# Functional Adaptation to High Altitude Hypoxia

Changes occurring during growth and development are of major importance in man's adapting to high altitudes.

A. Roberto Frisancho

During their conquest of the Incas of Peru, the Spaniards were the first to notice that high altitude environments could have adverse effects on the normal functioning of people accustomed to living at low altitudes (*1*). In 1590, the chronicler Jose de Acosta, in his *Historia Natural y Moral de las Indias*, gave the first clear description of mountain sickness experienced by lowland natives sojourning at high altitudes (*1*). Three centuries later, Jourdanet (*2*) and Bert (*3*) began their scientific observations of the effects on man of high altitudes and low barometric pressures. Since then, the study of the mechanisms whereby man adapts to the pervasive effects of high altitude hypoxia has been the concern of both biological and social scientists.

There is little doubt that man can adapt to oxygen impoverished environments—witness the large number of populations living at high altitudes. In becoming so adapted, the organism develops a variety of coordinated mechanisms that have been investigated intensively in recent decades, both at high altitudes and in low pressure chambers. In this article I describe the various adaptive mechanisms that enable both the lowland and the highland native to overcome the hypoxic stress of high altitudes and to attain physiological homeostasis under the conditions of high altitude hypoxia.

## The Nature of Hypoxic Stress

*The low pressure of oxygen.* The biological problem of adaptation to high altitude hypoxia depends mainly upon the partial pressure of oxygen in the atmosphere which decreases proportionately with an increase in altitude. The oxygen reaches the cells of man through the combined functions of the respiratory, cardiovascular, and hematological systems that facilitate passage of gas molecules from the atmosphere to the tissues. When the tissues receive insufficient oxygen, a physiological condition called "hypoxia" develops. Hypoxia can be produced by any physiological, pathological, or environmental condition that interferes with the oxygen supply to the tissues. For example, certain defects in the cardiopulmonary system can produce the condition known as anemic hypoxia. Hypoxia can also be produced by atmospheric conditions, for example, contamination of the air with carbon monoxide or other gases that displace oxygen, or by normal depletion of oxygen in the atmosphere such as occurs at high altitudes.

The amount of oxygen in the atmosphere, 20.93 percent, remains constant up to an altitude of 110,000 meters. However, because air is compressible, the number of gaseous molecules it contains is greater at low altitudes than at high altitudes and the barometric pressure, which depends upon the molecular concentration of the air, thus also decreases with an increase in altitude. This is the fundamental problem of high altitude hypoxia: the oxygen in the air at high altitudes is less concentrated and, consequently, is at a lower pressure than it is at low altitudes.

At sea level the barometric pressure is 760 millimeters of mercury and the partial pressure of oxygen ($pO_2$) is 159 mm-Hg (corresponding to the 20.93 percent of oxygen at 760 mm-Hg). At 3500 m (11,840 feet) the barometric pressure is reduced to 493 mm-Hg and the $pO_2$ is 103 mm-Hg; that is, at an altitude of 3500 m the oxygen has about 35 percent less pressure than at sea level. At 4500 m the $pO_2$ is decreased by as much as 40 percent (to 91 mm-Hg) with respect to the $pO_2$ at sea level (Fig. 1). Because of this decrease in $pO_2$ in the ambient air, the $pO_2$ of the air reaching the trachea and the alveoli is also reduced and this, in turn, reduces the amount of oxygen that is available to the tissues.

The decrease in $pO_2$ at high altitudes causes a reduction in the oxygen saturation of the arterial blood because the proportion of oxyhemoglobin formed depends on the $pO_2$ in the air reaching the alveoli. Thus, if the $pO_2$ of the ambient air is 159 mm-Hg and in the alveoli it is 104 mm-Hg, as it is at sea level, the hemoglobin in the arterial blood is 97 percent saturated with oxygen. On the other hand, if the $pO_2$ of the ambient air is 110 mm-Hg and in the alveoli it is 67 mm-Hg, as occurs at an altitude of 3000 m (9840 feet), the hemoglobin in the arterial blood is only 90 percent saturated. This means that at an altitude of 3000 m there is a decrease of 10 percent of oxygen for each unit of blood that leaves the lungs. Between an altitude of 4000 and 5000 m, this decrease might reach as high as 30 percent.

*Symptoms of high altitude hypoxia.* The initial symptoms of high altitude sickness include shortness of breath, respiratory distress, physical and mental fatigue, rapid pulse rate, interrupted sleep, and headaches intensified by activity. There may also occur some slight digestive disorders and in some cases a marked loss of weight. In other cases the individual may feel dyspnea, nausea, and vomiting. In very rare cases at altitudes above 4500 m there may occur a diminution of visual acuteness, painful menstruation, and bleeding of the gums. While some individuals appear to be predisposed to high altitude sickness, others may feel only mild effects that can be overcome with acclimatization. Among those individuals who appear to be predisposed to mountain sickness, some may lack the ability to become acclimatized and may develop chronic mountain sickness (*4*).

The effects of high altitude hypoxia also depend on physical and biological factors. Some physiological effects may be evident at 1500 m (4920 feet).

The author is research associate scientist of the Center for Human Growth and Development and associate professor of anthropology at the University of Michigan, Ann Arbor 48104.

Under rest conditions at this altitude there may not be any effects, but during physical activity hypoxia effects may become evident. Between 2000 and 3000 m (6500 to 9840 feet) the effects of hypoxia are felt during both rest and physical activity. Above 3000 m the physiological effects become increasingly evident and unavoidable and the physiological limits of human tolerance to high altitude hypoxia appear to be reached at 8545 m (33,000 feet).

### Adaptive Pathways

The various adaptive mechanisms triggered by exposure to high altitudes are directed toward increasing the availability of oxygen and increasing the pressure of oxygen at the tissue level. This is accomplished through modifications in (i) pulmonary ventilation, (ii) lung volume and pulmonary diffusing capacity, (iii) transportation of oxygen in the blood, (iv) diffusion of oxygen from blood to tissues, (v) utilization of oxygen at the tissue level.

*Pulmonary ventilation.* Upon exposure to high altitude hypoxia, lowland natives show, both at rest and during exercise, a progressive increase in pulmonary ventilation that may reach as much as 100 percent of the values at sea level (*5–8*). Such hyperventilation is both adaptive and nonadaptive. It is adaptive because it increases the $pO_2$ at the alveolar and arterial levels and consequently increases the diffusion gradient between the blood and the tissues (*5, 8, 9*). It is nonadaptive because it decreases the partial pressure of carbon dioxide ($pCO_2$) at the alveolar level and, if this is not compensated for, it may change the $p$H of the blood from a normal ($p$H 7.4) to an alkaline state ($p\text{H} > 7.4$) and result in alkalosis. Such alkalosis is prevented by rapid active removal of bicarbonate from the cerebrospinal fluid (*10*) and blood. This mechanism, which lowers the $p$H of the medullary chemoreceptors in relation to any given $pCO_2$, resets the level at which the arterial $pCO_2$ is regulated by changing the relation between the $pCO_2$ and the response of the medullary chemoreceptors to $p$H. In this manner the original homeokinetic relationship between the $p$H of the cerebrospinal fluid and the blood is restored to sea level values. It is the maintenance of this equilibrium that enables the lowland native to sustain an increased ventilation at high altitudes without the risks of alkalosis or hypocapnia.

As shown by recent analyses (*11*), in both the lowland and the highland native the magnitude of the increase in pulmonary ventilation during exercise is directly proportional to the increase in altitude. However, at a given altitude, as shown in Fig. 2, the pulmonary ventilation of the lowland native (sojourning on a short-term or long-term basis at high altitudes) is invariably higher than that of the high altitude native (*12–18*).

In summary, acclimatization to high altitude in the lowland native is associated unquestionably with an increase in pulmonary ventilation. In the highland native, however, acclimatization to high altitude is accompanied by a lesser increase in pulmonary ventilation. Since the increase in pulmonary ventilation permits the newcomer to maintain an increase in $pO_2$ at the alveolar level and an increase in arterial oxygen saturation (*11*), it would appear that a hyperventilatory response is critical to the acclimatization of the newcomer. However, after acclimatization occurs, the increase in pulmonary ventilation reaches a plateau, probably reflecting the operation of other adaptive mechanisms.

*Lung volume and pulmonary diffusing capacity.* Upon initial exposure to high altitude hypoxia, the vital capacity and residual lung volume of lowland natives is reduced, but after about 1 month of residency at high altitudes, such subjects attain values which are comparable to those they had at low altitudes (*19, 20*). The oxygen pulmonary diffusing capacity of lowland natives remains unchanged at high altitudes when compared to the capacity attained at sea level (*21, 22*).

In contrast, highland natives have a larger lung volume, and especially a larger residual lung volume (volume of air remaining in lungs after maximum expiration), than subjects from low altitudes, when adjustments are made for differences in body size (*12, 23–25*). Studies indicate that the enlarged lung volume of the high altitude native is attained through a rapid and accelerated development (*24, 26*). During childhood at low altitudes, growth in lung volume is associated with the proliferation of alveolar units and the consequent increase in alveolar surface area (*27*); among children raised at high altitudes, the rapid growth in lung volume is probably also associated

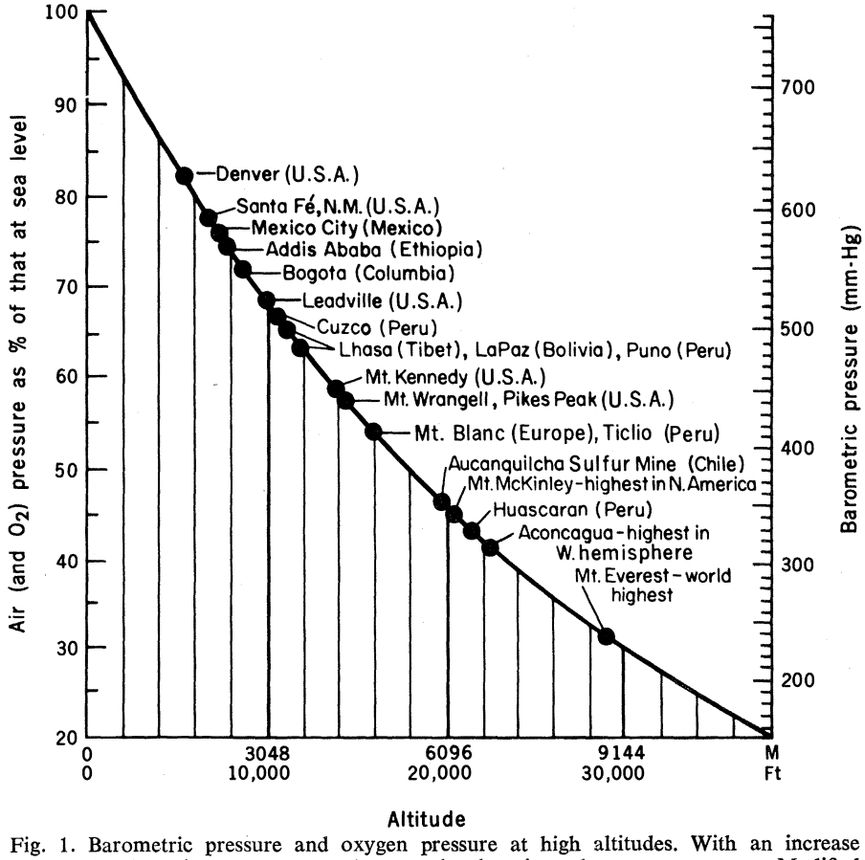


Fig. 1. Barometric pressure and oxygen pressure at high altitudes. With an increase in altitude there is a percentage decrease in the air and oxygen pressure. Modified from Folk (*66*).

with these factors. Studies invariably indicate that the pulmonary diffusing capacity of the highland native is systematically greater than that attained by lowland natives at low altitudes (*22, 28*). Since the pulmonary diffusing capacity is related in part to the alveolar surface area, the enhanced pulmonary diffusing capacity of the highland native is probably due to his having a greater alveolar area and an increased capillary volume.

In a recent investigation designed to determine the mechanisms of functional adaptation to high altitude hypoxia (*18, 25*), the forced vital capacity (maximum amount of air expired after maximum inspiration) of lowland subjects and high altitude natives was measured (see Table 1). The results demonstrated that lowland natives who were acclimatized to high altitude during growth, when adjusted for variations in body size, attained the same values of forced vital capacity as the highland natives. In contrast, lowland natives (Peruvian and white U.S. subjects) acclimatized as adults had significantly lower vital capacity than highland natives. It was thus postulated that the enlarged lung volume of the highland native is the result of adaptations occurring during growth and development (*18*).

This hypothesis is supported by experiments conducted on animals. Various studies (*29–32a*) demonstrate that young rats after prolonged exposure to high altitude hypoxia (3450 m) exhibited an accelerated proliferation of alveolar units, and an accelerated growth in alveolar surface area and lung volume. In contrast, adult rats after prolonged exposure to high altitude hypoxia did not show changes in alveolar quantity and lung volume (*32*). These findings suggest that in experimental animals and in man the enlarged lung volume at high altitude is probably mediated by developmental factors.

*Transport of oxygen in the blood.* The major function of the hemoglobin in the red blood cells is to transport oxygen from the lungs to the tissues. At high altitudes, in response to the insufficient amounts of oxygen, the bone marrow is stimulated by an erythropoietic factor to increase the production of red blood cells (*33*). For this reason, at altitudes above 4000 m, both lowland and highland natives have normal red blood cell counts ranging from 5 to 8 million per cubic millimeter compared to 4.5 million at low altitudes (*34, 35*). Along with the increase in the red blood cells, the hemoglobin is augmented so that at high altitudes the averages range from 17 to 20 grams per 100 milliliters compared to the 12 to 16 g/100 ml at sea level (*34*). In this manner, the oxygen carrying capacity of the blood at high altitudes is increased.

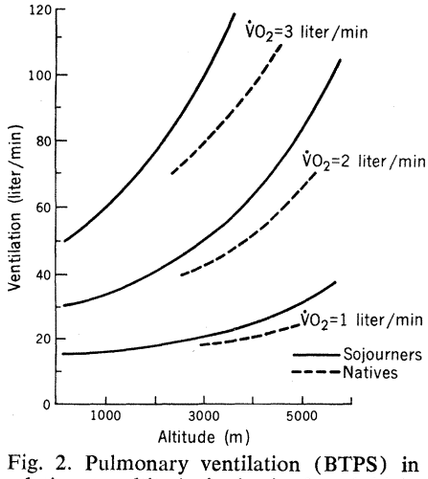


Fig. 2. Pulmonary ventilation (BTPS) in relation to altitude in lowland and highland natives measured at rest and at three levels of exercise. ($\dot{V}O_2$, maximum volume of oxygen consumed.) Adapted from Lenfant and Sullivan (*11*).

*Diffusion of oxygen from blood to tissues.* For the oxygen to be utilized, it must reach the cell mitochondria through a process of physical diffusion, and the rate of such diffusion depends on the $pO_2$. Because the oxygen is consumed as it goes through successive tissue layers, the $pO_2$ rapidly declines, and the more distance the oxygen has to travel, the greater the drop in the $pO_2$. At high altitude, where the $pO_2$ of the ambient air is already low, the organism must respond by shortening the distance the oxygen has to travel. This is accomplished by the opening up of existing and new capillaries. Through microscopic studies of experimental animals it has been found that the number of open muscle capillaries at high altitudes is increased by more than 40 percent compared to the number at low altitudes (*36–38*). A very important effect of the increased capillary bed is that it increases the blood perfusion and, thus, oxygen is more readily diffused per unit time into tissue despite the lowered oxygen tension of the blood before it reaches the capillaries (*39*). Since among highland natives the muscle myoglobin concentration is also increased (*40*), this, coupled with the increased capillarization, must certainly enhance the diffusion of oxygen at high altitudes.

Another mechanism which at high altitudes facilitates the diffusion of oxygen from the blood to the tissues is that shown by a rightward shift in the dissociation curve for oxygen and hemoglobin (*8, 41, 42*). This shift results from a decrease in the hemoglobin affinity for oxygen. This decrease appears to be related to an increase in intraerythrocytic 2,3-diphosphoglycerate (*8, 42, 43*).

At a given $pO_2$, the percentage of oxygen in the hemoglobin of venous blood is significantly lower at high altitudes than at sea level. Because of this difference, among lowland and highland natives, the proportion of the available oxygen that is delivered to the tissues is greater at high than at low altitudes (*8, 41*). However, the relative effectiveness of this mechanism is not well defined yet.

*Utilization of oxygen.* The last step in the process of adaptation to hypoxia involves variations in the rate of oxygen utilization and generation of energy at the cellular level. On the basis of studies on guinea pigs it has been postulated that at high altitudes glycolysis (anaerobic) proceeds by way of the pentose phosphate pathway rather than the Embden-Meyerhof pathway (*44*). The advantage of the pentose pathway appears to be related to the fact that no additional adeno-

Table 1. Covariance adjustment of forced vital capacity (adjusted for age, weight, and height) among subjects tested at high altitudes. *F*, variance ratio values; S.E., standard error; NS, not significant. After Frisancho *et al.* (*25*).

| *N* | Group | Forced vital capacity (ml) | |
|---|---|---|---|
| | | Mean | S.E. |
| | *Subjects tested at 3840 m* | | |
| 40 | High altitude natives | 4830.3 | 69.9 |
| 13 | Sea level subjects acclimatized as adults | 4504.6 | 122.1 |
| *F* ratio | | 5.19 | $P < .02$ |
| | *Subjects tested at 3400 m* | | |
| 20 | High altitude natives | 4990.3 | 128.6 |
| 21 | Sea level subjects acclimatized during growth | 5055.0 | 121.5 |
| *F* ratio | | 0.36 | NS |
| 10 | White U.S. subjects acclimatized as adults* | 4573.9 | 231.6 |
| *F* ratio | | 5.53 | $P < .02$ |

* When compared with the high altitude natives tested at 3840 and 3400 m.

sine triphosphate (ATP) is required to generate glyceraldehyde triphosphate as is necessary in the Embden-Meyerhof pathway. According to this mechanism (*44, 45*), at high altitudes, by relying on the pentose phosphate pathway, the organism saves energy (ATP) or produces more chemical energy with the same oxygen consumption. This hypothesis is supported by the finding that the activity of oxidative enzymes in the sartorius muscles is greater at high altitudes than at sea level (*44*). For example, in homogenates of whole cells the reduced diphosphopyridine nucleotide–oxidase system, the reduced triphosphopyridine nucleotide–cytochrome c reductase, and the transhydrogenase are significantly more active in the highland than in the lowland native (*44*). Thus, it appears that among highland natives the chemical and morphological characteristics related to energy utilization and energy production are qualitatively and quantitatively different from those of lowland natives. It is not known whether such characteristics may be acquired by lowland natives residing for long periods at high altitudes.

## Cardiovascular Traits

*Pulmonary circulation.* Histological studies have demonstrated that after the first month of postnatal development, children born at high altitudes show a thickening of the muscular layer and muscularization of the pulmonary arteries and arterioles that resembles the development of the fetal pulmonary vascular tree (*46*). These characteristics contribute to the increased pulmonary vascular resistance or pulmonary hypertension in the high altitude resident and native (*47–49*). Based on studies of steers, the hypothesis has been that pulmonary hypertension at high altitudes would favor a more effective perfusion of all the pulmonary areas, and, therefore, increase the effective blood-gas interfacial area of the alveoli (*50*). In this manner, perfusion of the entire lung coupled with an increased vascularization would enhance the diffusing capacity of the lung and should decrease the difference between the arterial and the alveolar blood. These changes would permit a more effective oxygenation of the arterial blood. However, one cannot assume that pulmonary hypertension would necessarily decrease the arterial-alveolar gradient in man, and the application of this hypothesis to the adaptation of human beings to high altitudes remains to be proved.

As a result of the increased pulmonary resistance or hypertension, the right ventricle of the heart of the high altitude resident and native is enlarged, as shown by anatomical and electrocardiographic studies (*51, 52*). The enlargement of the right ventricle may also be related to the high prevalence of patent ductus arteriosus among highland natives (*53*). Hence, because of the pressure differential between the aorta and pulmonary artery, the work of the right ventricle of the heart may be increased. The high incidence of patent ductus arteriosus may be a consequence of fetal and newborn hypoxia and may also be one of the sources of the pulmonary hypertension. Lowland natives with patent ductus arteriosus also commonly suffer from right ventricular hypertrophy and pulmonary stenosis.

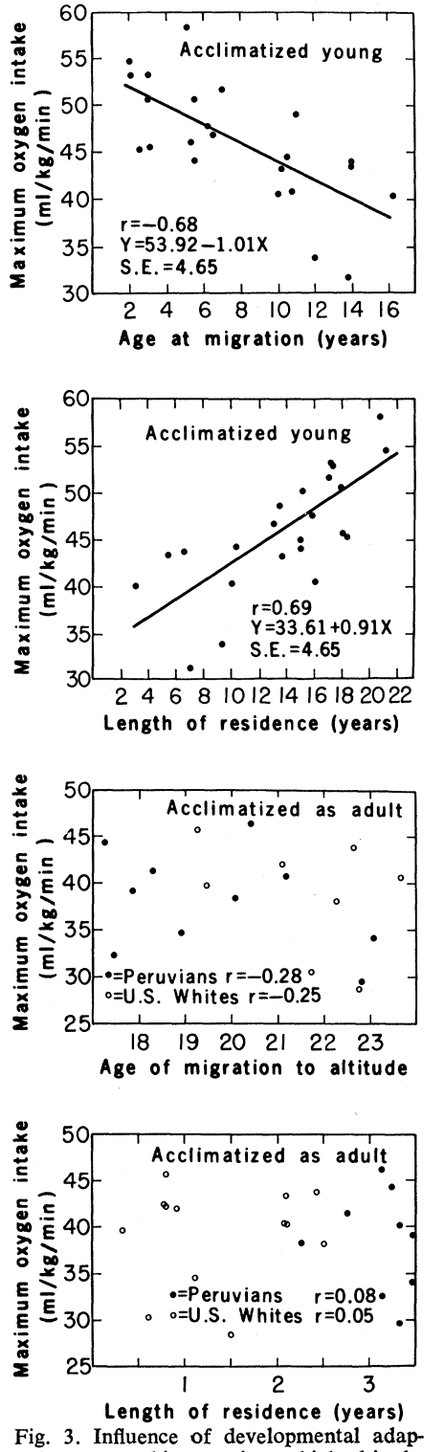


Fig. 3. Influence of developmental adaptation on aerobic capacity at high altitude. Among subjects acclimatized to high altitudes during the developmental period, age at migration and length of residency are significantly correlated with aerobic capacity, while this is not the case when the subjects are acclimatized as adults. Adapted from Frisancho *et al.* (*18*).

Although pulmonary hypertension and right ventricular hypertrophy may occur at all ages in both highland and lowland subjects in their native environments, these characteristics are accentuated among subjects exposed to insufficient supplies of oxygen during childhood and adolescence (*47, 48, 52, 54*). These findings demonstrate the influence of developmental factors in the acquisition of the cardiovascular characteristics of highland dwellers.

*Cardiac output.* Upon initial exposure to high altitude hypoxia, the resting pulse rate of the lowland native increases rapidly from an average of 70 beats per minute to as much as 105 beats per minute. This increase is associated both with a generalized increase in sympathetic activity and with an abrupt augmentation of the resting cardiac output (*55, 56*). With acclimatization, the cardiac output declines so that in about a week it equals or is below that attained at sea level (*57, 58*). This decline in cardiac output appears to be associated with a decrease in heart rate which usually remains above sea level values (*57*). The cardiac output of highland natives during rest and exercise was found to be equal to that of lowland natives at sea level (*49*). Therefore, the oxygen requirements of the body appear to be met by greater oxygen extraction rather than greater blood flow at high altitude.

*Systemic circulation.* Various studies indicate that the systemic blood pressure in adult highland natives is lower than it is in lowland natives at sea level (*47, 59–61*). Among highland natives, the frequency of systemic hypertension and ischemic heart disease is also significantly lower than among lowland natives at sea level

(*61*). Furthermore, recent studies (*60*) indicate a lowering of 10 mm-Hg or more in systolic and diastolic pressures in lowland subjects who resided for a long time (2 to 15 years) at high altitude.

The etiology of these differences has not been completely determined. Because exposure to high altitudes results in increased vascularization (*36, 38, 41, 62*), it is possible that the prevalence of low blood pressure at high altitude may be related to the reduction in peripheral vascular resistance to blood flow. In other words, lowering of blood pressure may be considered a by-product of tissue adaptation to high altitude hypoxia.

## Work Capacity

*Lowland newcomers to high altitudes.* During severe exercise the metabolic requirements for oxygen increase drastically so that all the processes involved in the transport, delivery, and utilization of oxygen are required to work at their maximum. For this reason, the effects of high altitude hypoxia are most evident during periods of hard work. Measurements of an individual's work capacity indicate the degree of success of the various adaptive responses made by the organism.

It is generally agreed that the maximum oxygen intake per unit of body weight (or aerobic capacity) during maximal activity is a measure of the individual's work capacity because it reflects the capacity of the working muscles to utilize oxygen and the ability of the cardiovascular system to transport and deliver oxygen to the tissues. Studies of newcomers to high altitudes demonstrated a reduction in aerobic capacity of from 13 to 22 percent (*6, 15, 16, 20, 63*). The maximum aerobic capacity of fit lowland natives at high altitudes, when expressed as a percentage of the values obtained at sea level, declines by 3.2 percent for every 300 m (1000 feet) ascended beyond 1500 m (5000 feet) (*15*). In contrast, the aerobic capacity of highland natives is comparable to that attained by lowland natives at sea level (*6, 14–17, 64*).

*Developmental response.* To determine the influence of developmental factors on functional adaptation to high altitude, my co-workers and I recently conducted an investigation on aerobic capacity (*18*). This study (see Table 2) demonstrated that lowland natives when acclimatized to high altitude during childhood and adolescence attained an aerobic capacity and pulmonary ventilation that was equal to that of the highland natives. Furthermore, in both groups the volume of air ventilated per unit of oxygen consumed, the increase in heart rate, and the volume of oxygen consumption per pulse rate are highly comparable.

In contrast, lowland natives (Peruvian and U.S. subjects) when acclimatized to high altitudes as adults attained significantly lower aerobic capacities and higher pulmonary ventilation than the highland natives. Similarly, these lowland subjects attained a significantly higher ventilation ratio and lower heart rate than the highland natives.

The extent to which developmental factors influence the attainment of aerobic capacity at high altitudes is illustrated in Fig. 3. These data show that, among lowland natives acclimatized to high altitudes during growth and development, the attainment of aerobic capacity is directly related to age at migration and length of residency. In contrast, when subjects were acclimatized to high altitudes as adults, age at migration and length of residency did not influence the attainment

Table 2. Physiological data of Peruvian and U.S. subjects during work on a bicycle ergometer at high altitude. Values are means ± standard deviations. After Frisancho *et al.* (*18*).

| Peruvians | | | U.S. subjects acclimatized as adults ($N = 10$) |
|---|---|---|---|
| Highland native ($N = 20$) | Acclimatized as young ($N = 23$) | Acclimatized as adults ($N = 10$) | |
| *Maximum volume of $O_2$ consumed (ml kg$^{-1}$ min$^{-1}$)* | | | |
| 46.3 ± 5.0 | 46.0 ± 6.3 | 38.0* ± 5.2 | 38.5* ± 5.8 |
| 51.2 ± 5.8† | 50.1 ± 5.4† | 42.3* ± 5.0† | 41.6* ± 5.6† |
| *Maximum pulmonary ventilation (liter/min)‡* | | | |
| 138.5 ± 22.4 | 139.7 ± 17.9 | 165.0* ± 17.2 | 175.3* ± 25.5 |
| *Ratio of maximum pulmonary ventilation to maximum $O_2$ consumed* | | | |
| 51.3 ± 6.5 | 50.7 ± 5.4 | 64.4* ± 7.2 | 75.5* ± 7.9 |
| *Maximum heart rate (beat/min)* | | | |
| 196.1 ± 6.6 | 193.2 ± 6.5 | 192.6* ± 6.0 | 187.2* ± 7.9 |
| *Volume of $O_2$ consumed per heart beat (ml/beat)* | | | |
| 13.9 ± 1.8 | 14.4 ± 1.7 | 11.1 ± 0.6 | 14.6 ± 2.4 |

* Significantly different from highland native at $P < .01$ level. † Related to fat-free weight. ‡ Corrected for body temperature and pressure, saturated (BTPS).

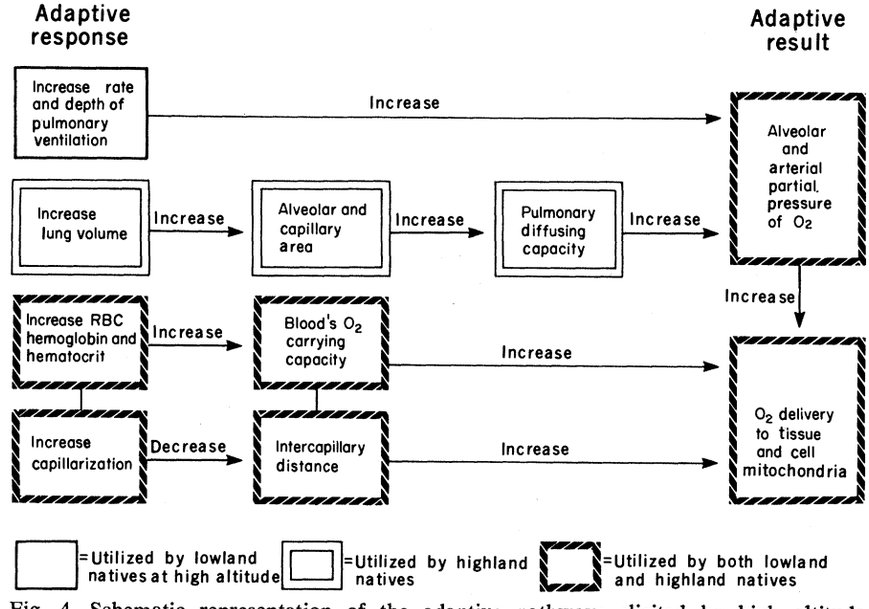


Fig. 4. Schematic representation of the adaptive pathways elicited by high altitude hypoxia. Adaptation to high altitude hypoxia results in the operation of a series of coordinated mechanisms oriented toward increasing the oxygen supply at the tissue level. The lowland and the highland native use different paths to acclimatize to high altitude hypoxia. While systems for the increase in oxygen carrying capacity of the blood and augmented capillarization are operative in both the lowland and the highland native, the increase in pulmonary ventilation is utilized mostly by the lowland native. RBC, red blood cell.

of aerobic capacity. In other words, from these investigations it appears that the attainment of normal aerobic capacity at high altitudes is influenced by adaptations occurring during the developmental period (*18*).

## Conclusions

The various adaptive mechanisms that enable both the lowland and highland native to overcome the hypoxic stress of high altitudes are summarized in Fig. 4. In both lowland and highland natives, adaptation to the low availability of oxygen at high altitudes results in the operation of a variety of coordinated mechanisms oriented toward increasing the supply of oxygen to the tissue (Fig. 4). However, the lowland native uses different paths from the highland native to acclimatize to high altitudes. While both the lowland and the highland native utilize the increase in oxygen carrying capacity of the blood, and augmented capillarization to acclimatize, it is mainly the lowland native who utilizes the increase in pulmonary ventilation. That acclimatization of highland natives does not depend on hyperventilation is perhaps due in part to their enlarged lung volume that facilitates the receiving of an adequate oxygen supply at the alveolar level. The low dependence on hyperventilation in spite of arterial hypoxemia in the highland native would suggest a difference in the reactivity of the peripheral chemoreceptors.

Recent investigations suggest that the acquisition of an enlarged lung volume and chest size (*24, 25, 65*) and attainment of normal aerobic capacity (*18*) at high altitude are influenced by developmental factors. Studies on cardiac morphology (*47*) indicate that the enlarged right ventricle of the heart that characterizes the high altitude native is acquired during development. Thus it is suggested that the differences between the highland and the lowland native in physiological performance and morphology are due, in part, to adaptations acquired during the developmental period.

During growth and development, environmental factors are constantly conditioning and modifying the expression of inherited potentials. The influence of the environment on the organism depends on the type of stress imposed and especially on the age at which the individual is subjected to the stress. Hence, the respective contribution of genetic and environmental factors varies with the developmental stage of the organism and, in general, the earlier the age, the greater the influence of the environment. For these reasons, it would be surprising if developmental processes did not influence the functional performance and morphology of the high altitude native. At present, however, the extent to which this conclusion is applicable to the other physiological traits of the highland native is not known. For example, it appears that the attainment of low systemic blood pressure at high altitudes does not depend on developmental factors because it can be acquired by lowland natives residing for long periods at high altitudes (*60*). Similarly, the mechanisms by which high altitude hypoxia induces the development of the characteristics of the highland native are not known.

Because high altitude hypoxia affects the major physiological processes it is conceivable that it may also influence the functional processes not only during growth but also during aging. Because aging in general results in a decreased capacity of the oxygen transport system, functional processes during aging may be expected to be affected at high altitudes to a greater extent than they are at sea level. Studies of human adaptation to high altitudes during aging would thus help to elucidate the various mechanisms whereby man overcomes the stress of low oxygen supply, such problems being of major importance to both lowland and highland populations. Therefore, future endeavors should be oriented to fill this gap in our knowledge.

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# Beginnings of Fruit Growing in the Old World

## Olive, grape, date, and fig emerge as important Bronze Age additions to grain agriculture in the Near East.

Daniel Zohary and Pinhas Spiegel-Roy

Fruit trees constitute an important element of food production in the countries bordering the Mediterranean Sea. The long standing of their economic importance is amply reflected in classical traditions. Five of the Biblical seven species (*1*) are fruit trees. Olive oil, wine, dry raisins, dates, and figs were, and still are, major agricultural products of the Near East and the Mediterranean Basin. Compared to the information available on the origin of cultivated cereals and pulses in the Old World, evidence on the beginnings of fruit growing is fragmentary. Yet recent examinations of plant remains in Neolithic and Bronze Age sites in the Near East and Greece have led to several critical discoveries which indicate that olives, dates, and probably also grapes, figs, and pomegranates were already under cultivation in protohistoric times. In this article we review the evidence we already have for answering the questions: (i) Which fruit trees were cultivated early in the Near East and what were their wild progenitors? and (ii) When and where were these plants brought under cultivation? As in previous evaluations of the origin of the Old World cereals (*2*) and pulses (*3*), the analysis is based primarily on two kinds of information: (i) "fossil" evidence obtained from examinations of plant remains in archeological excavations, and (ii) clues provided by living plants and particularly by wild relatives of the crops concerned. In addition, we evaluate several aspects of the genetic systems operating in the fruit trees and relate them to domestication. Attention is focused on the significance of the shift to vegetative propagation, and the possible role of hybridization between wild and cultivated forms in the establishment and expansion of cultivars.

### Olive (Olea europaea L.)

Olives make their appearance in Palestine in the fourth millennium B.C. Numerous well-preserved carbonized olive stones (Fig. 1) were discovered in the Chalcolithic Teleilat Ghassul (3700 to 3500 B.C.) north of the Dead Sea (*4*), in close association with cereal grains, dates, and pulses. These finds, from a classic Chalcolithic site, are supplemented by admirably preserved stones excavated in the "Cave of the Treasure" near Ein Geddi (3200 to 3100 B.C.) (*5*) and stones and wood charcoal retrieved from Chalcolithic horizons (3200 B.C.) of Tell Mashosh, 15 kilometers east of Beersheva (*6*). Some centuries later olive remains abound in early Bronze Age (2900 to 2700 B.C.) Arad (*7*) and early and middle Bronze Age Lachish (*8*). Carbonized stones and charred olive wood are available also from early and middle Bronze Age Ta'anach (Tell Taannek) and Afeq (*9*). So far there have been few early finds of olives outside Palestine. Helbaek (*10*) reported olive remains from third millennium Tell Soukas, Syria, and Renfrew (*11*) recorded them from early Minoan Myrtos in Crete. In the middle and late Bronze Age, olive cultivation (and the olive oil industry) seems to have been well established throughout the areas bordering the Mediterranean Sea, from Palestine and Syria to Greece. Carbonized stones

Dr. Zohary is professor of genetics at the Hebrew University of Jerusalem, Jerusalem, Israel. Dr. Spiegel-Roy heads the Horticultural Institute, Agriculture Research Organization, Beit Dagan, Israel.