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Developmental Adaptation to High Altitude Hypoxia

by

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ABSTRACT. — Experimental studies on animals and humans exposed to hypoxic stress have been reviewed. These data suggest that the influence of hypoxic stress, and the organism's response to it, are greater during growth than during adulthood. The organism's responses include alterations in the quantity and size of the alveolar units of the lungs, enlargement of the right ventricle of the heart, slower somatic growth as measured by birth weight and body size, increased aerobic capacity during maximal work, and greater control of ventilation. It is postulated that the organism is more sensitive to the influence of environmental factors during growth and development than during adulthood. Consequently, adaptive traits acquired during the developmental period have profound, long-term consequences, which are reflected in the physiological and morphological characteristics of the adult organism. It is concluded that the differences between the highland and lowland natives in their physiological performance and morphology are mostly due to adaptations acquired during the developmental period.

Attention is called to the fact that the principle of developmental sensitivity and plasticity does not imply equally adaptive responses in all biological parameters. In other words, what we consider a deficiency in a given variable may actually reflect the indirect influence of the adaptive success of another variable.

INTRODUCTION

During growth and development, environmental factors are constantly conditioning and modifying the expression of inherited potential. 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 contributions of genetic and environmental factors vary with the developmental stage of the organism and, in general, the earlier the age, the greater the influence of the environment. Thus, in previous publications we have postulated that the differences between the highland and the lowland native in terms of physiological performance and morphology are due in part to adaptations acquired during the developmental period (Frisancho, 1975; Frisancho, Velasquez and Sanchez, 1973; Frisancho et al., 1973). It is the purpose of the present article to summarize the evidence that supports this hypothesis.

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LUNG VOLUME AND PULMONARY DIFFUSING CAPACITY

Several investigations have documented that vital capacity and residual lung volume of sea level natives sojourning at high altitudes will remain unchanged, after an initial reduction, when compared to values attained at sea level (Consolazio et al., 1967; Rahn and Hammond, 1952). In contrast, after adjustments are made for differences in body size, highland natives have a larger lung volume, especially a larger residual lung volume, than subjects from low altitudes (Frisancho, Velasquez and Sanchez, 1973; Hurtado, 1932). As inferred from studies of children, the enlarged lung volume of the high altitude native is attained through a rapid and accelerated development during childhood and adolescence (Frisancho, 1969; Hurtado, 1932). Since at low altitudes growth in lung volume during childhood is associated with the proliferation of alveolar units and alveolar surface area (Dunnill, 1962), the rapid growth seen among highland children is probably also associated with an increase in alveolar units and alveolar surface area. Studies invariably indicate that the pulmonary diffusing capacity of the highland native is systematically greater than that attained by lowland natives at low altitudes (DeGraff et al., 1970; Guleria et al., 1971; Remmers and Mithoefer, 1969; Velasquez and Florentini, 1966). 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 a greater alveolar area and an increased capillary volume.

With a view toward determining the role of developmental factors in the attainment of enlarged lung volume, we recently studied the forced vital capacity of lowland subjects and highland natives. As shown in Table 1, the lowland natives who were acclimatized to high altitude during growth attained, after adjustments for variations in body size, the same values of forced vital capacity as the highland natives. In contrast, lowland natives (Peruvian and North American subjects) acclimatized as adults had significantly lower vital capacities than highland natives. We thus postulated that the enlarged vital capacity of the highland native is the result of adaptations occurring during growth and development (Frisancho, Velasquez and Sanchez, 1973).

TABLE 1. Covariance adjustment of forced vital capacity (adjusted for age, weight, and height) among subjects tested at high altitudes. After Frisancho, Velasquez and Sanchez (1973).

n	Group	Forced vital capacity (ml)	
		Mean	SE
	Subjects tested at 3,840 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<0.02
	Subjects tested at 3,400 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 North American subjects acclimatized as adults*	4573.9	231.6
F ratio		5.53	P<0.02

* When compared with the high altitude natives tested at 3,840 m and 3,400 m.

This hypothesis is supported by experiments conducted on animals. Various studies (Bartlett, 1972; Bartlett and Remmers, 1971; Burri and Weibel, 1971) have demonstrated that after prolonged exposure to high altitude hypoxia (3,450 m) young rats exhibit an accelerated proliferation of alveolar surface area and lung volume. In contrast, adult rats after similar exposure to high altitude hypoxia did not show changes in alveolar quantity and lung volume (Burri and Weibel, 1971; Cunningham, Brody and Jain, 1974). These findings suggest that in experimental animals and in man the enlarged lung volume at high altitude is probably mediated by developmental factors.

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 a muscularization of the pulmonary arterioles that resemble the development of the fetal vascular tree (Arias-Stella and Saldana, 1962). These characteristics contribute to the increased pulmonary vascular resistance or pulmonary hypertension in the high altitude resident and native (Banchero et al., 1966; Penaloza et al., 1963; Sime et al., 1963). Based on studies of steers, the hypothesis has been that pulmonary hypertension at high altitudes would favor a more effective profusion of all the pulmonary areas, and therefore, increase the effective blood-gas interfacial area of the alveoli (Grover et al., 1963). In this manner, perfusion of the entire lung coupled with an increased vascularization would enhance the diffusing capacity of the lung and should also 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 tested.

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 (Arias-Stella and Recavarren, 1962; Harris and Hansen, 1966; Penaloza et al., 1964; Rotta et al., 1956). The enlargement of the right ventricle may also be related to the high prevalence of patent ductus arteriosus among highland children (Marticorena et al., 1962). Hence, because of the pressure differential between the aorta and the 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 pattern ductus arteriosus also commonly suffer from right ventricular hypertrophy and pulmonary stenosis.

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 oxygen supplies during childhood and adolescence (Arias-Stella and Recavarren, 1962; Banchero et al., 1966; Penaloza et al., 1963; Sime et al., 1963). These findings demonstrate the influence of developmental factors in the acquisition of the cardiovascular characteristics of the highland native.

PRENATAL AND POSTNATAL GROWTH IN BODY SIZE

Petropoulos and Timiras (1974) have summarized the available evidence related to hypoxic effects on prenatal and postnatal growth. These studies indicate that prenatal growth, as judged from evaluations of birth weight, is retarded among experimental animals raised at high altitude when compared to sea level controls with equal dietary intakes (Delaquerriere-Richardson, Forbes and Valdivia, 1965; Johnson, Taylor and

DeGraff, 1965; Nelson and Srebnik, 1970). These findings are in agreement with those published for humans. Studies in the U.S. and Peru indicate that birth weight among high altitude populations is lower than in comparable sea level populations (Lichty et al., 1957; Baker, 1969; Frisancho, 1970; Grahn and Krathcman, 1963; Hoff, 1974; Kruger and Arias-Stella, 1970; McClung, 1967; Pawson, 1974; Sobrevilla et al., 1967; U.S. Publ. Hlth., 1965; Weinstein and Haas, 1975).

The decrease in birth weight among high altitude populations is not associated, however, with a decrease in placental weight. On the contrary, studies in animals (Nelson and Srebnik, 1970; Petropoulos, 1971) and on humans (Frisancho, 1970; McClung, 1969; Sanchez, 1963; Sobrevilla and Salazar, 1968) indicate that the placental weight at high altitude is either equal to or greater than that at sea level. In either case, the placental weight/newborn weight ratio at high altitude is higher than at sea level. It has been postulated that the relatively greater weight of the placenta reflects a prenatal adaptive mechanism to the low oxygen availability of high altitudes (Frisancho, 1970; McClung, 1969; Sobrevilla, 1971). However, as indicated by Petropoulos and Timiras (1974) this hypothesis remains to be experimentally substantiated.

The pattern of slow prenatal development inferred from studies of birth weight continues during postnatal development. In high altitude rats this retarded growth results in a 30% reduction in adult body weight, even in cases where birth weights were equivalent to sea level rats (Weihe, 1965; Kelley and Pace, 1968; Petropoulos and Timiras, 1974). Studies in humans indicate that growth in body size during infancy, childhood and adolescence is delayed at high altitude when compared to growth in sea level counterparts (Frisancho, 1969; Baker, 1969; Frisancho and Baker, 1970; Haas, 1973; Boyce et al., 1974). Using intra-and inter-populational comparisons of genetic similarities and parent-offspring correlation coefficients, it has been concluded that the retarded growth of high altitude children is related to the synergic influence of hypoxic stress and nutritional factors associated with high altitude environments (Frisancho, 1976).

WORK CAPACITY

LOWLAND NEWCOMERS TO HIGH ALTITUDES. — It is generally agreed that the maximum oxygen intake per amount of body weight during maximal activity (aerobic capacity) 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 demonstrate a reduction in aerobic capacity of from 13 to 22% (Adams et al., 1975; Balke, 1960; Buskirk et al., 1967; Consolazio et al., 1967; Dill et al., 1967; Faulkner et al., 1968; Grover et al., 1967; Kollias et al., 1968). The maximum aerobic capacity of fit lowland natives at high altitudes, when expressed as a percentage of the values attained at sea level, declines by 3.2% for every 300 m ascended beyond 1,500 m (Buskirk et al., 1967). In contrast, the aerobic capacity of highland natives such as Andean Quechuas and Himalayan Sherpas is comparable to that attained by lowland natives at sea level (Baker, 1969; Buskirk et al., 1967; Elsner, Bolstad and Forno, 1964; Grover et al., 1967; Kollias et al., 1968; Lahiri, 1966; Mazess, 1969; Velasquez, 1964).

DEVELOPMENTAL RESPONSE. — To determine the influence of developmental factors on functional adaptation to high altitude, my co-workers and I recently conducted an investigation of aerobic capacity (Frisancho, Velasquez and Sanchez, 1973; Frisancho et al., 1973). As shown in Table 2, the lowland natives, when acclimatized to high altitude during childhood and adolescence, attained an aerobic capacity and pulmonary ventilation 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 North American 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.

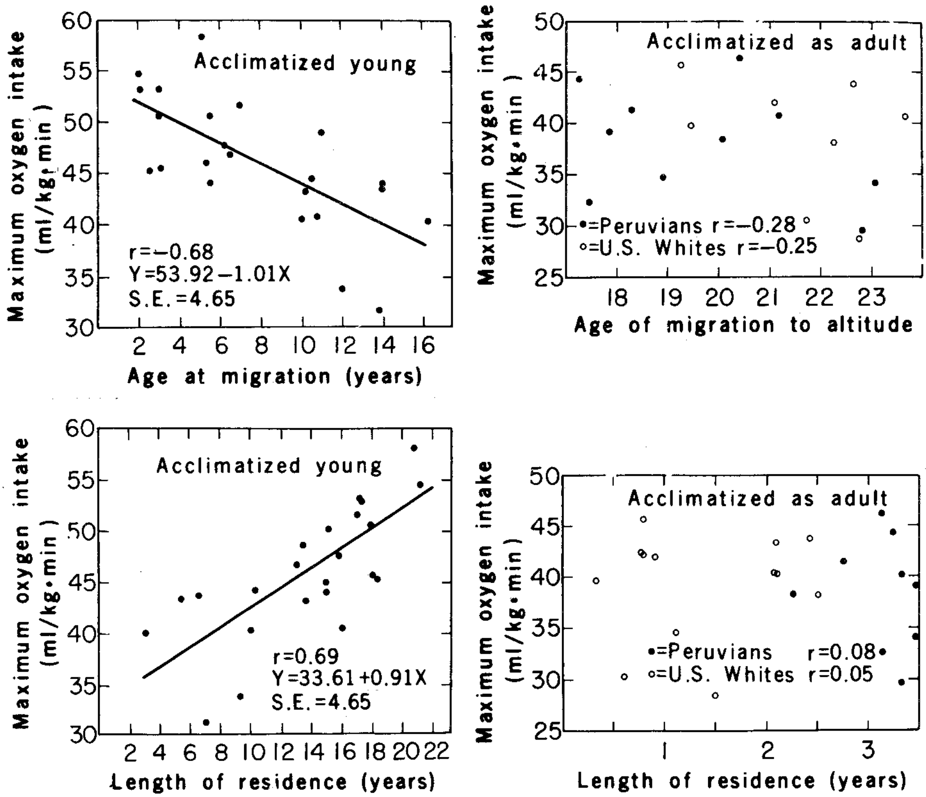

Fig. 1. Influence of developmental adaptation on aerobic capacity at high altitude. Among subjects acclimatized during the developmental period, age at migration and length of residency are significantly correlated with aerobic capacity, while this is not the case when the subjects are acclimatized as adults. Adapted from Frisancho et al. (1973).

The extent to which developmental factors influence the attainment of aerobic capacity at high altitudes is illustrated in Fig. 1. 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 of aerobic capacity. In other words, it appears from the investigations that the attainment of normal aerobic capacity at high altitudes is influenced by adaptations during the developmental period (Frisancho et al., 1973).

BODY SIZE AND AEROBIC CAPACITY. — As previously indicated it is generally

TABLE 2. Physiological data of Peruvian and U.S. subjects during work on a bicycle ergometer at high altitude. Values are means ± SD. After Frisancho et al. (1973).

Characteristics	Peruvians			U.S.
	Highland native (n = 20)	Acclimatized as young (n = 23)	Acclimatized as adults (n = 10)	North American subjects acclimatized as adults (n = 10)
$\dot{V}O_{2max}$ ml/(kg. min)	46.3 ± 5.0	46.0 ± 6.3	38.0* ± 5.2	38.5* ± 5.8
ml/(kg. min)[a]	51.2 ± 5.8	50.1 ± 5.4	42.3* ± 5.0	41.6* ± 5.6
$\dot{V}E_{max}$ (BTPS), 1/min	138.5 ± 22.4	139.7 ± 17.9	165.0* ± 17.2	175.3* ± 25.5
$\dot{V}E/VO_2$	51.3 ± 6.5	50.7 ± 5.4	64.4* ± 7.2	75.5* ± 7.9
HR_{max}	196.1 ± 6.6	193.2 ± 6.5	192.6* ± 6.0	187.2* ± 7.9
O_2 pulse, ml/beat	13.9 ± 1.8	14.4 ± 1.7	11.1 ± 0.6	14.6 ± 2.4

* Significantly different from highland natives, $P<0.01$. a $\dot{V}O_{2\,max}$ related to fat-free weight.

agreed that growth in body size at high altitudes is retarded when compared to that at sea level. As a result of this delayed growth, highland adult natives are shorter and lighter in weight than their sea level counterparts. It must be noted, however, that this delayed growth among highland children is not associated with any pathological symptoms, and that these adults have a work capacity comparable to that of sea level inhabitants. Therefore, the delayed growth found among high altitude children probably reflects part of the adaptive mechanisms that enable them to adapt to the highland environment. In other words, small body size both during development and adulthood may represent a byproduct of adaptive responses to the high altitude environment. In order to test this hypothesis we have studied the maximal aerobic capacity of young adult Quechua subjects selected for extremes of stature (Frisancho, Velasquez and Sanchez, 1975). The sample consisted of two subgroups of high-altitude young adult Quechua natives: 22 subjects characterized by small body size and 18 subjects characterized by large body size. The stature of the small body size group ranged from 150 to 159 cm, and the stature of the large body size group ranged from 162 to 174 cm. The

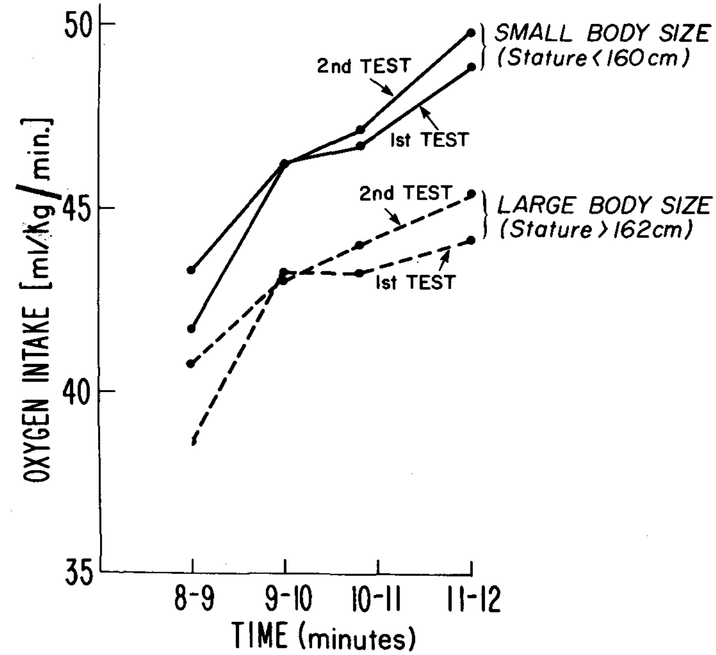

Fig. 2. High altitude Quechua natives tested at 3,840 m. Increased aerobic capacity is associated with small body size. Adapted from Frisancho, Velasquez and Sanchez (1975).

age in both groups ranged from eighteen to twenty-five years. These subjects were serving as soldiers at the Army Headquarters of the city of Puno (3,840 m). They were under the same training program and their length of service in the army ranged from 0.9 to 1.9 years. Their nutritional and health status was good, as judged by both the anthropometric measurements and the reports of the medical officers. They all were of blood type O and Rh+.

As shown in Fig. 2, during each minute of maximal work and in both tests the short subjects attained a significantly ($P<0.005$; $P<0.01$) greater oxygen intake (ml/(kg/min) than their tall counterparts. However, the ventilation rate and maximal work loads of the short subjects were comparable to those attained by the tall natives.

These findings suggest that small subjects at high altitude have an enhanced functional adaptation. Hence, it would appear that delayed growth leading to small body size among highland populations is part of the adaptive mechanism which enables these populations to adapt to the highland environment. However, the mechanisms whereby small individuals are able to maintain a higher aerobic capacity await clarification through experimental studies.

CONCLUSIONS

The present review has been concerned with evaluating the developmental adaptive responses that enable the organism to survive under hypoxic conditions. Recent publications by Petropoulos and Timiras (1974) and Mazess (1975) should be consulted for an updated review of the literature.

The available evidence suggests that developmental responses are of major importance in enabling man to attain a full functional adaptation to high altitude hypoxia. Thus, it is postulated that the differences between highland and lowland natives in physiological performance and morphology are mostly due to adaptations acquired during the developmental period. This postulate is supported by a recent investigation of Lahiri et al. (1976), which studied the control of ventilation by sea level and high altitude newborns, children and adults. The study demonstrated that the blunted ventilatory response to hypoxia and large lung volumes developed gradually after birth; the offspring of lowlanders born and raised at high altitude also showed the same ventilatory responses as the native highlanders.

The hypothesis that developmental adaptations account for most of the differences in physiological performance and morphology between highland and lowland natives is based upon the theoretical assumption that the respective contributions of genetic and environmental factors vary with the developmental stage of the organism, and in general the earlier the stage the greater the influence of the environment. It must be noted, however, that the principle of developmental sensitivity and plasticity does not necessarily imply greater adaptive responses in all biological parameters. This will depend on the developmental stage of the organism, the type of organism, and the particular functional process that is affected. Thus, an adaptive response in a physiological parameter does not necessarily imply an adaptive response in a morphological trait, although such a trait may depend on a successful functional adaptation. Weinstein and Haas (1975) studied women living in Leadville, Colorado (3,000 m) and found that those acclimatized to high altitude prior to adolescence had offspring with lower birth weights than those acclimatized after adolescence or during adulthood. These differences in birth weight, rather than being contradictory to the developmental hypothesis, are in my opinion probably related to the fact that, as previously indicated, hypoxia leads to growth delay and smaller adult body size, which in turn, may affect the physiological and morphological development necessary for adequate prenatal growth. In other words, what we consider a deficiency in a given variable may actually reflect the indirect influence of the adaptive success of another variable. Successful adaptation to high altitude hypoxic stress is a complex phenomenon which develops through a synchronized interdependence of various physiological and morphological reactants interrelated within the lifespan of the organism. Homeostatic interdependence does not imply uniform correlations for all physiological and morphological variables. Continuous exposure to hypoxic stress results in an integrated systemic potentiation of all homeostatic processes of the organism.

Future research, then, must be addressed to determining the specific critical period at which a given parameter is most affected and the specific period at which the most adaptive responses occur. In view of our drastically changing ecosystem, such information will improve not only our understanding of man's mechanisms of adaptation to high altitude hypoxia, but also will further our comprehension of man's capacity for adaptation to various adverse environments.

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