mountains and in decompression chambers was started. In Russia the first basic research in this field was carried out by N .. Sirotinin (1934), [41], P. I. Egorov (1937) [42], V. V. Streltsov (1938) [43-45], and I. R. Petrov (1949) [46]. One of the training methods was repeated "elevations" of pilots in decompression chambers in order to elevate their threshold altitude. The very first experiments (in Russia they were carried out by A. P. Apollonov, V. G. Mirolyubov, and later D. E. Rozenblyum [47]) demonstrated that even few "elevations" brought a good adaptation effect, essentially improving lung ventilation. In 1944 A. P. Apollonov and D. I. Ivanov validated the use of dosed hypoxia corresponding to an altitude of 5000 m as a functional test [39, p. 62].

Study of human adaptation to mountain conditions showed that "time reserve" and "threshold altitude" can be increased by preliminary high mountain acclillHltization. It was proven by N. N. Sirotinin's studies carried out in the Caucasus, Pamirs, Altai, and Tien Shan mountains (1930-1938). Moreover, in the 1950s N. N. Sirotinin for the first time suggested to use adaptation to high-altitude hypoxia for treating some diseases. Using the method of staged high-altitude adaptation at altitudes of 800 to 4800 m, which he developed in 1939, N. N. Sirotinin together with his colleagues detected favorable effects of high altitude (and pressure chamber training) in the treatment of schizophrenia (1950-1955), asthma (1957-1958), and leukemia (1970s) [48-50]. These studies were continued at the Elbrus Biomedital Station under the Academy of Sciences of Ukraine and led to wide use of high-altitude hypobaric hypoxia as a therapeutic and preventive method. In 1970 N. A. Agadzhanyan and M. M. Mirrakhimov proved the favorable effects of moderate hypobaric hypoxia on healthy human organism, which prompts the use of mountain acclimatization as a method improving the working capacity and endurance of athletes and aeronauts [5\].

An essential elevation of the "threshold altitude" and "time reserve" was observed in experiments with intermittent pressure chamber training (E. A. Kovalenko et al., 1970s [52, 53]) carried out first on animals and then on volunteers. Experiments with repeated (5-15 times) short-term (10-20 min) "elevations" during 30, \0, or 3 days showed that even 3-day decompression chamber training (15 x 1-2 min, up to 9000 m) had an appreciable positive effect.

Interestingly that decompression chamber training was used to get ready mountaineers for ascend the highest peaks in the world. Thus, in China in 1975 "elevations" of sleeping athletes in a decompression chamber to 1250 and 2800 m were used for 33 nights to accelerate adaptation to the altitude of 4500 m; this training had a notable positive effect on all parameters studied [54].

However decompression chamber training does not rule out the negative side effects on the organism; decompression disorders can occur even at "altitudes" of 2000-3000 m [55, 56]. It is particularly dangerous for those with underlying diseases.

That is why, in the 1930s, attempts at replacing decompression chamber training by inhalations of gas mixtures with decreased oxygen content under conditions of normal atmospheric pressure were made in practical aerospace medicine (N. N. Golubov, 1939 [57]: R. L. Levy et al., 1939 [58]; L. L.

Shik, 1940 [59]. In 1941 inhalations of normobaric hypoxic gas mixtures were first used for treating some diseases (mental and neurotic status, M. 0. Gurevich et al. [60].

Hence, the concept of interval normobaric hypoxia was created in Russia. By' the end of the 1980s it was regarded as an effective scientific method of nonspecific prevention, disease treatment, and rehabilitation of patients (R. B. Strelkov, A. Va. Chizhov et ai., [39,61]). The method is protected by Authors' Certificates of the USSR (1981, 1984) and the Russian Federation (1992) [6264] .

The method is based on dosed respiration with gas mixtures containing decreased (10-15 %) oxygen concentrations under normal atmospheric pressure. Short (3-5 min) exposures to hypoxic mixtures are alternated by 3-5 inhalations of atmospheric air. The exposures are gradually prolonged from session to session; a session consists of 4-12 cycles daily and the whole course takes 1-3 weeks [39, pp. 76, 390-392].

An effective form of interval normobaric hypoxia is the method of interval hypoxic training/therapy **(IHT),** developed at "Hypoxia Medical Academy" at the end of 1980s - the beginning of 1990s (E. N. Tkatchouk, 65-67]. The new method consists in repeated hypoxic exposures alternated by inhalations of atmospheric air under normal pressure. Transfer from normoxia to hypoxia is thus repeated for hundreds of times during 20-30 days. During IHT the systems responsible for oxygen transfer and utilization are trained at all levels of the organism, from local reactions to central regulation mechanisms, including the hypothalamo-pituitary-adrenalsystem. Different mechanisms are realized at different stages of adaptation. Some of them are still unknown. However it is obvious that IHT forms potent nonspecific adaptive mechanisms and fortifies the defense potential of the organism.

The safety of IHT was confirmed in placebo controlled experiments. However there are certain limitations and contraindications precluding the use of I HT: acute somatic and infectious diseases, decompensation of chronic diseases; pulmonary hypertension; oxygen saturation of arterial blood at rest below 92%; age over 70 years, as no clinical studies were carried out in this age group.

In modern medicine IHT occupies a remarkable place as a promising and effective method of nonspecific prevention and treatment of many diseases. Hundreds of monographs and some thousands of papers in many countries of the world describe effective use of I HT in various branches of medicine: obstetrics and gynecology, cardiology, pulmonology, neurology, gastroenterology, ophthalmology, surgery, athletic and airspace medicine. During the last year alone. more than a thousand reports on hypoxia in medicine were published.

Somebody of the Great has once said: "A hundred years is not the history; a hundred years is politics". We shall agree with it and not be in a hurry to rank the priorities or enumerate our outstanding contemporary colleagues. It is the privilege of Her Majesty the History. We would like just to mention that in the modern world at all continents of the Globe thousands of specialists study and successfully use hypoxia in medicine; tens of research institutes and hundreds of centers for hypoxia have been created.

"Hypoxia Medical Academy" (HMA) which initiated this conference is among them. Together with the Russian Academy of Medical Sciences, "Hypoxia Medical Academy" fruitfully works in this promising sphere in Russia and other countries. At the moment HMA is introducing in many countries a new original device for formation of gas mixtures - HypoxyComplex Hyp02 The device is fitted with a special programme block for delivery of gas mixture and monitoring the physiological parameters of the patient.

Starting from 1993, HMA Clinical Research Laboratory issues a journal *Hypoxia Medical* in Russian and in English, organizes International Scientific Conferences "Hypoxia in Medicine" with participation of world-known specialists in this field. The first three conferences took place in Moscow in 1994, 1996, and 1998. The Fourth International Conference "Hypoxia in Medicine" in Geneva continues this tradition.

The Organizing Committee of the Conference wishes all the participants and guests success in their noble work, happiness and well being.

Welcome to Geneva!

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