

## THE INFLUENCE OF ALTITUDE ON MAN<sup>1</sup>

Alberto Hurtado, M.D.<sup>2</sup>

*Hypoxia poses a major problem for people living at high altitudes, and also for patients suffering from various respiratory, cardiovascular, hematological, and other diseases. This paper reviews what is known about adaptations developed by permanent high-altitude dwellers and notes some areas where more information is needed. It was originally presented at Geneva as the Fourth Jacques Parisot Foundation Lecture.<sup>3</sup>*

It is an honor, the importance of which I fully appreciate, to present to this Assembly, with its great international authority and prestige, my observations on a topic which, apart from its bearing on physiology, clinical medicine, and public health, has biological implications for a large part of the world's population. I should like to offer my sincere and profound thanks to the Committee of the Jacques Parisot Foundation for having chosen me to deliver this lecture, which bears the name of a distinguished physician and public health worker who devoted his life, with remarkable vision and skill, to the study and progress of social medicine all over the world. I pay my modest homage to his memory and to those men of greater merit who have preceded me in speaking from this rostrum.

The world's population is growing at an increasing rate and, in a future that is probably not far distant, it will be necessary to utilize for

human habitation areas where environmental conditions are such that only the operation of adaptive and protective mechanisms will permit the inhabitants to enjoy a useful and active life. These include high-altitude areas. The influence of altitude on man and lower animal species has in recent decades become an important subject of research in many countries, enjoying world support and cooperation through the International Biology Program.

The first historical reference to this subject dates back almost four centuries, to the time of Father Acosta, a Jesuit missionary who accompanied the Spanish armies in their conquest of the vast territories of Inca Peru and gave a clear and accurate description of the symptoms he felt on ascending to the high regions of the Andes, attributing them, with surprising intuition, to the "delicate and subtle" nature of the air. Three centuries went by before Paul Bert, an eminent French physiologist and experimentalist, gave an adequate scientific explanation of this well-founded hypothesis by attributing the most important effects of altitude on the human body to the drop in atmospheric pressure.

Today it is well known that this phenomenon reduces the partial pressure of the oxygen in inspired air, so that the venous blood circulating through the lungs, on its return from the tissues, takes up less oxygen by diffusion. This gives rise to a condition termed "hypoxia"—deficient oxygenation of the hemoglobin and reduced tension of the small oxygen fraction dissolved in the plasma—which affects

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<sup>2</sup>Consultant to the High Altitude Research Institute, Cayetano Heredia University of Peru. Former Dean of the Faculty of Medicine of Cayetano Heredia University and the Faculty of Medicine of the University of San Marcos, Peru.

<sup>3</sup>To perpetuate the memory of the late Professor Jacques Parisot, President of the Ninth World Health Assembly, Mme. Parisot has established a foundation, administered by the Director-General of WHO, to provide for special lectures on scientific subjects at World Health Assemblies. This is the text of the fourth of these lectures, which was delivered in Geneva on 17 May 1972, on the occasion of the Twenty-fifth World Health Assembly.

the oxygen supply to the tissues as well as oxygen utilization by the metabolically active cells that must liberate the energy necessary for the maintenance of life. There are other environmental factors affecting human physiology at high altitudes, such as cold, the decreased density of the air, and the greater intensity of ultraviolet light, but hypoxia—or difficulty in obtaining and utilizing oxygen—is the most important and the subject of most research, since it cannot be tolerated without some process of adaptation.

Hypoxia develops when the altitude exceeds 3,000 m and is more sudden and severe above 4,000 m. The number of persons in the world who are exposed to it is not precisely known, but is estimated to be 20-30 million, distributed mainly over the high Andean areas of Peru and Bolivia in South America and the Himalayan area in Asia. Thus the study of the effects of high altitudes cannot be regarded as a somewhat obscure and limited branch of medical research, as it was in the past when only a few workers were interested in the problem. In reality, altitude is a biological challenge to a considerable portion of the world's population.

As a result of the systematic investigations initiated by Monge in Peru more than 40 years ago and subsequently extended by many other research workers, we know that the inhabitants of the Andes present morphological, functional, and biochemical characteristics that explain their high degree of tolerance of and acclimatization to reduced atmospheric pressure, and that differentiate them in many ways from people regarded as physiologically normal at sea level. In our opinion, the concept of acclimatization to high altitudes, i.e., adaptation to low atmospheric pressure, is applicable only to the behavior of persons who are born and live permanently at such altitudes; this is often forgotten by many workers, who employ the term "acclimatization" to describe or interpret the findings of short-term studies utilizing experimental decompression chambers. Furthermore, in these studies the pressure is often lowered to levels that are undoubtedly beyond the tolerance capacity of the body, thus causing

harm rather than producing tolerance or acclimatization.

We feel we should try, at this point, to enumerate briefly the most important characteristics of persons born and living at high altitudes. These characteristics show the enormous reserves the human body can draw on in order to live in balance and harmony—not only with constantly changing internal factors, but also with external factors, i.e., the environment. Extensive and reliable scientific documentation on the subject has been provided by many workers of different nationalities. However, in the limited time available, this aspect of the question can be discussed only in a general and superficial way.

High-altitude man, whether at rest or physically active, has greater pulmonary ventilation than the man of the plains or coastal areas under similar conditions, i.e., in a given period a larger volume of air enters and leaves the lungs, this partly compensating for the fall in the partial pressure of the oxygen in the air inspired. Also, factors operating in the lungs favor the exchange of gases between the air and the blood, since the alveolar cavities are dilated and the vascular network contains a larger amount of circulating blood. In the blood, there is a marked increase of hemoglobin, the vehicle transporting the oxygen contained in the red cells. Besides this quantitative increase, there is a qualitative change in the hemoglobin's ability to take up oxygen. The oxy-hemoglobin dissociation curve is displaced to the right, which signifies a lesser affinity for oxygen. This property facilitates the diffusion of the gas into the tissues, where it is required and utilized to maintain cell life and liberate energy.

Recent medical investigations have revealed the existence at this level, i.e., in the tissues, of adaptive processes of fundamental importance and great efficacy in persons born and living at high altitudes. In addition to an increase in myoglobin content and in the number of structures responsible for liberating energy, important changes occur in the enzymatic processes governing the utilization of oxygen inspired at a reduced pressure.

These and other properties of the cardio-

vascular system, such as hypertrophy of the right heart, moderate hypertension in the pulmonary circulation, and a larger number of capillaries in the tissues, together with the maintenance of adequate hormone production by the endocrine system, explain the high degree of efficiency shown by the indigenous inhabitants of high altitudes, even when their physiological requirements are increased, as during physical activity.

Our experimental studies have shown that the inhabitants of the Andes are able, despite adverse factors in the environment, to tolerate a given physical activity for a longer time than lowland dwellers can. This greater tolerance is associated with decreased lactate and pyruvate production, which makes up for the reduction in the buffering capacity of the circulating blood, indicating (curiously enough) that the metabolic pathway utilized is more aerobic than anaerobic.

The highly efficient physical performance of Andean man has not only been experimentally proven but is also evident in his work. In the busy mines of the high sierras of Peru, the indigenous inhabitants cope with the severe demands of their work most efficiently and with greater ease than miners from the coast, even when the latter have been living at a high altitude for some time. In other words, the "natural acclimatization" of Andean man is, in our experience, always greater and more complete than any "acquired acclimatization." There is experimental evidence to back this affirmation. We have brought people from the coast to high altitudes and studied them over periods corresponding to a year's permanent residence; even then their physical performance has been noticeably inferior to that of the indigenous inhabitants.

It is interesting to note that the high degree of acclimatization to their environment shown by people born and living permanently at high altitudes was not unanimously recognized by workers who studied the question in the past. In the nineteenth century Jourdanet, after studying the inhabitants of the Mexican *altiplano*, concluded that they were characterized by "marked debility"—an opinion that

was successfully refuted by Herrera and Vergara Lope in a classic work entitled *La Vida sobre las Altas Planicies*, published in Mexico in 1899. Barcroft, an eminent British physiologist who visited and investigated the Andean areas of Peru for a short time some 30 years ago, was of the opinion that the indigenous inhabitants of Cerro de Pasco, a mining town at an altitude of 4300 m, showed limited mental and physical ability.

From the results of our investigations and studies of high-altitude inhabitants, it is clear that such opinions are completely erroneous and consequently unacceptable. It is true that those living at altitudes above 3,000-4,000 m do not exhibit the physiological characteristics described as normal in the textbooks, but the fact must be admitted that their behavior, whether at rest or during mental or physical activity, reveals a perfect equilibrium with the adverse conditions of their environment. Furthermore, under certain circumstances high-altitude man shows superior behavior and performance in situations in which it is necessary to draw on the reserve mechanisms of the body. This occurs, for example, during severe physical effort.

In scientific research it is rarely, if ever, possible to assert that the investigations and experiments carried out have completely answered all the questions raised and thoroughly elucidated the problems under study. The problem of the influence of high altitudes on man and other animal species is no exception in this respect, and there are still important gaps to be filled.

Almost all studies of Andean inhabitants have been concerned with adult males, and little is known about the processes occurring in infancy and childhood, during aging, or in old age. There are, however, a few scattered data of interest in the medical literature. In recent years, studies in Peru by various workers have revealed that certain adaptive changes of a morphological nature in the placenta ensure an adequate supply of oxygen to the fetus. When the child is born, there is generally no polycythemia, i.e., the characteristic increase in red cells and hemoglobin found in adults living at

high altitudes. This has been repeatedly confirmed and suggests that, in this respect at least, the newborn infant may be regarded as a newcomer to high altitude and that it is only after a period of direct contact with the low-pressure environment that some or all of the adaptive mechanisms countering hypoxia come into play.

In connection with the newborn infant, it should be pointed out that the fertility rate of people living in high-altitude areas is the same as, or even greater than, that of people living at sea level. This is in contrast to the experience of the Spanish conquistadores, whose chronicles mention a sharp decline in births following settlement in high-altitude areas. It may be recalled that the capital of Peru, originally in the Andean sierras, was later transferred to the Rimac valley on the Pacific coast, now the site of Lima, the present capital.

Little is known of the chronology of sexual maturation at high altitudes or of the extent to which the adaptive processes differ in course and intensity according to sex. Some of these processes appear to be less marked in women; this may be partly due to the greater adaptive demands made on men as a result of the greater physical efforts required of them.

Again, little is known of involuntional changes during aging in high-altitude populations. In Peru, this gap in the research is explained by the fact that, in general, the areas studied have been mining centers where the indigenous personnel live only while they are still young enough to engage in heavy physical labor, after which they leave to work on the small farms they own lower down. It is extremely difficult to install modern research laboratories in these places, which are often primitive and remote. However, there can be no doubt about the importance and urgency of studying Andean man in his natural habitat, and not exclusively in industrial centers where his living, working, and eating habits are greatly modified.

There is also an urgent need for thorough and systematic studies of the role of genetic factors in acclimatization to high altitudes. It is certain that they must play an important part

in the adaptation of Andean man to his environment, since—according to historians and archaeologists—human life has existed in the Andean areas of South America for millennia, so that countless generations have been constantly exposed to the influence of the special environment there. In this connection, it may be noted that human skeletons discovered by Cardich, a Peruvian anthropologist, at Lauricocha in the southern Andean region of Peru were examined by the  $C^{14}$  radiocarbon dating method at the Smithsonian Institute in Washington and found to have an average age of 9,500 years.

Another question of great interest that has not yet been thoroughly investigated is that of the maximum altitude compatible with the existence of permanent settlements. From the medical and physiological point of view, the degree of hypoxia or oxygen deficiency resulting from the lower atmospheric pressure would seem to indicate that this is approximately 6,000 m, and in fact there are very few mining centers in Peru at anything near that altitude. Here it may be of interest to recall the discovery of a human mummy in the Andean area of northern Argentina at a height of 6,300 m. Its age was not investigated.

Thus, some important data are lacking on human life at high altitudes, notably as regards the influence of age and sex and the maximum altitude compatible with the permanent presence of human life.

The study of the influence of altitude on man is of interest in several ways. It can lead to a better knowledge not only of the adaptive mechanisms, genetic or acquired, that determine and govern human tolerance of the environment, but also of the physiological characteristics of the 20-30 million people all over the world in whom these mechanisms have been modified by the environment in which they are born and live. From the public health and clinical standpoint, it is also important to know what pathological changes or diseases may be directly dependent on the high-altitude environment and to what extent that environment modifies the morbidity and mortality rates for diseases that also occur at sea level.

The clinical picture of high-altitude diseases and pathological changes that is best known, since it occurs and has been described so often, is the one frequently found when a person residing at sea level is suddenly transported to a high altitude. The symptoms—which generally involve disturbances of the central and peripheral nervous system, i.e., the human tissues most susceptible to the effect of hypoxia—constitute acute mountain illness, or *soroche*, a word of Peruvian origin that has become universally known. We know that, basically, *soroche* is the clinical manifestation of sudden oxygen deficiency in the body, but we cannot yet explain certain important aspects, such as the great variability in its occurrence, even in the same individual, nor can we predict it by a medical examination before the ascent. There is no direct and definite relationship between *soroche* and physique or physiological characteristics.

A condition that has become known more recently—we ourselves originally described it in 1934—is the acute pulmonary edema that not infrequently develops in persons arriving at high altitudes. Its pathogenic mechanism is not yet well understood, although there are various theories on the subject, but it has been found to occur mainly in indigenous inhabitants of high-altitude areas, who were previously regarded as healthy, on their return from a short stay at sea level. It is interesting to note that this condition was frequent during the conflict between India and China that took place high in the Himalayas.

Writing in 1927, Monge indicated for the first time that indigenous inhabitants of Peru's high-altitude areas and persons from the coast who had lived at high altitudes for some time could lose their acclimatization to and tolerance of hypoxia, developing symptoms, mainly neurological, that might be sufficiently severe to oblige them to go down to a lower altitude or to sea level to recover. The clinical picture, characterized by a marked accentuation in the degree of hypoxia and polycythemia, has been given the name of chronic *soroche* or Monge's disease. No major studies have so far been made to elucidate the pathogenesis of this condition

or the mechanism involved, but we have found that the great majority of cases are characterized by a decrease in pulmonary ventilation, i.e., hypoventilation, caused apparently by a fall in the sensitivity of the respiratory center situated at the base of the brain to the stimulus of the carbon dioxide circulating in the blood. This gas is one of the chemical factors governing the functional activity of the center in question.

As for the incidence at high altitudes of diseases also seen at sea level, epidemiologic studies and immunologic investigations covering large sectors of the high-altitude population are urgently needed. Nevertheless, on the basis of studies in certain villages and mining centers, the experience garnered during many years of investigation, and statistics accumulated in hospital centers situated at high altitudes, certain provisional observations may be made, even though their epidemiologic significance is still limited.

At high altitudes there seems to be a greater incidence of certain congenital malformations of the heart and perhaps of other organs; of respiratory complaints; of post-operative complications such as volvulus; and of liver trouble. Infant mortality is high, but this may be due to a number of factors apart from environment. On the other hand, peripheral hypertension, myocardial infarction, diabetes, and leukemia are much less frequent at high altitudes. A fact that will be of interest to public health experts is that, in the mining centers of the Andean region, silicosis very frequently develops after a short period of work in the mines, which clearly shows that in the high-altitude environment special maximum permissible levels should be set in order to avoid occupational diseases of this kind.

In conclusion I should like to make a few brief comments on past and present research on the effects of altitude.

The influence exerted by the environment, and particularly by altitude and temperature, has been realized and appreciated for many centuries in a way that, however unscientific, shows a high degree of intuition and intelligence. There are some interesting historical

studies showing that certain aspects of social and administrative organization during the Inca period and in the early stages of Spanish domination were determined by the widely differing geographic and climatic conditions prevailing in part of the American continent. Now that I have mentioned the Inca period, I cannot resist the temptation to stress the high degree of culture attained by the civilization of the Incas, as demonstrated by objects of exquisite craftsmanship and by a number of impressive monuments, buildings, and irrigation works. All this, together with the advanced social organization of the period, offers historical proof that the effects of altitude as an environmental factor can be countered by a high degree of acclimatization.

For those of us who have long been concerned with the influence of altitude on man, it is particularly gratifying to observe how worldwide interest in this field of study is increasing. A number of countries in the various continents now have laboratories and institutes devoted exclusively to such studies, and we frequently receive welcome visits from research workers of different nationalities attracted by the facilities and opportunities offered by our Andean region for observation of the adverse climatic conditions to which man is exposed on arrival in a high-altitude environment and by the existence there of permanent settlements, many thousands of years old, where the inhabitants

have successfully developed and utilized adaptive mechanisms enabling them to carry out both mental and physical tasks with efficiency.

The worldwide interest in the subject has perhaps been partly due to the efforts deployed by science in recent years for the conquest of outer space. Among the many difficulties confronting this gigantic endeavor is that of ensuring the supply of oxygen necessary for carrying on vital activities. High-altitude man provides us with an excellent illustration of the way the human body modifies its characteristics to achieve a state of tolerance to, and almost perfect harmony with, an environment in which oxygenation is difficult.

Another reason for the present, almost universal interest in studies of the influence of altitude on man is that this problem has a bearing on clinical medicine. Hypoxia, the most important factor at high altitudes, can also result from various respiratory, cardiovascular, hematological, and other diseases. The clinician is consequently interested in knowing how the human body can successfully tolerate and compensate for this physiologically adverse condition. The best answer is to be found in the study of those living temporarily or permanently at high altitudes. Thus, as we have tried to show, high-altitude studies are far from being of purely local and academic interest.

### SUMMARY

A number of special conditions influence man's physiology at high altitudes, the most notable being "hypoxia"—deficient oxygenation of hemoglobin and reduced tension of the small oxygen fraction dissolved in the plasma. This affects both the oxygen supply to the tissues and oxygen utilization by the metabolically active cells that must liberate the energy needed for life.

Hypoxia develops at altitudes above 3,000 m, but is more sudden and severe above 4,000 m. The number of persons exposed to it in the world's high-altitude regions is estimated at 20-30 million. However, hypoxia can also result from various respiratory, cardiovascular, hematological, and other diseases at sea level. The

study of those living temporarily or permanently at high altitudes promises to shed light on the general question of how the body can tolerate and compensate for this physiologically adverse condition.

People born and living permanently at high altitudes show morphological, functional, and biochemical characteristics that explain their tolerance to reduced atmospheric pressure and distinguish them from people regarded as normal at sea level. These include greater pulmonary ventilation and increased blood circulation in the lungs, higher hemoglobin levels, and a decline in hemoglobin's affinity for oxygen—which facilitates diffusion of the gas into the tissues. Other features are hypertrophy

of the right side of the heart, moderate hypertension in the pulmonary circulation, and a larger number of capillaries in the tissues. Recent medical research has also revealed important adaptive processes in the tissues, consisting of an increased myoglobin content, a rise in the number of structures responsible for liberating energy, and changes in enzymatic processes governing oxygen utilization.

Despite the strides made by researchers in this field, many questions still remain unanswered. Little is known about processes occurring in infancy, childhood, old age, or during aging. Nor is there much information about the chronology of sexual maturity at high altitudes, the role of genetic factors, or the

maximum altitudes compatible with the existence of permanent settlements.

The best-known of the pathological changes or diseases resulting from exposure to high altitude is *soroche*, the clinical manifestation of a sudden oxygen deficiency in the body. Another is acute pulmonary edema in persons arriving at high altitudes—usually indigenous inhabitants recently returned from a short stay near sea level. Also, persons that have lived at high altitudes for a long time sometimes develop Monge's disease, which can result in a loss of acclimatization and sufficiently severe symptoms so that the patient must go to a lower altitude to recover.

#### CHOLERA IN 1972

From 1 January to 1 November 1972 there was no extension of cholera into countries not previously infected. The number of cases reported for the first ten months of 1972 was some 90,000 cases fewer than for the corresponding period in 1971. As of 1 November 1972 eighteen African and 14 Asian countries had reported approximately 53,000 cases and 6,600 deaths. Unofficial reports of minor outbreaks in some previously infected territories have not been confirmed by official sources. Despite incomplete reporting, it appears that the cholera situation in general has been calmer than it was in 1971. [*Weekly Epidemiological Record* of the World Health Organization, 47 (45) 271, 1972.]