LIFE AT HIGH ALTITUDES

PAN AMERICAN HEALTH ORGANIZATION

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NOTE

At each meeting of the Pan American Health Organization Advisory Committee on Medical Research, a special one-day session is held on a topic chosen by the Committee as being of particular interest. Experts in the field under discussion are invited to participate. At the Fifth Meeting, which convened in June 1966 in Washington, D.C., the session explored the natural and acquired acclimatization of man to high altitudes, examining its morphological, physiological, clinical, and demographic patterns and delineating areas in which increased research efforts are desirable. This volume records the papers presented and the accompanying discussions.

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LIFE AT HIGH ALTITUDES

Moderator: Last year's decision by the Advisory Committee on Medical Research of the Pan American Health Organization to hold this special session on life at high altitudes was taken because several million people in this hemisphere, especially in Peru and Bolivia, live permanently at over ten thousand feet. Other populations, in Argentina, Colombia, and Mexico, live just a little lower. As we shall see later, this environmental factor modifies many characteristics, both functional and organic, of people subjected to it. We are beginning to recognize that such factors also have implications for disease incidence and evolution, and consequently for sanitary and public health matters. I feel certain that today's session will demonstrate that high altitude is an excellent laboratory in which to study how the human body is able to respond and adapt to the environment in which it lives provided that physiological reserves and limitations are not exceeded. There are yet many problems to be investigated and answers to be found.

I am happy to propose Dr. Hermann Rahn of the United States and Dr. Carlos Monge of Peru as rapporteurs.

Dr. Rahn is also our first speaker.

INTRODUCTION TO THE STUDY OF MAN AT HIGH ALTITUDES: CONDUCTANCE OF O_2 FROM THE ENVIRONMENT TO THE TISSUES

Hermann Rahn

Normal function in man requires a continuous delivery of oxygen to the tissues. At rest this is about 300 ml O_2 per minute. However, it must also be delivered above the "critical" O_2 pressure for optimal oxidative enzyme reactions. If we choose a value of 3.5 mm Hg pO_2 for this pressure (10), then oxygen delivery *below* that value at the site of the mitochondria is synonomous with some degree of hypoxia. One might predict that the average O_2 tension in the cytoplasm surrounding the mitochondria (tissue or cellular O_2 tension) would be considerably higher. This O_2 tension of a cell must not only provide an adequate O_2 gradient between the cytoplasm and its own mitochondria but must also serve neighboring cells further removed from the capillary. In addition, one might expect a slight reserve or cushion in case of interruption in the O_2 transport. Even so, some tissues, such as the retina, will begin to cease functioning in as little as three seconds when the blood supply is interrupted (2).

Experimental data suggest that the "critical" pO_2 of the venous blood below which tissue function is impaired is 18 mm for cat brain (13), 14 for contracting dog soleus muscle (14), 15 for cerebral cortex (4), and 28 and 29 for cat and dog muscles at rest (12, 14). Thus one might say that the normal tissue O_2 tensions are at least 15 and may be as high as or higher than venous blood tensions (5). The particular value, however, will also depend upon such factors as the diffusion distance between the capillary and the cells and the metabolic rate of the particular tissue.

If we assume these to be the normal values, then we must ask what the values are at high altitude and during the adaptation to high altitude. What can the over-all O_2 transport problem do to maintain the minimal tissue O_2 tension requirements? What are the immediate responses of man to preserve the necessary O_2 pressure? What are the long-term adaptations? I should like to contrast the problems of O_2 transport at sea level, where the inspired pO_2 is 150 mm Hg, with those that exist at eighteen thousand feet, where the inspired value is less than half—namely, 70. This is about the highest altitude to which man can become acclimatized—at which he can live and work for months (16) and years (6).

Man at sea level

If the tissue must have an average environment of about 10 mm pO_2, then 150–10, or 140 mm, can be used in the over-all transport. Figure 1 indicates the pressure levels at different distances along the transport chain. The oxygen flow is constant at any level. It is delivered from the infinite reservoir of the atmosphere and cascades down the transport chain to disappear

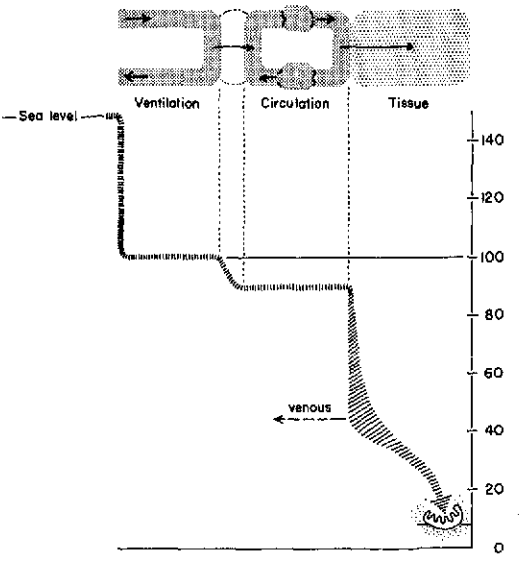


Figure 1. THE O_2 TENSIONS IN MAN LIVING AT SEA LEVEL FROM THE INSPIRED GAS TO THE TISSUE LEVEL

in the "hungry mouths" of the mitochondria. So long as the O_2 flow is delivered at the proper pressure, optimal oxidative enzyme reactions occur; if, on the other hand, the pressure falls below this critical level (ca. 4 mm pO_2) some degree of hypoxia is imminent.

In Table 1, I have given approximate values for the O_2 pressure drop at various levels. If we assume a vO_2 of 300 ml/min we can describe the O_2 conductance at each level. Thus the O_2 conductance for ventilation is 6 ml of O_2 for every mm pO_2 drop. The O_2 conductance for the circulation is the same. The tissue conductance is 10 if we assume a 30 mm pO_2 drop between the venous value and the mitochondria, and that for the lung is very high—namely, 30. (The over-all conductance is 2.14 and is equal to the reciprocals of each individual conductance or equal to the oxygen uptake divided by the total pressure drop.)

$$O_2 \textit{ Conductance} = \frac{\dot{V}_{O_2}}{\Delta P_{O_2}}$$

	$\dot{V}_{O_2}$	ΔP_{O_2}	Cond.
Ventilation	300	50	6
Lung	300	10	30
Circulation	300	50	6
Tissue Diffusion	300	30	10
Total Conductance	300 ÷ 140 =		2.14

O_2 Conductance of:

Ventilation	= k	$\dot{V}_A$	alveolar ventilation
Lungs	= k	D_L	diffusion capacity
	= k	Distr.	$\dot{V}_A/\dot{Q}$ distribution
	= k	1/Shunt	venous admixture
Circulation	= k	$\dot{Q}$	cardiac output
	= k	Hb	Hb concentration
	= k	S	slope of diss. curve
Tissues	= k	$\alpha \cdot d$	constant
	= k	1/diff. dist.	no. of capill./mm^2

In Table 2 I have broken down the four major conductances into their various component parts and defined them. These will be discussed in more detail below. Suffice it here to point out that there are many factors indeed that play a role in the conductance of O_2, some of them more important than others in man's adaptation to high altitude.

Man at high altitude

When man goes to altitude and the inspired O_2 falls, the O_2 conductance must obviously increase (Figure 2). At eighteen thousand feet, where the inspired O_2 is 70, the over-all conductance must at least double if the tissue tension is to remain the same, since the vO_2 is unaltered. The question, then, is, Do all the conductances increase equally or are some more efficient than others in adapting to the increased demand? In Table 3 I have given some comparative estimates for man at sea level and at eighteen thousand feet. Most of the values for

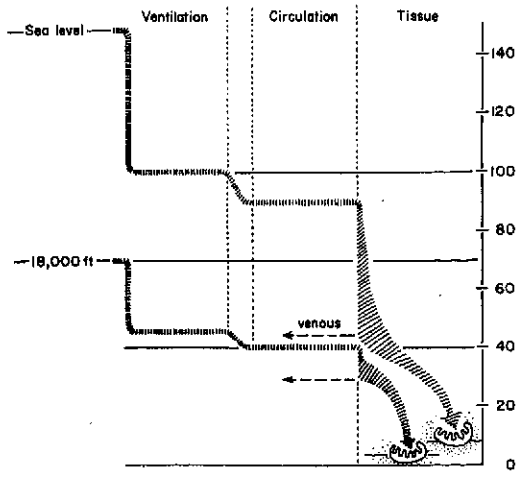


Figure 2. A COMPARISON OF THE O_2 TENSIONS IN MAN AT SEA LEVEL AND AT 18,000 FEET

		Acclim.	Dissoc.	ΔP_{O_2} sea level	ΔP_{O_2} altitude	Cond. sea level	Cond. altitude
Ventilation	k $\dot{V}_A$	✓		50	32	6	9.5
Lungs	k D_L	✓					
	k Distr.	✓	✓	10	3	30	100
	k 1/Shunt		✓				
Circulation	k $\dot{Q}$						
	k Hb	✓		50	15	6	20
	k S		✓				
Tissues	k a·d						
	k 1/diff. dist.	✓		30	15	10	20
				140	*65*	*2.14*	*4.62*

altitude are based upon or calculated from the data of Dill *et al.* (6) and Hurtado *et al.* (8, 9).

Ventilation. The increased ventilation at altitude reduces the ΔpO_2 from 50 to 32 and increases the conductance from 6 to 9.5 ml O_2/mm pO_2.

Lungs. The diffusion capacity may increase somewhat at altitude (15). This would increase the conductance. The distribution factor as it affects the arterial-alveolar O_2 difference is expected to decrease (7) as a result of the shift of the alveolar gases down on the steep part of the oxygen dissociation curve. For similar reasons a shunt would also become less effective in producing an alveolar-arterial O_2 difference. Altogether, I have assumed a total alveolar-arterial O_2 difference of 3 mm. This increases the conductance from 30 at sea level to 100 at altitude. During exercise, however, the alveolar-arterial O_2 may increase at altitude (1); the conductance change would then be smaller.

It is of interest here to speculate whether the increase in pulmonary artery pressure at altitude is simply a way of providing more even distribution of pulmonary blood flow and as a consequence a smaller alveolar-arterial O_2 difference. However, it seems that so little is actually gained in terms of O_2 conductance that we must look for other explanations for the occurrence of this hypertension.

Circulation. One obvious way to increase the O_2 conductance is to increase the cardiac output. By doubling it we can double the conductance. However, in the long run this is a rather costly approach in terms of the extra energy requirements of the myocardium. The evidence suggests (9, 1) that the cardiac output is not appreciably altered at rest and changes with exercise in much the same fashion as in sea-level man (1). The increase in Hb, however, is important. A doubling in Hb should double the conductance. However, the change in the slope of the oxygen dissociation curve is of equal importance. The steeper the slope the higher the conductance, and combined with an increase in Hb it provides one of the major contributions to the increased O_2 conductance at altitude (from a value of 6 to 20 ml/mm pO_2).

Tissues. We have finally to consider the diffusion conductance of the tissues. The diffusion coefficient and α for O_2 ($\alpha \cdot d$) is independent of altitude. However, one can reduce the diffusion distance between the capillary and the cells furthest removed—the intracapillary distance—by increasing the number of capillaries/mm^2. By doubling the number of capillaries one can reduce by about half the O_2 diffusion gradient from the capillary to the periphery of its tissue cylinder. With this assumption the ΔpO_2 for the tissues in Table 3 is reduced from 30 at sea level to 15 at altitude and thus O_2 conductance is doubled.

The total O_2 pressure drop as shown in Table 3 is 140 at sea level and 65 at altitude. Since the vO_2 is 300 in both cases, the over-all conductance is 300/140, or 2.14, at sea level and 300/65, or 4.62, at altitude. The various factors that contributed to the increase in conductances at altitude have been checked under two headings in Table 3. One column has been labeled *Dissoc.* Since the physiological range of the O_2 dissociation curve has now been displaced to its steep part, there is an automatic reduction in the O_2 differences that normally arise from the presence of the distribution factor, the shunt factor, and the slope of the oxygen dissociation curve. This shift on the O_2 dissociation curve therefore increases the O_2 conductances and takes place automatically upon exposure to low O_2 without requiring any active response. These effects are well known.

The other column, labeled *Acclim.*, represents

active responses that come into play to increase the O_2 conductance. The increase in ventilation is well known. It is of interest to note, however, that the increase in conductance is relatively small—from 6 to 9.5. The O_2 conductance of the lung is increased about threefold. Being very high to start with, it does not contribute very much by increasing further. The changes in the diffusion capacity of the lung are probably small at rest, and the better distribution of the vA/q achieved by the increased pulmonary artery pressure is probably also negligible at rest. However, both of these must be considered at least contributory factors that are achieved slowly during the acclimation process.

The increase in hemoglobin is also achieved gradually as well as the reduction in the diffusion distance. Recent evidence presented by Cassin *et al.* (3) suggests that the increase in capillarization at altitude represents not simply an opening up of previously closed vessels but an actual growth of new vessels. Both the changes in Hb and the new blood vessels are important contributors to the increased O_2 conductance. However, they require time for their ultimate expression. Thus other conductances must take over during the acute exposure. An increase in cardiac output and a greater alveolar ventilation are frequently seen in newcomers; they may represent compensation for the more slowly acquired compensatory devices, such as the changes in diffusion capacity, pulmonary hypertension, increased hemoglobin, and number of capillaries. In general it will be noted that by far the biggest change in O_2 conductance is contributed by the circulation and the tissues.

Tissue Diffusion. Finally, we must look more closely at the O_2 diffusion process from the capillary to the tissues. This is a much neglected area that deserves closer scrutiny, since the O_2 tensions are not easily measured. We must therefore still depend upon various models such as were proposed originally by Krogh (11) and later by many others. The most recent model, by Diemer (5), provides a new approach based upon the observation that in adjacent capillaries of the brain the blood flows in a countercurrent fashion. I should like to use the old Krogh-Erlang equation and adapt it from the excellent analysis recently provided by Landis and Pappenheimer (12).

In Figure 3 are shown the tissue O_2 tensions for various tissues as a function of their intercapillary distances, and also the number of capillaries/mm². I have assumed that the capillary pO_2 was 40 for all tissues. The number following each tissue indicates the qO_2, ml O_2/min/100 gm of tissue. For example, brain tissue has approximately 300 capillaries per mm², which corresponds to an intercapillary distance of about 58 μ (5). If qO_2 is 5, the pO_2 at the periphery of each tissue cylinder surrounding the capillary is 22 (see solid circle).

On the other hand, the resting gracilis muscle of the rat (3) has about 100 capillaries/mm². If the resting qO_2 is only 0.3 its tissue pO_2 is 37, as is shown by the open circle marked I. One may now predict the changes in tissue tension during work. If the O_2 uptake increases thirty-three-fold ($qO_2=10$) and the number of capillaries increases four-fold, from 100 to 400/mm², the new O_2 tension is now reduced to 20, as is shown by the new open circle. Cassin *et al.* (3) have also determined the increase

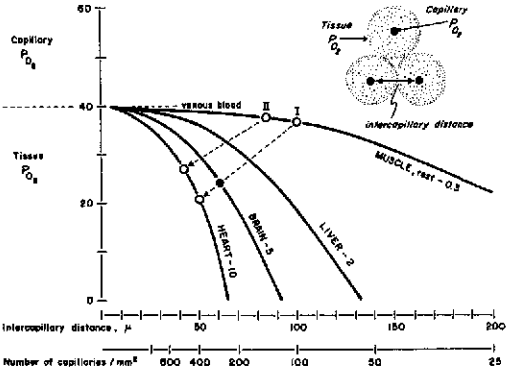


Figure 3. THE TISSUE O_2 TENSION IN VARIOUS TISSUES AS A FUNCTION OF THE NUMBER OF CAPILLARIES AND THE INTERCAPILLARY DISTANCE. THE qO_2 (ML O_2/MIN/100 GMS TISSUE) IS SHOWN AFTER EACH TISSUE. FOR DETAILS SEE TEXT. (Adapted from the presentation of Landis and Pappenheimer [12])

in capillaries of the same muscle after a thirty-six-day period of acclimation to an altitude of twenty thousand feet. In this case the resting muscle had 150 capillaries/mm² and its resting tissue O_2 tension is shown by the open circle marked II. If it now changes its O_2 uptake and capillarization during contraction in the same manner as the unacclimatized muscle, its pO_2 is reduced only to 27.

These examples serve simply to emphasize the importance of capillarization in the O_2 conductance through tissues. Thus we see that the increase in the number of open capillaries plays a most important role not only in daily life at sea level but particularly during acclimation to high altitude by changing the O_2 conductance. Unfortunately, our models are still very crude and possibly misleading. Until we have more exact measurements of actual pO_2 values in the tissue, this approach must suffice.

The description of the O_2 transport from the inspired gas to the venous blood has now been well established for man at sea level and at altitude. Our understanding of the last step from the capillaries to the mitochondria is incomplete, based largely upon models. It is this last link in the description that may turn out to be the most exciting, particularly if we can tie it in to the changes of the tissue enzyme system during acclimation to altitude.

Moderator: I have a few words to say about general concepts of high-altitude physiology. Then Dr. Javier Arias-Stella and Dr. Donald Heath will discuss morphological patterns.

NATURAL ACCLIMATIZATION TO HIGH ALTITUDES: REVIEW OF CONCEPTS

Alberto Hurtado

The term *acclimatization,* in reference to a high-altitude environment, does not have a precise and uniform significance among investigators and in the related medical literature. Very frequently, it has been applied to designate the changes found after a brief exposure, of days or even hours, in low-pressure chambers or in elevated places. In my opinion, according to experience obtained in many years of observation, this common interpretation is not justified.

When subjected to a constant condition of hypoxia, or oxygen deficiency, the human body needs a long time to develop fully adequate adaptive mechanisms, functional and organic. And even when such tolerance is apparently present, there are always, or nearly always, some qualitative differences between a man born and reared in the hypoxic environment and one who has been subjected to it temporarily. It seems logical, therefore, to make a distinction between these two experimental subjects. There is a tendency, I believe a proper one, to use the terms *natural acclimatization* for the characteristics of native high-altitude dwellers and *acquired acclimatization* for the adaptation reached after more or less prolonged exposure. It also seems appropriate to rate the effectiveness of acclimatization in terms of similarity to what is found in the native inhabitant, who is the man best adapted, and not exclusively from the usual standpoint of deviations from sea-level physiology.

Another source of variability in the findings reported, and in their interpretation, refers to the level of the given or simulated altitude investigated and the consequent degree of hypoxia. Quite frequently—especially when low-pressure chambers are used—the level of altitude is far beyond the possibilities of tolerance or adaptation by the human or animal subjects. What is being investigated in that case is not exactly acclimatization or tolerance but rather deterioration. I could mention many examples, but I shall limit myself to one. We know that hypoxia stimulates erythropoietic activity, and one well-known adaptive response is an increase in the circulating red blood cells and hemoglobin. Some evidence, however, suggests that when the hypoxia is very severe its effect becomes depressive.

On the other hand, not infrequently a level of altitude is used at which the decrease in the partial pressure of oxygen and the saturation of the blood with it are extremely moderate or insignificant, and so there is not a real and active need for the development of compensating mechanisms. The degree of hypoxia, like the duration of the exposure, is a very important factor in determining the nature and the degree of responses. These considerations are not always taken properly into account. Because of the peculiar shape of the oxygen dissociation curve, the relationship between level of altitude and degree of hypoxia is not a linear one. Ascending five hundred meters at an altitude of two to three thousand meters does not have the same consequences and significance as a similar displacement at four to five thousand meters.

Despite some fundamental contributions made by early investigators, such as Paul Bert and Jourdanet, and later by Haldane, Barcroft, Mosso, and others, there was a tendency in the past to consider this field a sort of hobby in physiological research. In recent decades the attitude has changed. There are several reasons for this. One is the realization that there are many millions of people living in elevated areas and that they have functional and organic characteristics not entirely similar to what is found at sea level, where most of the world's population lives. It has become important to

look for new physiological patterns in relation to the environment, to have a correct view as to what constitutes normality, and to be able to estimate the changes that take place when pathological processes set in.

Another factor that has added special interest to altitude research is the awareness that hypoxia is not exclusive to low-pressure environments. In many diseases affecting the respiratory and circulatory systems, the circulating blood, and the metabolic and chemical activities of the tissue cells, difficulties may arise in the acquisition of oxygen at lung level or in its transport and adequate distribution or in its utilization in body chemistry. It has therefore become of interest to the clinician and the clinical investigator to know how the body may develop mechanisms that will compensate for a deficiency responsible for signs, symptoms, and disability. High-altitude research activities are not, in fact, remote from everyday clinical implications.

Finally, I may call attention to one of the great scientific events of the present century—the struggle and the determination to conquer space. This endeavor poses great and numerous difficulties, and one has to do with the need for providing a constant oxygen supply to maintain life. Conditions at high altitudes, where men are living or can live, are not quite like those in space; all the same, it has become important to know how man may best compensate for oxygen deficiency and how he can be helped toward longer tolerance of it.

I should like to conclude these brief introductory remarks with some emphasis on the significance of the study of natural acclimatization. As I have said, the man born and raised at a high altitude is the one best adapted to it. This acclimatization process is the result not of a single adaptive mechanism but rather of the interrelation of many processes, apparently different in nature but all with the same objective: to make possible a normal level of vital activities despite the limited availability of oxygen. The simultaneous consideration of all, or nearly all, the processes involved in this common purpose gives an excellent demonstration of integrated physiology; it helps to provide an understanding of how the body is able to coordinate multiple defense mechanisms to counteract a harmful or strange condition. There is now evident in both clinical and basic-research medicine a rather unfortunate tendency toward the fragmentation of knowledge and interpretation, toward thinking only in terms of isolated and unrelated facts. I feel certain that the data to be presented and the discussions to follow will demonstrate the advantages of an attempt to interrelate and evaluate all the different components of the body's response to an aggression—in this case, hypoxia.

MORPHOLOGICAL PATTERNS: MECHANISM OF PULMONARY ARTERIAL HYPERTENSION*

Javier Arias-Stella

Early in the study of the biology of the Andean regions Peruvian investigators proved that high-altitude natives and residents showed an enlarged cardiac silhouette compared with what was seen in sea-level subjects (1, 2, 3, 4). In line with these observations electrocardiographic differences were also demonstrated. Rotta (5) and later Peñaloza *et al.* (6, 7) pointed out that the electrocardiographic changes indicated preponderance of the right ventricle. In 1956 the existence of a moderate degree of pulmonary hypertension in high-altitude natives was described (8). The interesting work of Peñaloza *et al.* (9, 10, 11) has defined this form of pulmonary hypertension. Thus, it has been established that its level is higher in children than in adults (12), that it increases with altitude (13), that it reaches very high values during exercise (14), and so on. It has been demonstrated in other species (15, 16).

Although the hypertension is moderate it is accompanied by definite anatomic changes in the heart, in the pulmonary trunk, and in the lungs (17–22). Studies carried out in our laboratory have shown that from the fourth month of life there is right ventricular hypertrophy in the high-altitude native. This hypertrophy is greater at the base of the ventricle (17, 18)—a finding that goes along well with the characteristics of the electrocardiogram. The pulmonary trunk is thicker and richer in elastic fibers than at sea level (21, 22) and has a greater elastine content, behaving like a resistant vessel to physical deformations (25).

Although Campos and Iglesias (26), in routine histologic studies, found no differences in the small pulmonary vessels of a group of subjects autopsied at La Oroya, the investigations performed in our laboratory leave no doubt that definite differences do exist in the small pulmonary arterial branches.

Using a quantitative histologic procedure, we have shown that after the first month of life there is a greater muscularization in the small pulmonary arterial branches in people born and living at high altitudes (23, 24). Our findings correlate with the report by Peñaloza *et al.* (10) of increased pulmonary vascular resistance in high-altitude natives. We therefore can now locate the anatomical point of origin of the pulmonary hypertension at the level of the peripheral pulmonary arterial branches. In the genesis of the hypertension augmented blood flow and capillary engorgement have, on sound physiologic bases, been ruled out as possible factors (8, 10, 24). However, the contributing role played by increased blood viscosity is debatable (27).

The first problem that should be elucidated is whether the anatomical differences are present in high-altitude subjects from birth or before, or whether the changes take place later.

Our anatomical investigations have demonstrated that up to the seventh postnatal day there are no differences between high-altitude and sea-level subjects in the weight of the right ventricle (17). This finding agrees with the observations of Peñaloza *et al.* (12), who have shown that at birth there are no differences in EKG between infants from high altitudes and those from sea level. Very recently we have found that there are also no differences in the characteristics of the peripheral arterial branches in stillborns from sea level (28). These results suggest that at birth the pulmonary hemodynamics are essentially identical at sea level and at high altitudes. It can be predicted, therefore, that if hemodynamic studies are carried out in high-altitude

* This differs from the author's presentation at the Special Session under the heading "Natural Acclimatization to High Altitudes: Morphological Patterns."

and sea-level humans at the end of intrauterine life, no differences will be found in the levels of pulmonary arterial pressures.

From what has been said it can be concluded that the changes we described in the pulmonary vasculature of high-altitude people dating from the first month of life (24) are an acquired postnatal phenomenon. Now we need an explanation to the question, Why are the peripheral pulmonary arterial branches structurally different at high altitudes? And what is the mechanism that gives rise to this difference?

Since we are dealing with an acquired postnatal difference it is reasonable to think of the role played by environmental factors as causal agents. Beyond any doubt, the level of oxygen tension in the atmosphere is the fundamental physical factor of biological importance in high-altitude environments.

Abundant information has been accumulated indicating that diminished oxygen tension can affect the physiology and the structure of the pulmonary vascular system (16, 29, 30, 31, 32). The experiments of Von Euler and Liljenstrand (29) were the first to show that an increment in pulmonary arterial pressure due to vasoconstriction followed a fall in the tension level of breathed oxygen. A similar observation has been made in sea-level animals placed at high altitudes (16). The vasoconstrictive effect is demonstrated by the fact that, in these experiments, when oxygen is administered the elevated pulmonary arterial pression is immediately reduced to the original normal levels. When the hypoxic situation is maintained for subacute or subchronic periods, as in the experiments of Grover and Reeves, the pulmonary hypertension is found to be associated with vasoconstrictive effects and with anatomic changes in the form of increased arterial muscularization (16). In this case the oxygen administration reduces the elevated blood pressure, but to a level above the original normal sea-level value. This demonstrates that the oxygen acts on the vasoconstrictive physiologic phenomena but has no effect on the anatomic changes.

Our findings in high-altitude natives after birth (24) accord with the experiments of Grover and Reeves (16). We have found suggestive evidence of vasoconstriction in the peripheral pulmonary arterial branches in high-altitude infants. On the other hand, Peñaloza *et al.* (12) reported an increased pulmonary vascular resistance at high altitudes, which is greater in children under five years than in those from six to fourteen.

Taking into account (a) the proved effect of the level of oxygen tension on the vascular "tone" of the small pulmonary arterial branches, (b) the fact that at birth there are no differences in the weight of the right ventricle and in the characteristics of the pulmonary arterial branches at sea level and high altitudes, (c) the observations showing that the anatomic differences described at high altitudes begin after the first week of life, (d) the demonstration that the physiologic and anatomic changes bear a close correlation with altitude levels, and (e) Cannon's basic principle of homeostasis, one can attempt an explanation of the probable mechanism through which the high-altitude pulmonary hypertension occurs.

During intrauterine life the fetus develops in a markedly hypoxic environment, one that is not comparable to any in which normal human life exists. Mithoefer (33) has emphasized the fact that during intrauterine life the arterial oxygen tension in the fetus is 20, which would correspond to an atmospheric oxygen tension of approximately 61—that is, to an altitude of about eight thousand meters above sea level. Therefore, at birth, wherever it occurs, the fetus passes from a hypoxic to a better-oxygenated environment. Even at fourteen or fifteen thousand feet above sea level the newborn is a "lowland" newcomer. The chain of events that takes place in the newborn after birth are related to the equilibrium established with the environment. Those environmental factors that are able to exert biological actions are the ones that have to be taken into account.

As for the pulmonary vascular system, I have already mentioned that clearly the most signifi-

cant environmental factor is the level of oxygen tension.

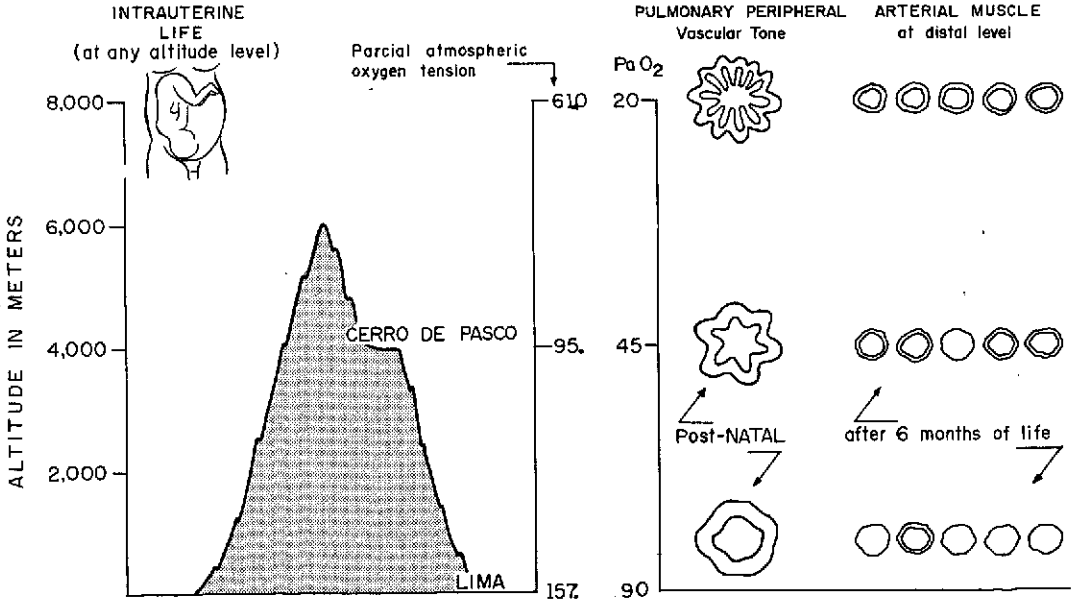
At birth the newborn enters for the first time into contact with what is going to be its permanent environment, and a homeostatic equilibrium with it takes place. The elevated pulmonary arterial pressure due to the increased pulmonary vascular resistance characteristic of fetal life is suddenly reduced at birth, mainly as a result of the alveolar expansion (34). Once this mechanical readjustment has occurred, the pulmonary vasculature enters into equilibrium with the atmospheric factor that influences it—that is, the atmospheric oxygen tension level. The figure below gives an idea of the sequence of physiologic and anatomic events during this stage of equilibrium.

Since the fetus passes from a less to a more oxygenated medium and the effect on the pulmonary peripheral arterial system is a relaxing one, a relaxation occurs in the small muscular pulmonary arteries. This effect has been well documented in lambs (32).

If *vascular tone* is defined as the state of tensile equilibrium of a vessel with its environment, and a greater postnatal pulmonary arterial relaxation corresponds to higher oxygen tension, we have here a diminished "vascular tone." To lower oxygen tension levels corresponds a lesser degree of arterial relaxation or, in other words, a greater vascular tone. The figure depicts the changes thought to occur in the pulmonary vascular tone according to the different altitude levels at which birth takes place. The vascular tone and its consequence, the degree of pulmonary arterial resistance, in the immediate postnatal stage are thus determined by the particular level of the atmospheric oxygen tension.

The anatomic changes in the pulmonary vasculature during the postnatal period, which include among other things an involution in the muscularization of the peripheral pulmonary arterial branches and in the mass of the right ventricle, evolve up to a point corresponding to the level of pulmonary arterial pressure that has been determined by the pulmonary vascular resistance.

The figure illustrates the anatomic changes in the pulmonary vasculature at various altitude levels. As the anatomic modifications evolve



FETAL PULMONARY VASCULAR STRUCTURE AND POST NATAL CHANGES ACCORDING TO ALTITUDE. SCHEME TO EXPLAIN THE MECHANISM OF ORIGIN OF HIGH-ALTITUDE PULMONARY HYPERTENSION.

slowly, compared to the physiologic changes, the fetal vestiges persist for a while after birth. This explains why the pulmonary arterial pressure is greater during early infancy than thereafter.

In the figure it can be seen that to each level of oxygen tension corresponds a different degree of physiologic and anatomic postnatal readjustment. This explains the demonstrated fact that the hemodynamic and anatomic changes differ according to the altitude level (13, 21). It is clear to us that differences exist among people born at different altitude levels, but when the altitude difference is slight the changes are minimal and pass unnoticed. Only when we compare sea-level with high-altitude places, as I have done here, do they become obvious and easily detectable.

The explanation advanced by Grover and Reeves (16) that a moderate increment in pulmonary arterial pressure favors a better perfusion in those pulmonary areas subjected to the effect of hydrostatic pressures is helpful toward an understanding of the objective of this type of equilibrium.

In the same way that the body surface changes with external temperature to augment or diminish heat irradiation and thus maintain an optimal internal temperature, so the level of atmospheric oxygen tension determines the anatomic and physiologic changes described, which together with some others tend to assure better utilization of the atmospheric oxygen.

The cardiovascular phenomena of high altitudes are therefore not a special characteristic of life in rarefied atmospheres but another example of a homeostatic adjustment.

As with any homeostatic mechanism, the capacity for physiologic equilibrium has some limits. We are gathering evidence, based on the magnitude of the anatomic changes and the frequency of deaths due to right ventricular failure, that for the variables *atmospheric oxygen tension/pulmonary arterial pressure,* this limit is reached at around forty-seven hundred meters above sea level.

MORPHOLOGICAL PATTERNS: THE STRUCTURE, COMPOSITION, AND EXTENSIBILITY OF THE PULMONARY TRUNK AT SEA LEVEL AND HIGH ALTITUDE IN PERU

Donald A. Heath

Last year members of the High Altitude Research Unit of the Cayetano Heredia Medical School, Peru, and of the Faculty of Medicine of Birmingham University, England, undertook a joint study of the pulmonary trunk of people indigenous to high altitudes (1). We investigated its extensibility in people living at sea level in Lima and at a high altitude in the Andes. At the same time we carried out histological studies of the elastic tissue pattern of its media and chemical determinations of the proportions of elastin and collagen within it. We were stimulated to undertake this study by the fascinating observation that the configuration of the elastic tissue in the media of the adult pulmonary trunk of those indigenous to high altitudes may resemble that of the aorta (2). This is in striking contrast to the state of affairs in persons living at sea level.

In fetal life the magnitude of the pulmonary arterial pressure is comparable to the aortic and the configuration of the elastic tissue in the media of the pulmonary trunk is very similar to that of the aorta. In both arteries there is a dense network of long, parallel elastic fibrils. By the end of the first month of extrauterine life in those living at sea level or low altitude the blood pressure in the pulmonary arteries falls to the low level maintained for the rest of adult life. A group of us working at the Mayo Clinic have shown that normally, during the first two years of extrauterine life, the elastic tissue in the wall of the pulmonary trunk undergoes involution, becoming fragmented and subsequently forming an open network of branched fibrils (3).

The tissues of the media of the normal pulmonary trunk of an adult at sea level are more extensible than those of the aorta (4, 5)—probably because they include a lower proportion of elastin, although differences in the proportion of collagen may also play a part. With increasing age there is a progressive decrease in extensibility, and we have previously ascribed this to the apparent increases in the proportion of collagen visible in histological sections (5).

When pulmonary hypertension has persisted from birth, as a result of a large congenital "post-tricuspid shunt" (4), the pattern of the elastic tissue of the media of the pulmonary trunk retains its fetal appearance and is thus similar to that of the aortic media (3). In such patients the media of the pulmonary trunk is less extensible than normal (6). In contrast, when pulmonary hypertension arises later in life as a result of a "pretricuspid shunt" (4) or mitral stenosis, the elastic tissue of the pulmonary trunk remains of the normal adult type (3) and the extensibility of the wall is normal (6). It has been shown that the Peruvian Indian native to high altitude sustains physiological pulmonary hypertension (7) and in such people the appearance of this tissue may resemble that of the aorta (2).

During the course of our studies in Peru we investigated the extensibility of the pulmonary trunk in people living at sea level and at a high altitude and compared this physical property of the media with its histological pattern of elastic tissue and with its chemically determined proportions of elastin and collagen. We examined rings of pulmonary trunk from seventy-three subjects. Sixty-six had died in Lima, which is at sea level, but some of these had spent most of their lives at a high altitude and had died during transit through Lima or else had lived in Lima for only a short time before their death.

Seven had lived and died in the vicinity of Cerro de Pasco, which is at 14,200 feet.

Three portions of pulmonary trunk were examined in each case. After the adventitia had been stripped off the media, the extensibility of a circumferential strip was measured in the manner we have described previously (5). The volume of the arterial strip was assessed by weighing it and assuming its specific gravity to be unity. The cross-sectional area was calculated by dividing the volume by the length. A series of extensile loads up to 100 gm were used, and the results were expressed as the percentage extension for a given extensile force (dynes/mm^2 cross-sectional area).

A second adjacent portion of pulmonary trunk was subsequently examined histologically to determine the type of elastic tissue pattern in the media. The sections were stained by the Lawson modification of the Weigert-Sheridan method.

The remainder of the pulmonary trunk, free of adventitia, was cut into small pieces and put in a vacuum desiccator. After the material was dry it was ground with a mortar and pestle and placed in the desiccator once again for subsequent chemical analysis. Collagen and elastin were estimated in this dried material by the method of Lawry, Gilligan, and Katersky (8), with the modifications that the first extraction with sodium hydroxide was prolonged to forty-eight hours and that autoclaving was carried out at 15 lb/sq. in. for fifty-four hours. Measurements of collagen were made on thirty-one specimens and of elastin on forty-five specimens.

The results of our studies were as follows.

Histology

The elastic tissue pattern of the media of the pulmonary trunk was classified as one of the three types that we have designated previously: "adult pulmonary," "aortic," and "transitional" (3). Sixty-three of the sixty-six cases from Lima and four of the seven who had lived all their lives at Cerro de Pasco showed an adult pulmonary configuration consisting of an open network of branched, irregularly shaped elastic fibrils (Figure 1). There was much variation in the amount of elastic tissue present, a feature that we have noted previously in low-altitude cases (9). The appearances were similar to those found in a series of cases in Birmingham, England (5). It was frequently possible to determine, from examination of the elastic tissue of the media, that a subject was over forty years of age—the fibrils showed a fuzziness of outline, a background elastosis of very fine connecting fibrils, and they tended to take up stains for elastin less well than those of the younger age group.

Figure 1. TRANSVERSE SECTION OF PULMONARY TRUNK FROM PERUVIAN INDIAN AGED 14, SHOWING ADULT PULMONARY PATTERN OF ELASTIC TISSUE. Such a configuration of elastica is characteristic of persons living at low altitude (Elastic/Van Gieson; × 150)

Five subjects showed an aortic pattern of elastic tissue in the pulmonary trunk media. They included two of the seven subjects from Cerro de Pasco and the remaining three of the subjects from Lima, who had, however, spent most of their lives at a high altitude. The elastic fibrils were long, uniform, and parallel and formed a dense network (Figure 2) in contrast to the open network of branched fibrils already described as characteristic of the normal adult pulmonary trunk at sea level. One of the subjects from Cerro de Pasco showed a "transitional" configuration of elastica (2). The

Figure 2. TRANSVERSE SECTION OF THE PULMONARY TRUNK FROM A PERUVIAN INDIAN AGED 18 YEARS, SHOWING AN AORTIC PATTERN OF ELASTIC TISSUE. Such a configuration of elastica is characteristic of persons living at high altitude (Elastic/Van Gieson; × 150)

pattern more closely resembled the adult pulmonary than the aortic type and for the purposes of statistical analysis has been included in the adult pulmonary group.

The mean thickness of the fresh media of the pulmonary trunk in this series was 1121μ (S.D. $=58\mu$). The range of thickness of the medias showing an aortic pattern of elastic tissue was 960 to 1220μ.

Extensibility

The relation between length and tension was a curved one similar to that found in previous studies (5, 6). In the subjects with an adult pulmonary configuration, extensibility decreased as age increased (Figure 3). The average values of extension for a series of common extensile forces shown in Figure 3 were obtained by drawing separate length-force curves for each case and estimating the degree of extension for a given extensile force by interpolation.

The relation between the age and the logarithm of the degree of extension approximated to a straight line, the slope and intercept of which varied with the extensile force. Thus, for a particular extensile force, the relation between age and extension could be given by

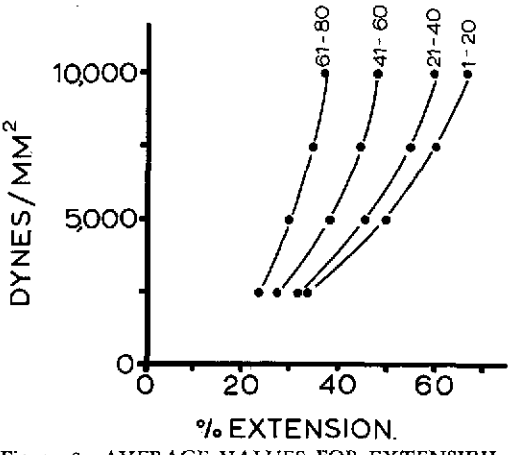


Figure 3. AVERAGE VALUES FOR EXTENSIBILITY OF PULMONARY TRUNK IN DIFFERENT AGE GROUPS

$$\Delta l = a\ 10^{b \times age}$$

where Δl is the percentage increase in length and a and b are constants. The values of a and b varied according to the extensile force and a number of them were calculated from regression equations relating $\log_{10} \Delta l$ to age. There was no simple formula relating these constants and the magnitude of the extensile force as in our previous study (5), so the relations between the two constants and the extensile force are shown graphically (Figures 4 and 5).

It thus proved possible to assess the expected degree of extension for any given extensile

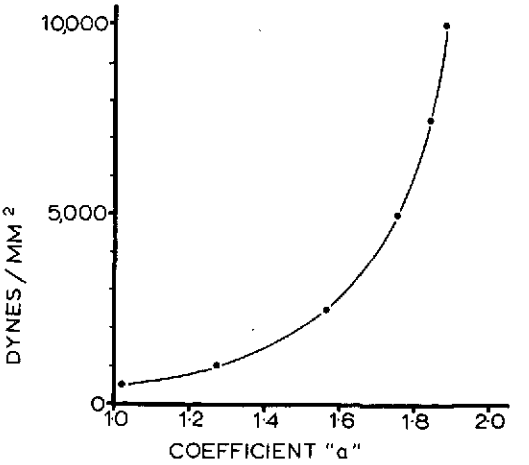


Figure 4. RELATION BETWEEN EXTENSILE FORCE AND COEFFICIENT 'A'

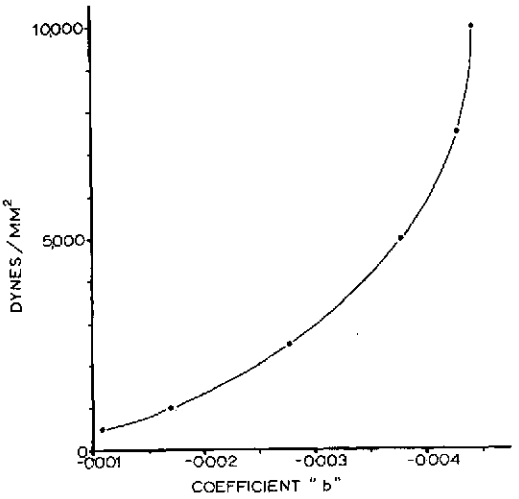


Figure 5. RELATION BETWEEN EXTENSILE FORCE AND COEFFICIENT 'B'

force by substituting the obtained values of *a* and *b* together with the age of the subject in the formula. In Figure 6 we see the degree of extension predicted in this manner, plotted against the observed degree of extension in forty-two specimens with a normal adult pulmonary configuration of elastica in the media of the pulmonary trunk.

It proved possible, in addition, to plot the observed degree of extension against that predicted from our equation in the five specimens with an aortic pattern of elastic tissue in the media (Figure 7). Also included in this graph is the line of the normal regression equation with lines at a distance of twice the standard error. It will be noted that the extensibility of these five specimens is less than normal.

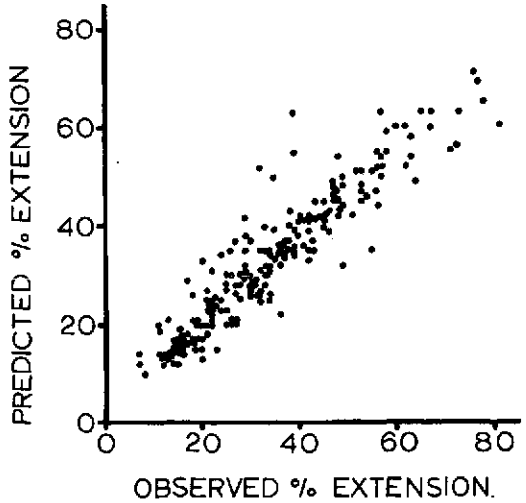


Figure 6. RELATION BETWEEN PREDICTED AND OBSERVED VALUES FOR PERCENTAGE EXTENSION

Chemical Analyses

Collagen was estimated in twenty-eight specimens with an adult pulmonary pattern of elastic tissue, and the average content was 31.0 per cent (S.D. = 4.0 per cent); the slight tendency for the content to decrease with age was readily attributable statistically to chance (Figure 8). Collagen was also estimated in three specimens with an aortic pattern of elastica, and the contents were 28.3, 31.7 and 37.9 per cent, which did not differ appreciably from the group with the normal adult pulmonary pattern (Figure 8).

Elastin was estimated in forty-one specimens with an adult pulmonary pattern of elastic tissue, and the average content was 27.2 per cent (S.D. = 4.8 per cent). There was a tendency for the content to increase with age (Figure 9) that was statistically unlikely to have arisen by chance. In four specimens with an aortic pat-

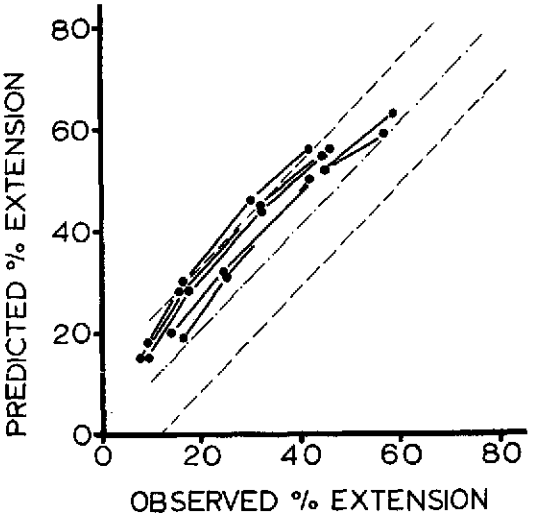


Figure 7. RELATION BETWEEN OBSERVED DEGREE OF EXTENSION AND THAT PREDICTED FROM EQUATION 1 IN FIVE SUBJECTS WITH AORTIC PATTERN OF ELASTIC TISSUE. "Normal" regression line of equation 2 is shown, together with lines at a distance of twice the standard error of the estimate

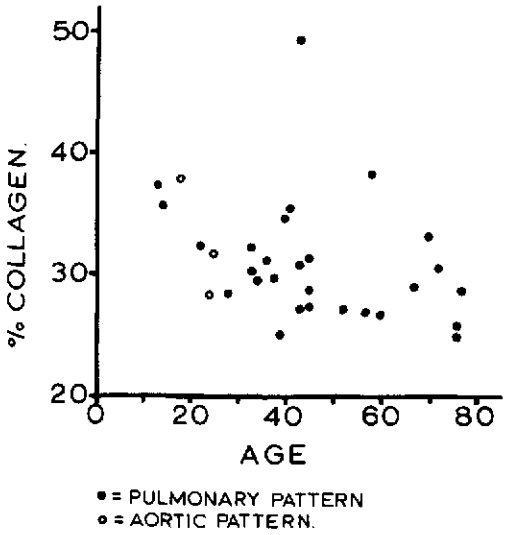


Figure 8. RELATION BETWEEN AGE AND CONTENT OF COLLAGEN (% DRY WEIGHT)

tern of elastica, the elastin contents were 31.0, 31.4, 37.9 and 40.0 percent. The average age of these four subjects was only 22.5 years compared to an average age of 45.4 years for the low-altitude group. These figures hence confirm that there is a higher proportion of elastin in the pulmonary trunk with an aortic configuration of elastica.

Collagen and elastin were both estimated in twenty-seven specimens with an adult pulmonary pattern of elastic tissue (Figure 10). There was a positive relation between the ratio of elastin to collagen and the age of the subject. Collagen and elastin were both estimated in three specimens with an aortic pattern of elastic tissue; in these three subjects the ratio was inappropriately high for the age (Figure 10), and the difference was statistically unlikely to have arisen by chance more often than once in a thousand times.

Discussion of Results

These results show that in Peruvians living at sea level in and around Lima the pulmonary trunk has a normal adult pulmonary pattern and its extensibility is similar to that which we have previously demonstrated in a group of subjects in Birmingham, England (5). Our previous observation that this extensibility decreases with age (5) has also been confirmed in Peruvians.

The curved shape of the force-extension diagram of the walls of arteries has been ascribed to the shorter relaxed length of the elastic fibrils relative to that of collagen (10). The more horizontal initial part of the curve was

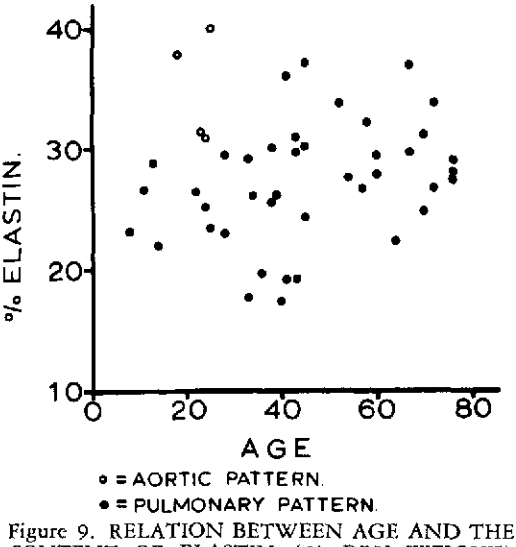


Figure 9. RELATION BETWEEN AGE AND THE CONTENT OF ELASTIN (% DRY WEIGHT)

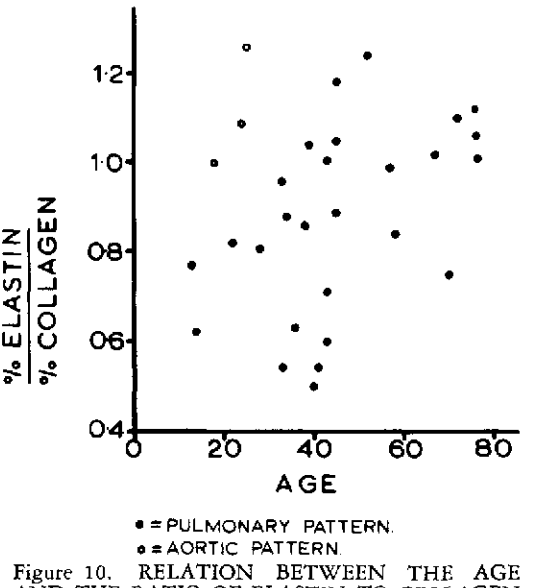


Figure 10. RELATION BETWEEN THE AGE AND THE RATIO OF ELASTIN TO COLLAGEN

considered to be due mainly to the extension of the elastic tissue, while the development of the more vertical later part of the curve coincided with the gradual involvement of collagen fibres.

If this view is accepted, the slope of the curve should be related to the proportion of elastin present. Plotting the degree of extension against age at a small extensile force of 2,500 dynes/mm² reveals that in specimens with an adult pulmonary pattern the degree of extension falls with age (Figure 11). This finding is consistent with the increasing proportion of elastin found chemically in our investigation. When the degree of extension produced by this small force is plotted against the proportion of elastin there is a negative relation (Figure 12) in cases with adult pulmonary and aortic patterns of elastica.

The slope of the initial part of the force-extension curves becomes steeper with increasing age (Figure 3), but the increasing steepness of the later part of the curves proceeds at an even greater rate. An elementary expression of the curvilinearity of the curve is given by calculating the ratio of the degree of extension at 10,000 dynes/mm² to that at 5,000 dynes/mm². This ratio would decrease from a value of 2.0 in the presence of a rectilinear relation to a theoretical minimum of 1.0 as the curvilinearity increased. When the ratio is plotted against

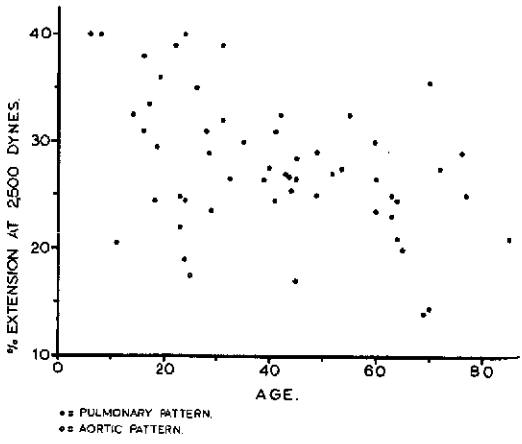


Figure 11. RELATION BETWEEN AGE AND THE DEGREE OF EXTENSION AT 2,500 DYNES/MM²

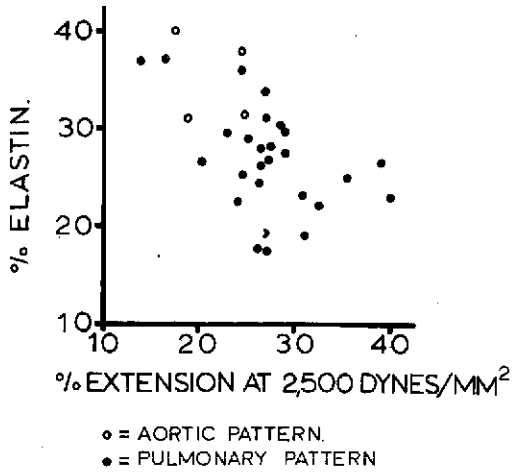


Figure 12. RELATION BETWEEN DEGREE OF EXTENSION AT 2,500 DYNES/MM² AND CONTENT OF ELASTIN (% DRY WEIGHT)

age there is a negative correlation when there is an adult pulmonary pattern of elastic tissue.

The progressive decrease in exensibility with age in the later steep portion of the force-extension curve has been ascribed to an increased proportion of collagen in both systemic (11) and pulmonary arteries (5). Our reason for supposing this to be the case was the apparent increase in collagen with age in sections stained with Van Gieson's stain. The present investigation, however, has shown that chemical estimations do not support the idea of an increase with age in the amount of collagen in the pulmonary trunk. A similar discrepancy is found in Fallot's tetrad, where there is an increase in collagen seen in histological sections of the pulmonary trunk (3) but not confirmed chemically (12). It may be that collagen becomes less extensible with age; there have certainly been reports that the bulk modulus of collagen increases with age (13, 14). Alternatively, it may be that the collagen fibers become straighter with increasing age so that they become stretched earlier. However, we must bear in mind that the geometry of the pattern of the elastic and collagen fibers in the pulmonary trunk will also influence its extensibility, and any minor modifications of this pattern with increasing age might also play a part in diminishing extensibility.

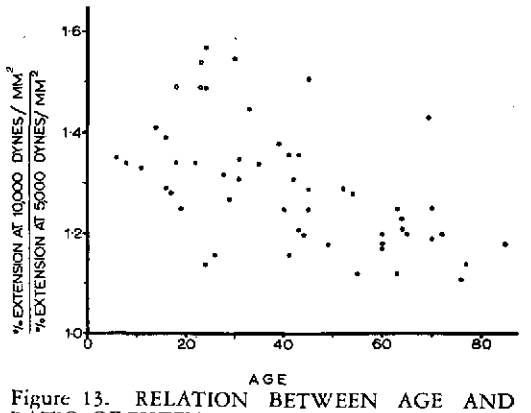


Figure 13. RELATION BETWEEN AGE AND RATIO OF EXTENSIBILITIES AT 10,000 DYNES/ MM² AND 5,000 DYNES/MM²

In the Peruvian Indians with an aortic pattern of elastic tissue in the pulmonary trunk, chemical studies showed an abnormally high amount of elastin for the person's age. This fitted in well with the histological appearances. The same is true in cases of congenital heart disease (12). These subjects indigenous to high altitudes showed an abnormally low extensibility of their pulmonary trunk at a low extensile force of 2,500 dynes/mm², and this is consistent with the presence of excess elastin (Figure 2). These Indians also showed a normal proportion of collagen in the pulmonary trunk, so that the ratio of elastin to collagen was abnormally high (Figure 10). This is an explanation for the abnormally high ratios of the ratio of extension at 10,000 dynes/mm² to that at 5,000 dynes/mm² (Figure 13).

When the degree of extension is shown as a percentage of that predicted it is seen that four out of the five pulmonary trunks with an aortic pattern in these subjects indigenous to high altitudes show a maximal decrease in extensibility at low degrees of extension (Figure 14). In Figure 15 the average for these five specimens is compared with the average of two specimens with an aortic pattern of elastic tissue in the pulmonary trunk due to congenital heart disease (6). Both groups show a maximal diminution in extensibility at low degrees of extension. These observations may further be contrasted with a group of subjects with Fallot's tetrad (6) (Figure 15). In such persons there is an abnormally small proportion of elastic tissue and an abnormally high proportion of collagen visible histologically. In Figure 15 we note that in these specimens the extensibility becomes lower with increasing extension. This

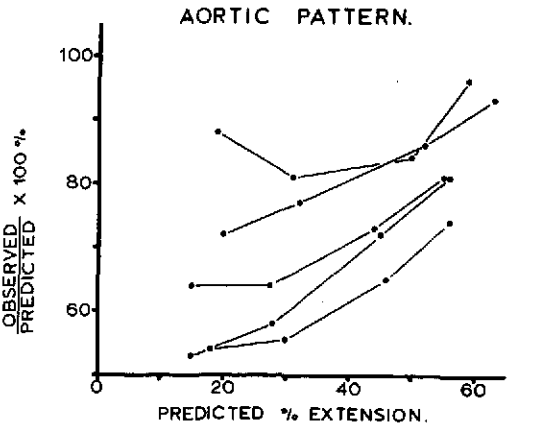


Figure 14. RELATION BETWEEN DEGREE OF EXTENSION AND DEGREE OF EXTENSION EXPRESSED AS PERCENTAGE OF THAT PREDICTED IN SUBJECTS WITH AORTIC PATTERN OF ELASTIC TISSUE

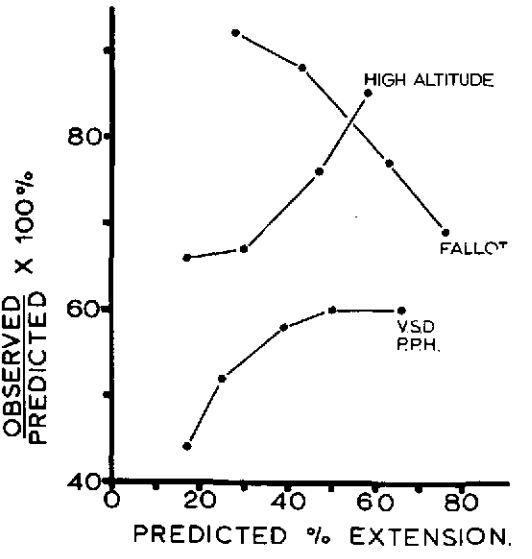


FIGURE 15. RELATION BETWEEN DEGREE OF EXTENSION AND DEGREE OF EXTENSION EXPRESSED AS A PERCENTAGE OF THAT PREDICTED. Average values of three groups are shown: (a) aortic elastic pattern due to high altitude; (b) Aortic elastic pattern due to ventricular septal defect and primary pulmonary hypertension; (c) Fallot's tetrad

is the opposite situation to that of the two groups with an increased proportion of elastin.

It is clear from these data that we now have a considerable understanding of the structure, chemical composition, and biophysical behavior of the pulmonary trunk of those indigenous to high altitudes. We still lack, however, even a simple description of the microscopical anatomy of the terminal air passages and the state of the pulmonary capillary bed in the high-altitude lung. Such observations are of fundamental importance to any understanding of the problem and, furthermore, can now be made with considerable accuracy by use of the techniques of lung morphometry introduced by Weibel (15). The application of morphometric techniques will enable us to determine the magnitude of the internal surface area of the lung and the numbers of alveolar spaces within it both in healthy subjects indigenous to high altitudes and in the unfortunate minority who have developed chronic mountain sickness (Monge's disease).

Internal surface area and numbers of alveolar spaces in the lungs in 7 cases of emphysema and 3 cases in which there was no evidence of heart or lung disease

CONDITION	NUMBER STUDIED	INTERNAL SURFACE AREA (M^2) PER 6,000 ML LUNG VOLUME	NUMBERS OF ALVEOLI IN UNITS OF 10^5 PER ML OF LUNG
Normal	3	58.5 to 83.4	106 to 127
Bronchiolar Emphysema	3	25.0 to 55.1	20 to 80
Alveolar Emphysema	4	17.2 to 40.3	19 to 34

It is important for us to be frank and admit that at the moment we have no inkling about the basic morbid anatomy of Monge's disease. During my visit to the Andes I was intrigued by the similarity of the clinical picture of Monge's disease to that of cor pulmonale complicating bronchiolar emphysema that we see not uncommonly in the industrial areas of Great Britain. Hypoxia, hypercarbia, polycythemia, and certain pulmonary vascular changes are common to both. I think we should make every effort to ascertain whether the reduction of internal surface area of pulmonary capillary bed found in bronchiolar emphysema (16) is also seen in Monge's disease. Our studies in lung morphometry in Birmingham, England, have revealed a considerable reduction in this area in cases of bronchiolar and alveolar emphysema (see table) (16). Is it possible that cases of so-called chronic mountain sickness are in fact simply people with emphysema, especially of the bronchiolar type, who happen to be living on mountaintops rather than persons who are showing a pathological, exaggerated response to the hypoxia of high altitude?

I am glad to be able to report that we are making plans to resolve this problem. Dr. Kruger of the High Altitude Research Unit at Lima has just spent two months with us at Birmingham to learn these methods of lung morphometry and has now returned to the Andes to collect these much-needed data on the internal surface area of the lung. We hope that we shall soon be getting some idea as to the nature of the basic morbid anatomy of Monge's disease.

Moderator: We shall now hear from Dr. Mithoefer.

PHYSIOLOGICAL PATTERNS: THE RESPIRATION OF ANDEAN NATIVES

John C. Mithoefer

Conventionally, the study of adaptation to life at high altitudes is approached entirely from the standpoint of the lowlander—the invader of high-altitude cultures. Comparisons are made between natives of high altitudes and ourselves and we marvel at their adaptation to what to us is a hypoxic environment, as though they had changed from what we are or as though they were meant to be like us but have somehow had the misfortune to be stuck at the top of a mountain. Adaptation can be looked at in another way if it is realized that we share an intrauterine heritage of hypoxia with those at high altitudes and that, in fact, our adaptation to relatively high environmental oxygen tensions may represent a greater postnatal readjustment than they are required to make. If the difference in the rate of scientific development that now exists between low-altitude cultures and those of the *altiplano* had been reversed, the people in the mountains might now be studying our adaptation to hyperoxia with the same wonder and condescension that we tend to show them.

Figure 1 summarizes this concept. It indicates an intrauterine umbilical artery oxygen tension of about 20 mm—equivalent to an altitude of about seventy-five hundred meters (1). The

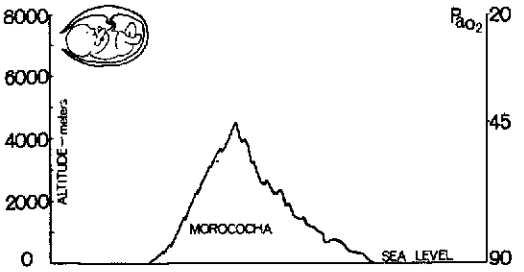


Figure 1. ARTERIAL pO_2 AND EQUIVALENT ALTITUDE OF FETUS IN UTERO (AT SEA LEVEL), RESIDENTS OF MOROCOCHA AND SEA LEVEL

umbilical artery oxygen tension of the human fetus in the Andes is not known but is probably lower. It would appear that neonatal adaptation requires less physiological modification at high altitudes than at sea level.

The respiratory adaptation of the extraordinary population of Andean natives who live and work at an altitude of three miles has been principally studied by two groups of investigators—in Morococha, Peru, by Hurtado and his colleagues, among whom have been many fortunate visitors from the United States, and in Mina Aguila, Argentina, by Chiodi. As is appropriate to this symposium, my description of the respiration of native residents at high altitudes will be based primarily on the work of these two groups.

The inspired oxygen pressure at sea level is 150 mm, in Morococha and Mina Aguila about 84. It is presumably this difference in environment oxygen that results in the differences that have been observed between the respiration of Andean natives and of people at sea level. The discussion to follow is concerned with how the respiratory system at high altitudes copes with the low ambient oxygen tension and in doing so serves its function as an adequate ventilator of the blood. The discussion is organized under the following headings: lung volume; volume and frequency of ventilation; alveolar gas tensions; regulation of ventilation; alveolar-arterial oxygen gradients; and arterial gas tensions and pH.

Lung Volume

Figure 2 compares the lung volumes of natives of Morococha (4,540 m) with those at sea level (2). There is an increase in the volume of all compartments of the lung, but the striking differences are in the volume of gas remaining

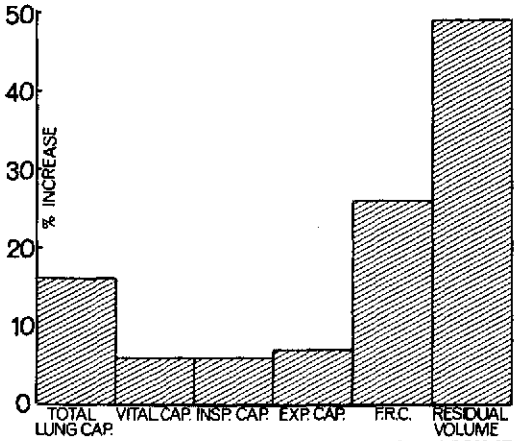


Figure 2. COMPARTMENTS OF LUNG VOLUME OF RESIDENTS OF MOROCOCHA AS COMPARED BY % INCREASE TO RESIDENTS OF LIMA (2)

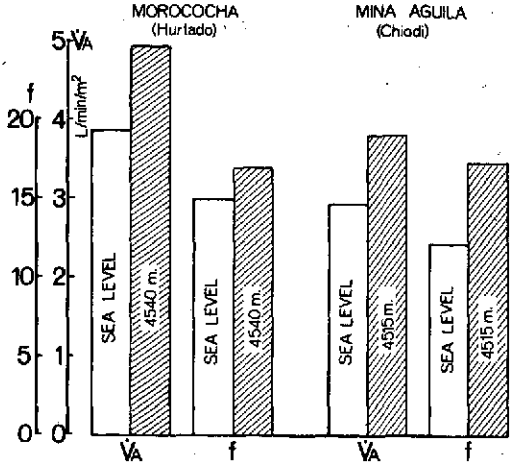


Figure 3. COMPARISON OF ALVEOLAR VENTILATION AND RESPIRATORY FREQUENCY BETWEEN HIGH-ALTITUDE AND SEA-LEVEL RESIDENTS IN TWO STUDIES (2, 5)

in the lung at the end of a normal expiration (FRC) and that remaining after a forced exhalation (residual volume). At high altitudes the lungs are held in a position of increased inflation. This same change, but of smaller magnitude, can be observed in newcomers to a high altitude during their period of adaptation (3). There has been considerable speculation as to the reason for this difference. It has been assumed that the increased inflation of the lungs enlarges their surface area and thereby facilitates the diffusion of oxygen (4). This would indeed be a favorable adaptation, but it is not certain that overinflation does increase the surface area of the lungs or that such expansion has a favorable effect on pulmonary blood flow or on the distribution of ventilation and perfusion. Our present state of knowledge does not permit a final interpretation of these differences in lung volume.

Volume and Frequency of Ventilation

The only difference in ventilation between high-altitude residents and those at sea level is an increased frequency of ventilation in the former. As Figure 3 shows, the respiratory frequency was found to be 17 breaths per minute in both studies on Andean natives (2, 5). Alveolar ventilation increased about equally in both studies (24 and 29 per cent); there was no change in tidal volume. This hyperventilation, by its effect on alveolar gas tensions, is the most important response of the respiratory system at high altitudes in coping with the low ambient oxygen tension.

Alveolar Gas Tensions

Alveolar gas tensions measured by Hurtado (2) are shown in Figure 4. The difference in the ambient oxygen tensions is in part compensated for by hyperventilation resulting in a 30-per-cent decrease in the pressure gradient between the oxygen tensions of ambient air and

	SEA LEVEL		MOROCOCHA (4540 m.)	
$P_{I_{O_2}}$ mm Hg	150	50 mm	84	34 mm
$P_{A_{O_2}}$ mm Hg	100		50	
$P_{A_{CO_2}}$ mm Hg	40		30	

Figure 4. COMPARISON OF AMBIENT OXYGEN PRESSURE, ALVEOLAR OXYGEN PRESSURE, AND ALVEOLAR CARBON DIOXIDE PRESSURE BETWEEN RESIDENTS OF MOROCOCHA AND OF SEA LEVEL (2)

alveolar gas, which produces an alveolar pO_2 of 50 mm and an alveolar pCO_2 of 30 mm in the natives of Morococha. If ventilation in these subjects remained equal to that at sea level, alveolar oxygen tension would fall to 34 mm, a critically low level considering the slope of the oxygen dissociation curve (see Figure 7 on page 24).

Regulation of Ventilation

The mechanism by which alveolar ventilation is maintained at a high level in native residents at high altitudes is not clear. When an unacclimatized subject ascends to a high altitude, there is an immediate increase in ventilation—the result of hypoxia, since ventilation returns to sea-level values if oxygen is breathed. The hypoxic hyperventilation in unacclimatized man results in alkalemia, which is gradually corrected during the first week of high-altitude residence by the renal excretion of excess bicarbonate. After the first week of acclimatization the subject is left with a pCO_2 that is lower than normal, a reduced bicarbonate concentration, and a normal pH.* This change is associated with an increased ventilatory response to CO_2, presumably as a result of greater increase in hydrogen-ion activity per incremental rise in pCO_2 (6) (Figure 5; see the section on arterial gas tension and pH). As this compensation is taking place, hypoxia becomes progressively less responsible for the sustained hyperventilation until in fully acclimatized man oxygen breathing at high altitude does not decrease ventilation but, in fact, in some subjects stimulates it (2, 5). After the initial ventilatory response to hypoxia, the acclimatization process appears to return the regulation of ventilation to the same pCO_2 — pH mechanism as at sea level but with the mechanism set at a lower level of pCO_2 and bicarbonate.

* This is often incorrectly referred to as a decreased buffer capacity for CO_2. Actually, in respiratory acidosis or alkalosis, bicarbonate does not buffer CO_2; rather, its concentration determines hydrogen-ion activity through its mass-action effect on the dissociation of carbonic acid.

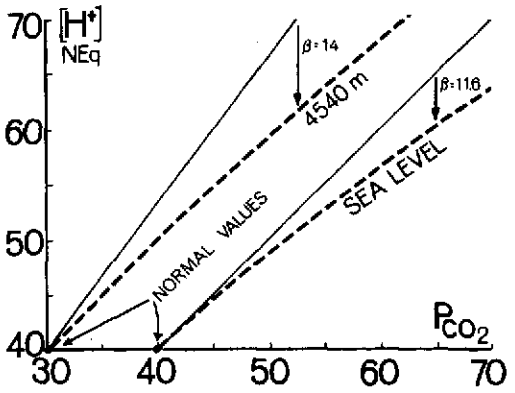


Figure 5. CALCULATED IN VIVO TITRATION CURVES (BROKEN LINES) FOR RESIDENTS OF HIGH ALTITUDE AND SEA LEVEL (For explanation see text)

If such a regulatory mechanism is responsible for the resting hyperventilation of native residents at high altitudes, their lowered bicarbonate concentration would be expected to result in an apparent increased "sensitivity" to CO_2 through greater formation of free hydrogen ions per increment rise in pCO_2 (Figure 5). Such an increased ventilatory response to inspired CO_2 has been demonstrated by Hurtado in thirty-four normal high-altitude residents (2). His results after a fifteen-minute period of breathing an inspired pCO_2 of 37 mm are shown in Figure 6. The steeper slope of the CO_2-ventilatory response curve at a high altitude as compared to sea level indicates an

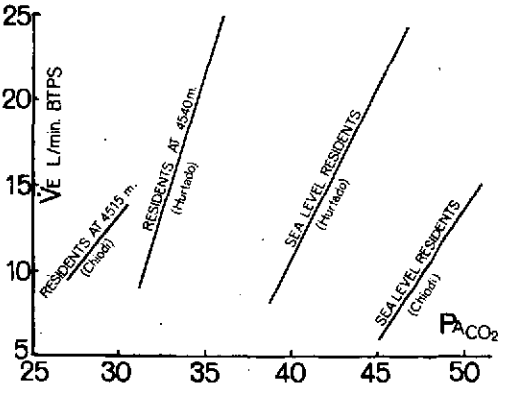


Figure 6. EFFECT OF CHANGES IN ALVEOLAR pCO_2 ON VENTILATION FROM DATA OF TWO STUDIES (2, 5)

augmented response. On the other hand, Chiodi (5), studying the ventilatory response to CO_2 of two natives at 4,515 meters, found no change in the slope of the response curve as compared to sea level (Figure 6). It may be that Chiodi's two subjects were not representative of the high-altitude population; there is wide individual variation in responsiveness at sea level (7). Nevertheless, his findings are not consistent with the mechanism of control that has been discussed, and the study should be repeated.

Alveolar-Arterial Oxygen Gradients

In normal man at sea level the oxygen tension in arterial blood is not as high as that of alveolar gas because of a combination of three factors: a diffusion barrier for oxygen, unequal distribution of ventilation and perfusion, and the existence of a true veno-arterial shunt. As a result of these factors, a 10-mm oxygen gradient exists between alveolar gas and arterial blood. From the standpoint of the quantity of oxygen carried by the arterial blood, this gradient is relatively unimportant at sea level but at high altitude becomes important because of the steep slope of the oxygen dissociation curve at lower pressures (Figure 7). This gradient, therefore, is a potential site for adaptation to high altitudes. Indeed, Hurtado found a gradient of only 1 mm on ambient-air breathing in natives of Morococha (2). His subjects were seated, and the arterial oxygen tension was determined indirectly from an oxygen dissociation curve. The results are consistent with the reported increased pulmonary diffusion capacity for oxygen in these subjects (8).

More recently, the alveolar-arterial oxygen gradient has been studied in this same population at three levels of oxygenation with measurements of arterial oxygen tension by direct polarography (9). The subjects were in the supine position. The results, which are shown in Figure 8, did not confirm the finding of a reduced gradient. On ambient air at high altitude the gradient was 10 mm, about equal to the ambient-air gradient at sea level and

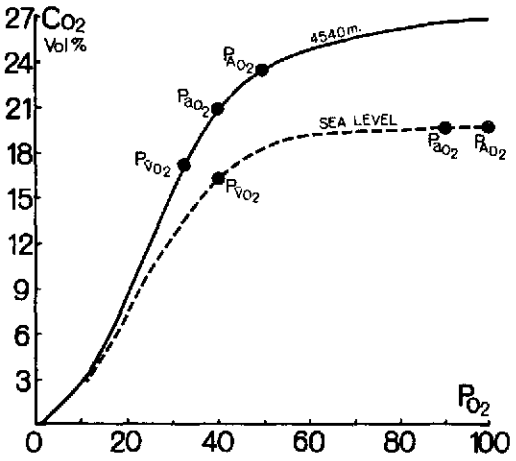


Figure 7. OXYGEN DISSOCIATION CURVES FOR BLOOD OF HIGH-ALTITUDE (SOLID LINE) AND SEA-LEVEL (BROKEN LINE) RESIDENTS. POINTS REPRESENT ALVEOLAR OXYGEN PRESSURE (P_AO_2), ARTERIAL OXYGEN PRESSURE (P_aO_2) AND MIXED VENOUS OXYGEN PRESSURE (P_VO_2)

greater than that found at low inspired oxygen tensions at sea level. This indicates that the diffusing capacity for oxygen is not increased, but may be decreased in Andean natives. This result is consistent with observations on acclimatized newcomers to high altitudes (10) but not with previously reported measurements on permanent residents (8).

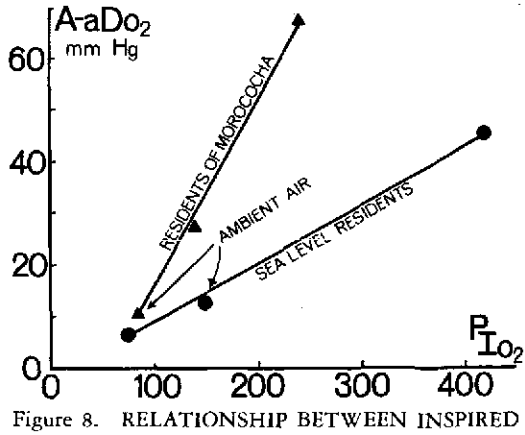


Figure 8. RELATIONSHIP BETWEEN INSPIRED OXYGEN PRESSURE (P_IO_2) AND ALVEOLAR-ARTERIAL OXYGEN DIFFERENCE IN RESIDENTS OF MOROCOCHA AS COMPARED TO SEA LEVEL (9)

Andean natives appeared to have a higher oxygen gradient when the inspired tension was raised to ambient sea-level values (27 mm), which suggests a more unequal distribution of ventilation and perfusion than exists in man at sea level (12 mm).

When the inspired oxygen tension was raised to 240 mm in high-altitude natives, the gradient was 67 mm. This is greater than would be expected in residents at sea level. It suggests, but does not prove, that there is a greater true veno-arterial shunt in high-altitude residents than in people at sea level.

These observations indicate that a reduction in alveolar-arterial oxygen gradient is not part of the process of adaptation in permanent residents at high altitudes; they imply that these people survive in spite of an increased inequality of distribution between ventilation and perfusion and an increase in true veno-arterial shunting. Measurements of alveolar-arterial oxygen gradient and diffusing capacity should be repeated in high-altitude residents because of the disagreement that now exists in the literature.

Arterial Gas Tensions and pH

Figure 5 shows the differences calculated to exist *in vivo* between high-altitude and sea-level residents for a change in hydrogen-ion concentration as the result of a change in arterial pCO_2. The normal values that exist under ambient conditions are indicated. The solid lines show the behavior of a pure bicarbonate solution, the slope of the lines being determined solely by the initial concentration of bicarbonate (24 mEq./L at sea level; 18 mEq./L at 4,540 m). In such solutions, the lower the initial bicarbonate level the larger the increase in hydrogen-ion concentration produced by a given increase in pCO_2. This is because the degree of dissociation of carbonic acid is determined by the initial bicarbonate concentration through its mass-action effect, not because it acts as a buffer (proton acceptor) in respiratory acidosis.

The buffering of carbonic acid by the blood ($\beta = \Delta[HCO_2]/\Delta pH$) is accomplished primarily by hemoglobin ($\beta = 1.7$ mEq./L bicarbonate per unit pH change per gram hemoglobin per 100 cc blood) and to some extent by protein and phosphate (at normal concentrations $\beta = 8$ mEq. bicarbonate per unit pH change). These values are for blood *in vitro;* recent data that *in vivo* buffering is about 38 per cent that of blood *in vitro* (13). In high-altitude residents at Morococha, the hemoglobin concentration is 20 gms per cent as compared to 15 gms per cent at sea level (2).

On the basis of these facts, it can be calculated that the *in vivo* value for β in high-altitude residents is about 14 and in sea-level dwellers 11.6. The broken lines in Figure 5 represent the calculated *in vivo* whole-body titration curves for high-altitude and sea-level residents. They show the differences in displacement from the line of pure bicarbonate solutions caused by the difference in hemoglobin concentration at the two altitudes. The increase in the hemoglobin concentration at high altitude does in part overcome the effect of the lowered initial bicarbonate level by decreasing the slope of the titration curve. The *in vivo* slope at high altitude remains greater than the slope at sea level, however, and hence a rise in pCO_2 in Andean natives is accompanied by a greater rise in hydrogen-ion concentration than in man at sea level. This difference is of particular importance in the interpretation of the ventilatory response to CO_2 at high altitudes. It must be emphasized that the curves shown in Figure 5 are theoretical; the actual *in vivo* values for β should be measured directly.

The increased alveolar ventilation of high-altitude residents results in an arterial pCO_2 of about 30 mm as compared to 40 mm at sea level. Although the pH is equal to that at sea level, there appears to be a slight shift of the oxygen dissociation curve to the right (11) This tends to suppress the uptake of oxygen by hemoglobin in the lung but favors its release at the tissues.

Figure 7 shows the oxygen dissociation curves for blood at high altitudes and at sea level with oxygen content in volumes per cent plotted

on the ordinate. The oxygen capacity of natives at Morococha is 28 volumes per cent (20 gms per cent Hb); at sea level 20 volumes per cent (15 gms per cent Hb) (2). It can be seen that even though the arterial oxygen tension is 50 mm lower at high altitudes, the blood actually carries more oxygen per unit volume than at sea level. It is also apparent that the greatest protection against low oxygen tension at high altitude comes from the slope of the dissociation curve through its effect on the mixed venous oxygen tensions. The mixed venous points are derived from an arterial-venous oxygen-content difference at both altitudes of 4 volumes per cent. At sea level, the delivery of this quantity of oxygen to the tissues is associated with a fall in pressure from arterial to mixed venous blood of 50 mm Hg, whereas at high altitude the pressure drop is only 8 mm and the mixed venous blood is left with a higher oxygen content than at sea level.

Summary

The following differences between the respiratory systems of residents at high altitudes in the Andes and their counterparts at sea level are well established:

1. The lung volume is increased in all its compartments at high altitudes, the largest expansion being in functional residual capacity and residual volume. The significance of these differences in terms of adaptation is not known.

2. The respiratory frequency is increased at high altitudes without a change in tidal volume. The consequent increase in alveolar ventilation reduces the oxygen pressure gradient from ambient air to alveolar air by 16 mm as compared to sea level and reduces alveolar pCO_2 to 30 mm.

3. The increased alveolar ventilation is not the direct result of hypoxia.

4. In spite of a decreased arterial oxygen tension at high altitudes, arterial blood carries more oxygen than at sea level because of an increase in hemoglobin concentration.

5. The greatest protection against tissue hypoxia at high altitudes comes from the shape of the oxygen dissociation curve rather than from major changes in the respiratory system.

The following differences have been described but are not firmly established and deserve further study:

1. The ventilatory response to increased pCO_2 is probably greater in high-altitude natives than in sea-level residents. If this is true, it represents a useful adaptation to a low-oxygen environment.

2. There is controversial evidence regarding the alveolar-arterial oxygen gradient and diffusing capacity at high altitudes. The most recent studies indicate that the oxygen gradients on ambient air at high altitudes and at sea level are equal but that at high altitudes there is a more unequal distribution of ventilation and perfusion and a larger veno-arterial shunt.

3. As a result of the lower bicarbonate concentration in the blood at high altitudes, there is a greater change in hydrogen-ion concentration of blood and extracellular fluid per unit change in pCO_2. By calculation this difference is not fully compensated for *in vivo* by the increased buffering power contributed by the greater hemoglobin concentration at high altitudes.

Native residents at high altitudes and man at sea level must both make a postnatal adaptation from the hypoxic environment *in utero* to a relatively higher ambient oxygen tension. In this sense, the adaptation to high altitudes that has been achieved by native residents may represent adjustments of lesser magnitude than those required of the newborn entering the higher-oxygen environment of sea level.

Moderator: Dr. Peñaloza will now speak on cardiovascular characteristics.

PHYSIOLOGICAL PATTERNS: CARDIOVASCULAR CHARACTERISTICS OF HEALTHY MAN

Dante Peñaloza*

Healthy people born and living permanently at high altitudes exhibit special cardiovascular characteristics that are related in some way to the mechanisms of natural acclimatization. Because large populations around the world, particularly in America and Asia, live at great altitudes, it is important to know these characteristics. Here they are briefly reviewed as they exist in people residing in altitudes of over fourteen thousand feet.

Heart and Pulmonary Circulation

Figure 1 shows the evolution with increasing age of the mean QRS vector, mean pulmonary artery pressure, and Hermann's and Wilson's index at sea level and at high altitudes. In newborns at both levels the anatomical and electrocardiographic data indicate the same degree of right ventricular preponderance (1, 2, 3). Mild pulmonary hypertension has been observed in the newborn of sea level by Rudolph *et al.* (4) and James and Rowe (5). We have no information on pulmonary pressures in the high-altitude newborn, but from the figures obtained for older children we can infer for them similar values of pulmonary pressure. Pulmonary hypertension in newborns is related to the fetal structure of the pulmonary vasculature reported at birth, both at sea level and at high altitudes (6, 7, 8).

After birth, definite differences become evident between infants born and living at high altitudes and those of sea level. At sea level, a few weeks after birth the pulmonary artery pressure drops almost to adult level (9, 10), and between the fourth and the eleventh months of life the left ventricle takes on anatomical and electrical preponderance (1, 3). At the same time the pulmonary vasculature acquires the adult pattern (7, 8). At high altitudes, on the other hand, the degree of pulmonary hypertension and the structural characteristics of the pulmonary vasculature decrease very slowly with age (6, 11, 12), as does the anatomical and electrical predominance of the right ventricle (1, 2). The degree of pulmonary hypertension and right ventricular preponderance decreases slightly after five years of age, but the physiological left ventricular preponderance seen

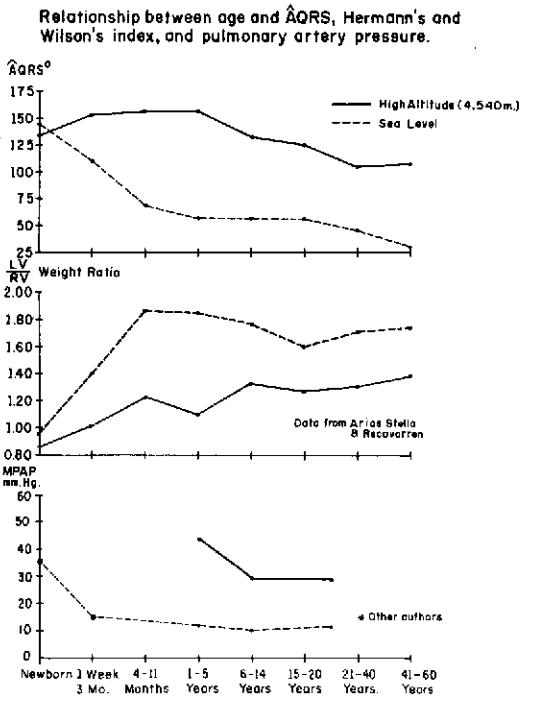


Figure 1. EVOLUTION WITH INCREASING AGE OF THE MEAN QRS VECTOR, MEAN PULMONARY ARTERY PRESSURE AND HERMANN'S AND WILSON'S INDEX AT SEA LEVEL AND AT HIGH ALTITUDES. DELAY OF THE PHYSIOLOGIC AND ANATOMIC EVOLUTION OCCURS AS CONSEQUENCE OF CHRONIC HYPOXIA

* This paper was written in collaboration with Drs. Francisco Sime, Natalio Banchero, Luis Ruiz, and Emilio Marticorena.

at sea level is never attained at high altitude.

Figure 2 shows the electrocardiographic and vectorcardiographic curves in a healthy high-altitude child four years of age. An electrical pattern of severe right ventricular hypertrophy is observed, and the curves are entirely similar to those seen in cases of congenital heart disease with pulmonary stenosis.

When the changes occurring with age at sea level and at high altitudes are compared, it is obvious that the physiological and anatomical evolution in the heart and pulmonary circulation of high-altitude dwellers is delayed, as a consequence of chronic hypoxia. Right ventricular hypertrophy and pulmonary hypertension in high-altitude inhabitants do not mean abnormality and are not associated with any kind of symptoms. The pulmonary hypertension of high-altitude natives is associated with increased pulmonary vascular resistance (11, 12), which in turn is related chiefly to the structural characteristics described in the pulmonary arterial bed by Arias-Stella and Saldaña (6). Cardiac output and pulmonary wedge pressure are normal in high-altitude residents (13).

With exercise, cardiac output in high-altitude natives increases similarly to that in sea-level subjects (14). Figure 3 shows the relation of cardiac output to oxygen uptake at rest and during exercise. Our mean values fit well with the pattern of cardiac output response to increasing exercise observed by several authors at sea level (15-18). They are in accord-

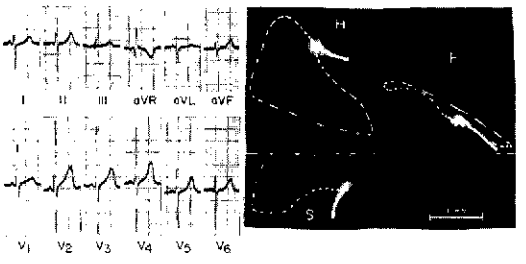


Figure 2. ELECTROCARDIOGRAM AND VECTORCARDIOGRAM IN A HEALTHY 4-YEAR-OLD CHILD BORN AND LIVING AT A HIGH ALTITUDE. QRS AND T WAVES AND LOOPS CORRESPOND TO THE PATTERN OF MARKED RIGHT VENTRICULAR HYPERTROPHY

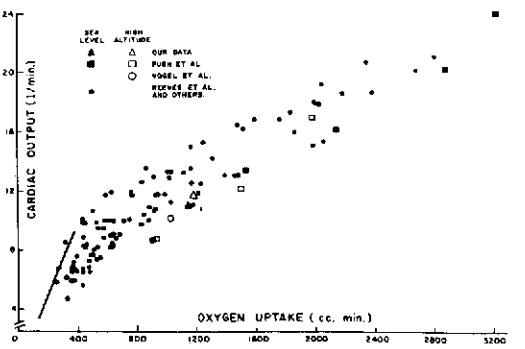


Figure 3. PATTERN OF CARDIAC OUTPUT RESPONSE TO INCREASING OXYGEN UPTAKE DURING SEVERAL DEGREES OF EXERCISE. CHANGES IN CARDIAC OUTPUT AND OXYGEN UPTAKE DURING EXERCISE ARE RELATED TO THE INTENSITY OF THE WORK PERFORMED AND ARE INDEPENDENT OF THE LEVEL OF ALTITUDE

ance with those reported by Vogel and his coworkers (19) in Leadville, Colorado, at 10,150 feet, and also with those obtained by Pugh (20), of the Himalayan and Mountaineering Expedition, who studied cardiac output at sea level and at nineteen thousand feet for several degrees of muscular exercise. These observations indicate that the variations in cardiac output and oxygen uptake during exercise are related to the intensity of work performed and are independent of the altitude.

Despite a similar rise in cardiac output during exercise in sea-level and in high-altitude subjects, we obtained an increment of nearly 100 per cent in mean pulmonary artery pressure in the high-altitude group and only 50 per cent in the sea-level group. Figure 4 shows the pattern of pulmonary pressure response to increasing cardiac output during several intensities of exercise at sea level. In calculating the normal regression equation, we have used our data and those from other laboratories. The pulmonary pressure responses of the sea-level and the high-altitude groups are quite different. The higher pulmonary pressure response on exertion at high altitudes is related to the increase in cardiac output in the presence of a thick muscular layer in the small pulmonary arteries (13, 14). It

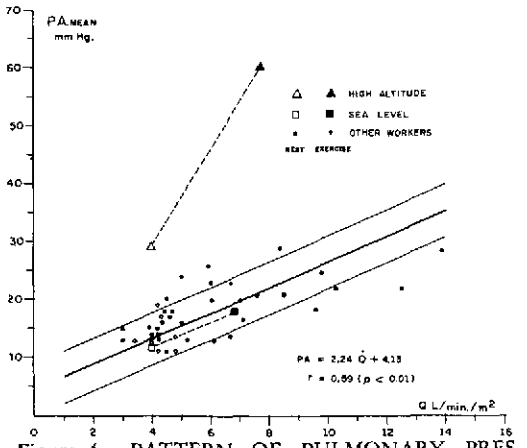


Figure 4. PATTERN OF PULMONARY PRESSURE RESPONSE TO INCREASING CARDIAC OUTPUT DURING SEVERAL INTENSITIES OF EXERCISE AT SEA LEVEL. NOTE THE POSITION OF THE DATA OBTAINED AT HIGH ALTITUDE

has been demonstrated, however, that functional factors play a part.

Figure 5 shows two typical examples of the influence of oxygen and acetylcholine on pulmonary artery pressure and cardiac output at rest and during exercise. At rest there is a slight reduction in mean pulmonary artery pressure, indicating that besides the structural characteristics of the pulmonary vascular bed there is a secondary functional factor in the pulmonary hypertension of the high-altitude natives (21). On exertion there is a considerable difference in pulmonary pressure response, which suggests that vasoconstriction at precapillary level is an important factor in the mechanism of the accentuated pulmonary hypertension observed during exercise at high altitude (21). Vasoconstriction may be related to the marked degree of hypoxemia found during exercise at high altitudes.

Figure 6, showing the decrement in oxygen saturation of arterial blood during exercise at different levels of altitude, gives our data from near sea level and at high altitude and those of other workers at several altitudes (13, 14, 19, 22). The decrement is greater as the altitude increases, and for the same altitude the oxygen saturation decreases as the intensity of the exercise increases. The fall in arterial oxygen saturation during exercise is associated with a decrement in the arterial pO_2 in spite of an increased pulmonary diffusing capacity (14). This may be explained by the slower transfer

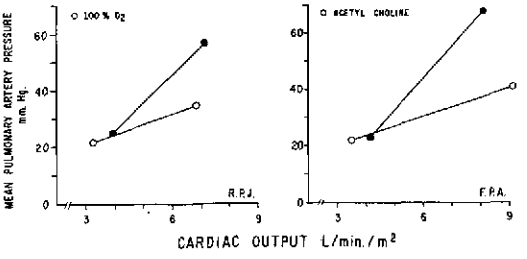


Figure 5. TWO TYPICAL EXAMPLES OF THE INFLUENCE OF OXYGEN AND ACETYL CHOLINE ON PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT AT REST AND DURING EXERCISE. VASOCONSTRICTION IS AN IMPORTANT FACTOR IN THE MECHANISM OF PULMONARY HYPERTENSION DURING EXERCISE

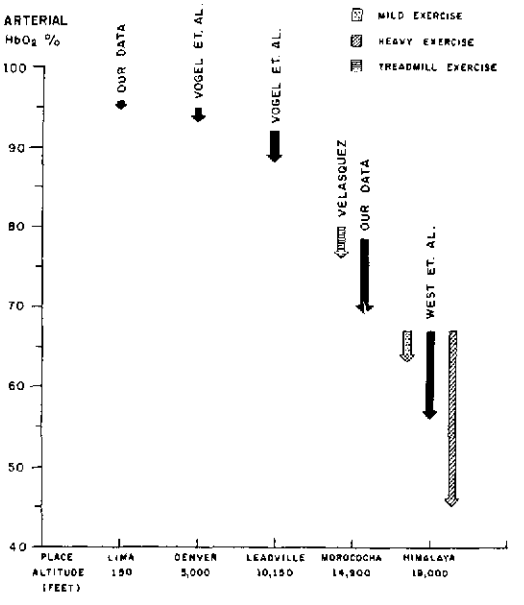


Figure 6. CHANGES IN OXYGEN SATURATION OF ARTERIAL BLOOD DURING EXERCISE AT DIFFERENT LEVELS OF ALTITUDE. AS THE ALTITUDE INCREASES THE MAGNITUDE OF DECREMENT IN ARTERIAL OXYGEN SATURATION ALSO INCREASES

of oxygen at the alveolocapillary level in an environment of low oxygen tension (23).

The magnitude of reduction in pulmonary artery pressure produced by oxygen inhalation at high altitudes is different from that observed after prolonged residence at sea level. Figure 7 shows the changes observed in eleven high-altitude natives after two years' residence at sea level. In all the subjects the resting values of the mean pulmonary pressure reach normal figures, and this may be ascribed to regression of the structural characteristics in the pulmonary vasculature. The lower pulmonary pressure response to increments in pulmonary blood flow is also related to regression of the pulmonary vascular pattern. (24).

The foregoing observations indicate that the effects of chronic hypoxia on the heart and pulmonary circulation are different from those of acute hypoxia. This is summarized in Figure 8. Pulmonary hypertension due to acute hypoxia is ascribed to vasoconstriction at precapillary level, and it is released by oxygen inhalation. Tachycardia and increased cardiac output are other effects of acute hypoxia. Pulmonary hypertension due to chronic hypoxia is ascribed primarily to structural changes of the pulmonary vasculature and secondarily to some functional factors. Heart rate and cardiac output are normal in people living permanently in

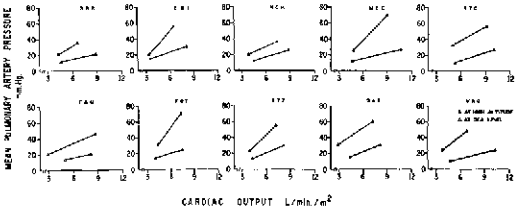


Figure 7. CHANGES IN PULMONARY ARTERY PRESSURE AND CARDIAC OUTPUT AT REST AND DURING EXERCISE IN ELEVEN HIGH-ALTITUDE NATIVES AFTER TWO YEARS OF RESIDENCE AT SEA LEVEL. PULMONARY MEAN PRESSURES REACH NORMAL VALUES AT REST. A LOWER PULMONARY PRESSURE RESPONSE IS OBSERVED DURING EXERCISE

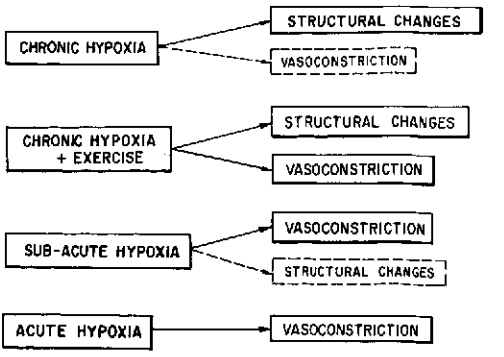


Figure 8. PULMONARY HYPERTENSION DUE TO ACUTE HYPOXIA IS ASCRIBED TO VASOCONSTRICTION AT THE PRECAPILLARY LEVEL WHILE PULMONARY HYPERTENSION DUE TO CHRONIC HYPOXIA IS PRINCIPALLY ASCRIBED TO STRUCTURAL CHANGES OF THE PULMONARY VASCULATURE

an environment of chronic hypoxia. Vasoconstriction becomes an important contributing factor in the mechanism of pulmonary hypertension when high-altitude subjects are exercising. Finally, in men or animals moved to a high altitude for several weeks or months there exists a condition of subacute hypoxia, and pulmonary hypertension is partially released by breathing oxygen. An incipient development of structural changes has been observed in animals submitted to these experiments (29). In short, the relative importance of functional and structural factors in the mechanism of pulmonary hypertension due to hypoxia varies with the time of exposure to it.

Systemic Circulation

Clinical observations and intra-arterial measurements made along with hemodynamic studies (12) suggest that the blood-pressure levels in healthy adults native to high altitudes are lower than those observed at sea level. Furthermore, the incidence of essential arterial hypertension appears to be less at high altitudes. An epidemiologic survey of a population of twenty-five thousand in Cerro de Pasco, at an altitude of 14,200 feet, has been initiated with the support of the World Health Organization.

TABLE 1. Changes in Systemic Blood Pressure Observed in Sea-Level Males Residing at High Altitudes

RESIDENCE (Yrs.)	NO.	AGE (Yrs.)	SYSTOLIC (mm Hg)		DIASTOLIC (mm Hg)	
			Initial	Final	Initial	Final
6-9	30	35	129	113	79	72
2-5	33	40	130	117	81	73
10-15	37	45	132	120	79	76*

* Not significant.

Preliminary observations have been made at other altitudes. With the sphygmomanometric technique, systemic pressure values somewhat lower than those at sea level have been obtained in three hundred subjects born and living in La Oroya, at 12,300 feet (25). Observations at the same altitude have also been made in one hundred sea-level males aged between twenty-five and sixty-six, most of them originally from North America and Europe, residing at La Oroya for periods ranging from two to fifteen years. These subjects were of a higher social class and income than high-altitude natives, and their diet was fairly similar to that of their country of origin. The systemic blood pressure values were taken from their annual clinical records.

In Table 1 the subjects are divided into three groups according to their length of residence at the high altitude. The mean values of systolic and diastolic pressure obtained in the last control differed significantly ($p<0.01$) from those obtained during the first examination. The only exception was for the diastolic pressure in the group with longer residence.

TABLE 2. Prevalence of Arterial Hypertension in 100 Sea-Level Males After 2-15 Years of Residence at High Altitudes (in per cent)

SBP mm Hg	INITIAL	FINAL
Systolic > 140	18	6
Diastolic > 90	7	4
Systolic > 160	2	1
Diastolic > 95	4	4

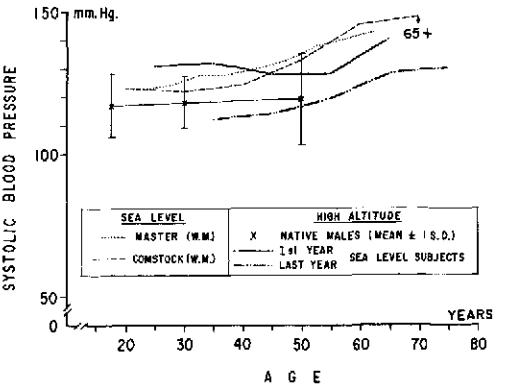


Figure 9. CHANGES IN SYSTOLIC BLOOD PRESSURE WITH AGE. AT SEA LEVEL THE SYSTOLIC PRESSURE INCREASES WITH AGE. THIS IS NOT THE CASE IN ADULTS NATIVE TO HIGH ALTITUDES. DECREMENT IN SYSTOLIC PRESSURE IS OBSERVED IN SEA-LEVEL SUBJECTS AFTER LONG RESIDENCE AT A HIGH ALTITUDE

In Table 2 two different criteria have been applied to these subjects to evaluate the prevalence of arterial hypertension after a long residence at a high altitude. It may be observed that the number of subjects diminished beyond the conventional limits proposed.

Figure 9 shows the changes in systolic blood pressure with age. Two representative series for white males at sea level, those of Master *et al.* (26) and Comstock (27), are represented here to illustrate that normally the systolic pressure increases gradually with age. This is not the case in adults native to high altitudes. However, as has been previously reported (28), this difference is not clear cut when children are compared. In sea-level subjects living at high altitudes the systolic pressure values have been grouped by decades according to their ages at the first and the last examinations. The last curve is lower than the first and closely similar to that for natives, which suggests some decrease in systolic pressure after residence at high altitude. Lesser decrements were observed for diastolic pressure in the same subjects.

Moderator: Dr. César Reynafarje will now talk on the hematological aspects.

PHYSIOLOGICAL PATTERNS: HEMATOLOGICAL ASPECTS

César Reynafarje

Polycythemia is one of the adaptive mechanisms to altitude hypoxia. Although respiratory and circulatory adjustments are the immediate response to pO_2 variations, erythropoietic activity is also stimulated from the very onset of exposure to hypoxia (two hours at least). The resulting hyperactivity of erythropoiesis produces the increase in the iron turnover rate. Subsequently intestinal iron absorption is stimulated. Finally, the red-cell mass increases to a value that supplies the oxygen needed by the tissues. Ten months are necessary to reach the maximum red-cell level; this is lower than in high-altitude natives (4).

The opposite is observed when altitude polycythemic subjects are brought down to sea level. The change to a milieu of normal oxygenation causes a progressive decrease in bone-marrow activity. The mobilization and utilization of iron decrease progressively, reaching a minimum after two or three weeks. The red-blood-cell mass diminishes slowly and after two months is even lower than is found in normal sea-level subjects. This suggests the development of an anemic condition, which, however, disappears in the ensuing months (4).

The exact mechanism of the action of the oxygen pressure changes on erythropoietic activity is not fully understood. Although it is generally accepted that the hypoxic stimulus acts through a humoral factor, erythropoietin, little attention has been given to this factor in relation to acute and chronic exposure of man to high altitude (2, 3). We have studied the problem in three groups of men (5): natives of Morococha, at 4,540 meters of altitude; newcomers to Morococha, after twenty-four and seventy-two hours and after ten days; and sea-level subjects.

The plasma obtained was processed by the method of Borsook (1). This material was tested in albino rats. Red-cell radioactive iron incorporation was the method of assay to determine the erythropoietic activity of the plasma injected in rats.

An increase in the secretion of erythropoietin was found in the group of rats injected with the plasma filtrates from newcomers to high altitude after twenty-four hours of exposure. No increase of erythropoietin titers was found after seventy-two hours or ten days of high-altitude exposure (Table 1). Similarly, the high-altitude natives showed no increases in the erythropoietic-stimulating factor. These findings are in agreement with the concept that erythropoietin is a hormone utilized by the erythropoietic tissue and that it increases in the circulating blood for a few hours only when there is a great need for red-blood-cell production.

In order to elucidate whether the decrease in erythropoietic activity in high-altitude natives brought down to sea level is due to a diminution in the amount of the erythropoietic-stimulating factor alone or to a humoral factor that produces depression of the red cell directly, studies were undertaken in natives of Moro-

TABLE 1. Plasma Erythropoietic Factor During Exposure to High Altitude

	CONTROL AT SEA LEVEL	AFTER 24 HRS.	AFTER 72 HRS.	AFTER 10 DAYS	NATIVES OF ALTITUDES
Mean ± S.E.	5.5 ± .38	9.0 ± 1.3	5.5 ± 1.4	5.4 ± 1.2	4.2 ± 1.2
No. of Rats	8	7	5	8	7

cocha after several periods of time at sea level by testing their plasma in rats. Blood samples were obtained from these subjects twenty-four and seventy-two hours and ten and twenty days after their arrival at sea level. The plasma filtrate was prepared by the Borsook method. The red-cell production in the rats was previously stimulated by exposing them to a simulated altitude of eighteen thousand feet for twenty-four hours, in order to make them more sensitive to an eventual depressing factor. The plasma filtrates were injected intraperitoneally (1 cc). Simultaneously, 1 microcurie of ^{59}Fe was administered in the same way. A second injection of plasma filtrate was given four hours later. The iron incorporation into the red cells was studied twenty-four hours after the radioactive material was given.

Table 2 illustrates the results of this experiment. Filtrates of plasma from polycythemic Morococha subjects brought to sea level caused a statistically significant depression of erythropoiesis in the groups of rats receiving the plasma obtained from the subjects at all four intervals.

In a second series of experiments, rats were injected with filtrate of plasma from high-altitude natives ten days after their arrival at sea level. One cc of this material, equivalent to 4 cc of the original volume of plasma, was given during seven days to one group of rats and during fourteen days to a second group. Hemoglobin determinations were performed before and after treatment. Observations of the same type were carried out in rats receiving either plasma filtrates of normal sea-level subjects or saline. The differences in the mean values of hemoglobin before and after the experiments are shown in Table 3. There was a reduction in hemoglobin only in the group of rats receiving plasma filtrates from high-altitude natives after ten days at sea level.

Both experiments seem to indicate that an inhibitory humoral factor exists in the plasma of high-altitude natives brought down to sea level. The presence of such a factor could explain the depression of red-cell formation that occurs in these subjects. If this is true, the control of erythropoiesis during altitude changes might depend upon an equilibrium in the plasma of the erythropoietic-stimulating factor and the erythropoietic-depressing factor. The predominance of one of these humoral factors

TABLE 2. Effect of Plasma Filtrate from Altitude Natives Brought Down to Sea Level in Rats Subjected to Simulated 18,000-Foot Altitude

GROUP	NUMBER OF RATS	TREATMENT ^{59}Fe	UPTAKE
I	13	sea-level plasma	41.6 ± 2.76
II	7	24-hour plasma	35.3 ± 3.48
III	7	72-hour plasma	30.1 ± 4.04
IV	14	10-day plasma	28.5 ± 2.46
V	7	20-day plasma	28.4 ± 2.50

TABLE 3. Effects on Hemoglobin of Normal Rats of Plasma Filtrate from Altitude Natives After 10 Days at Sea Level, Plasma Filtrate from Sea-Level Subjects, and Saline

TREATMENT	NO. OF RATS	DAYS OF TREATMENT	*Hb (gms %), mean ± S.E.* BEFORE TREATMENT	AFTER TREATMENT	MEAN DIFFERENCE	P VALUE	RETICULOCYTES (%)
Plasma of Altitude Natives After 10 Days at Sea Level	5	7	14.0 ± .25	13.5 ± .52	− 1.5	< 0.05	2.6 ± .63
	5	14	16.2 ± .14	12.7 ± .99	− 3.5	< 0.01	3.1 ± .85
Plasma of Sea-Level Subjects	5	7	15.5 ± .21	15.6 ± .18	+ .1		1.9 ± .45
	5	14	15.6 ± .22	15.3 ± .42	− .3		2.0 ± .50
Saline	5	7	15.9 ± .19	16.1 ± .26	+ .2		1.7 ± .48
	5	14	16.1 ± .17	16.4 ± .23	+ .3		2.1 ± .55

TABLE 4. Peripheral Blood in Camelids as Compared with Man

NUMBER	ALTITUDE (METERS)	ERYTHROCYTES (MILLIONS), MEAN ± S.E.	HEMOGLOBIN (GMS %), MEAN ± S.E.	HEMATOCRIT (%), MEAN ± S.E.	MEAN CORP. V (μ^3), MEAN ± S.E.	M.C. HB ($\mu\mu$gm) MEAN ± S.E.
12 alpacas	4,200	14.4 ± 0.37	13.8 ± 0.27	35.5 ± 0.86	24.8 ± 0.30	9.5 ± 0.3
12 llamas	4,200	13.7 ± 0.59	15.1 ± 0.45	38.1 ± 1.21	28.0 ± 0.37	10.8 ± 0.4
12 vicuñas	4,300	13.1 ± 0.34	13.5 ± 0.51	36.0 ± 0.85	27.4 ± 0.57	10.2 ± 0.3
50 humans	4,540	6.5 ± 0.10	20.2 ± 0.22	60.0 ± 0.7	92.0 ± 0.81	31.8 ± 0.3

TABLE 5. Peripheral Blood in Camelids

NUMBER	ALTITUDE (METERS)	RBC DIAMETER IN MICRONS: GREATER MEAN	RBC DIAMETER IN MICRONS: LESSER MEAN	HB CONCENTRATION OF RBC (%), MEAN ± S.E.	RETICULOCYTES (%), MEAN ± S.E.
6 alpacas	4,200	6.56	3.30	38.8 ± 0.40	0.92 ± 0.15
9 llamas	4,200	6.48	3.32	39.7 ± 0.52	1.3 ± 0.07
6 vicuñas	4,300	6.30	3.26	37.5 ± 0.39	1.3 ± 0.23

would depend on two closely related variables: the oxygen pressure and the actual amount of red-blood-cell mass.

Animals Native to High Altitudes

The hematological aspects of adaptation to high altitudes have been studied mainly in human beings, but these studies have obvious limitations. A better comprehension of the intimate mechanisms of the phenomenon can be obtained by studying some animal species whose permanent habitat is above four thousand meters, such as alpacas, llamas and vicuñas, which are presumably the most outstanding examples of adaptation to high altitudes. Recently we have carried out some observations on the erythrocytic balance in these animals (6). The results show that those observed in Corpacancha, at forty-two hundred meters, have a very high red-blood-cell count (above 13,000,000; see Tables 4 and 5), but the values for hemoglobin and hematocrit are lower than in man. The red blood cells are small (MCV = 30μ^3) and elliptical in shape. The bone marrow shows hyperplasia of the red elements. The relationship between granulocytes and nucleated red cells is 1:1. The iron metabolism studied by means of ^{59}Fe indicate that the iron turnover rate is greater in alpacas, llamas, and vicuñas than in human natives of high altitude (Table 6). The life span of the red blood cells is about sixty days.

These findings indicate hyperactivity of the erythropoietic tissue in alpacas, llamas, and vicuñas with a compensated red-cell destruction

TABLE 6. Iron Metabolism: Fe Turnover Rate in Camelids as Compared with Man

NUMBER	ALTITUDE (METERS)	PLASMA IRON PER 100 CC	FE UPTAKE (%)	PLASMA FE TURNOVER RATE MG FE/DAY/KG	RED-CELL FE TURNOVER RATE MG FE/DAY/KG
6 alpacas	4,200	156 ± 11	82.4 ± 4.4	0.52 ± 0.04	0.43 ± 0.04
6 llamas	4,200	192 ± 11	84.8 ± 3.6	0.59 ± 0.12	0.52 ± 0.10
6 vicuñas	4,300	113 ± 6.6	90.6 ± 3.3	1.11 ± 0.32	1.03 ± 0.34
6 humans	4,540	94 ± 3.8	92.0 ± 2.4	0.52 ± 0.01	0.39 ± 0.01

rate. As a result-balance, these animals have a red-blood-cell mass of between 24 and 31 cc/kg wt, which is less than that found in human natives of the same altitude (Table 7).

It is interesting to note that llamas, alpacas, and vicuñas apparently need less hemoglobin than humans do to adapt to high altitude. Some findings already described could explain this phenomenon. The small size of the red cells, together with a high red-cell count, leads to a greater surface area for a more efficient contact with oxygen in the lung. In addition, the elliptical shape of the red cell may facilitate its movement into small capillaries.

On the other hand, it must be mentioned that some observations have shown a greater affinity of hemoglobin for oxygen as a compensatory mechanism of adaptation for the altitude hypoxia in these animals. Finally, another possible mechanism of adaptation could be that in camelids the ability of tissues to utilize oxygen is greater.

Moderator: Now I shall call on Dr. Moncloa, who will discuss endocrine factors, and then on Dr. Baltazar Reynafarje, who will speak on enzymatic changes.

TABLE 7. Blood Volume in Camelids and Man

NUMBER	ALTITUDE (METERS)	TOTAL CC/KG WT MEAN ± S.E.	PLASMA CC/KG WT MEAN ± S.E.	ERYTHROCTES CC/KG WT MEAN ± S.E.	HEMOGLOBIN CC/KG WT MEAN ± S.E.
10 alpacas	4,200	72.0 ± 5.3	45.3 ± 3.4	24.3 ± 2.2	9.7 ± 0.8
10 llamas	4,200	65.2 ± 4.1	40.2 ± 2.1	25.0 ± 1.4	9.9 ± 0.7
10 vicuñas	4,300	86.6 ± 2.1	56.0 ± 1.4	31.3 ± 0.9	11.9 ± 0.3
10 humans	4,540	88.1 ± 1.5	33.1 ± 0.9	55.0 ± 1.3	17.6 ± 0.5

PHYSIOLOGICAL PATTERNS: ENDOCRINE FACTORS

Federico Moncloa

The present paper presents a review of findings on endocrine physiology in high-altitude natives as compared with sea-level natives obtained from work done in our laboratory or reported in the literature.

Materials and Methods

We have studied men born over ten thousand feet above sea level and others living for more than a year either in Morococha (14,900 feet) or in Cerro de Pasco (14,000 feet). Our controls have been sea-level-native residents of similar age. The methods have been previously described (9–12).

Adrenal Cortex

The physiology of the human adrenal cortex has been explored in high-altitude natives by several investigators (3, 11, 12, 15, 18).

The urinary excretion of 17,21-dihydroxy-ketosteroids (17-OHCS) and 17-ketogenic steroids (17-KGS) has been found within the normal range (3, 11, 12, 18). These results are in accord with a normal cortisol secretion rate and with a normal plasma cortisol concentration (see Table 1). These last two findings allow us to state that the metabolic clearance rate (MCR) is the same in both populations. Using the formula recommended by Tait (20), MCR = Cortisol secretion rate/plasma cortisol concentration, we have found in high-altitude natives the MCR is 176.6/24 hrs and in sea-level natives 162.3/24. This is reinforced by our observation that the amount of 17-OHCS appearing in the urine after the intravenous injection of 100 mg of cortisol was the same in the two groups (12). The interrelationship between the hypophysis and the adrenal cortex has been studied by us and others (3, 11, 18). The responses to dexamethasone inhibition (12) and the methopyrone test (11) were again similar (see Table 2).

Stimulation with adrenocorticotrophin (ACTH) gave interesting results. When the dose used is in excess of the amount capable of eliciting maximal stimulation, high-altitude natives behave like sea-level natives (3, 11); but with small doses, such as 1, 2, or 5 U, their response is lower in terms of urinary excretion

TABLE 1. Urinary Excretion of Some Steroids, Cortisol Secretion Rate and Plasma Cortisol Concentration in High-Altitude and Sea-Level Natives

VARIABLE MEASURED	SEA LEVEL, MEAN ± SE	HIGH ALTITUDE, MEAN ± SE	REFERENCES
Urinary 17-OHCS mg/24 hrs	6.2 ± 0.3 (10) *	5.4 ± 0.5 (10)	3
	6.5 ± 0.4 (21)	5.7 ± 0.3 (15)	18
	6.2 ± 0.3 (42)	5.5 ± 0.2 (28)	11
Urinary 17-KGS mg/24 hrs	15.8 ± 1.2 (15)	14.3 ± 0.9 (10)	11
Cortisol secretion rate mg/24 hrs	18.8 ± 1.4 (7)	16.7 ± 1.4 (10)	11
Plasma cortisol μg/100 ml	11.6±0.7(20)	9.5 ± 0.9 (16)	

* The figures in parenthesis are the number of determinations.
The differences are not statistically significant.

TABLE 2. Urinary 17-OHCS (mg/24 hrs) Under Dexamethasone, Methopyrapone and ACTH Tests in High-Altitude and Sea-Level Natives

TEST	SEA LEVEL MEAN ± SE	HIGH ALTITUDE MEAN ± SE	p VALUES	REFERENCES
ACTH 1U	14.7 ± 0.8 (20)	11.5 ± 0.8 (15)	<.01	11
ACTH 2U	15.3 ± 1.0 (21)	11.0 ± 1.0 (15)	<.01	18
ACTH 5U	23.3 ± 1.2 (21)	16.9 ± 1.5 (15)	<.01	18
ACTH 20U	20.2 ± 1.3 (11)	18.8 ± 1.1 (13)	N.S.	11
ACTH 25U	15.1 ± 0.7 (10)	14.0 ± 0.9 (10)	N.S.	3
Methopyrapone	17.9 ± 1.8 (10)	14.9 ± 2.1 (7)	N.S.	11
Dexamethasone (2nd day of administration)	1.4 ± 0.1 (10)	1.2 ± 0.2 (13)	N.S.	12

of 17-OHCS and 17-ketosteroids (17-KS) (11, 18). The explanation postulated for this observation is that ACTH has a faster catabolism in high-altitude natives. In favor of this hypothesis are the results shown in Figure 1. After a single intravenous injection of ACTH the time at which the plasma cortisol concentration starts to fall depends on the ACTH concentration (6). If the amount of ACTH injected is the same for both groups and if the cortisol starts to fall earlier in one of them, this should indicate that ACTH concentration is falling at a faster rate in that group. After the intravenous injection of 0.25 U of ACTH per kg of body weight, the maximal cortisol concentration occurs in high-altitude natives at 120 minutes and in sea-level natives at 135 minutes.

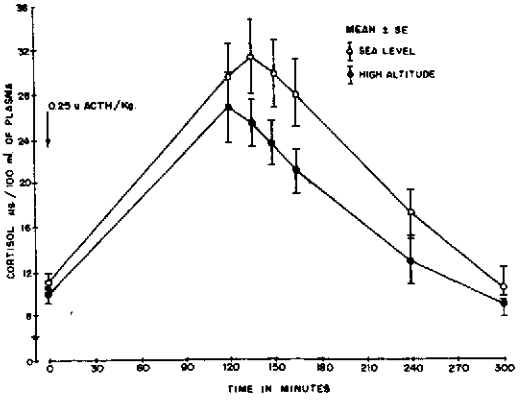


Figure 1. PLASMA CORTISOL CONCENTRATION AFTER A SINGLE INTRAVENOUS INJECTION OF ACTH (0.25 U/Kg)

Further experiments are being made in an attempt to settle this point. An alternative explanation could be a lower sensitivity of the adrenal cortex to ACTH.

Thyroid

The thyroid is one of the main regulators of oxygen consumption, and its physiology depends upon iodine metabolism. The relationship between hypoxia and thyroid physiology has been investigated in acute hypoxia and in experimental animals. However, little information is available on chronic hypoxia except that the basal metabolic rate is normal (7) or slightly increased (13), that endemic goiter is seldom found in high altitudes (2, 4), and that iodine disappearance from the iodine space is slower in high-altitude than in sea-level natives (9).

The plasma disappearance curve of ^{131}I is illustrated in Figure 2. The curve corresponding to the high-altitude group has a less pronounced slope than that for the sea-level group. The biological half-life in the high-altitude group is 3.8 hrs and in the sea-level group 3.1 hrs. The urinary excretion is represented in Figure 3. It can be seen that the high-altitude natives excrete a smaller proportion of the ^{131}I dose;

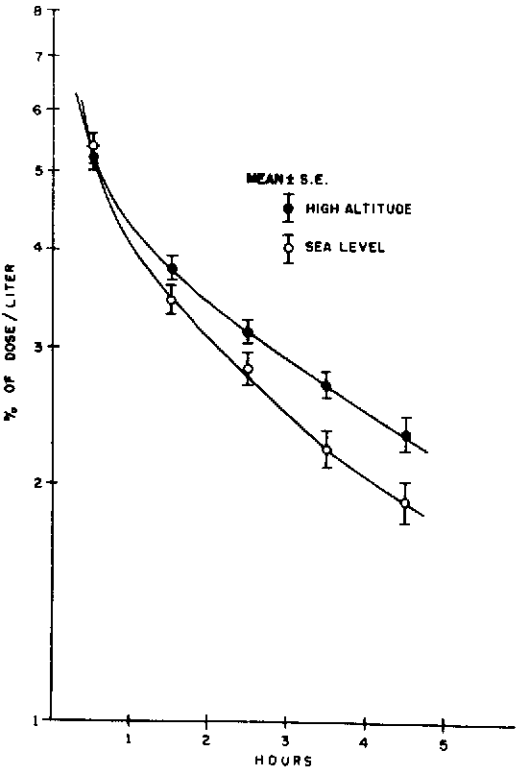


Figure 2. PLASMA ^{131}I DISAPPEARANCE CURVE—INTRAVENOUS INJECTION

the differences between the two groups have a statistical significance in all cases of less than $p<0.01$. The thyroidal uptake is shown in Figure 4. The high-altitude group—because of the results of the urinary excretion and the shape and values of the thyroidal uptake curve—resembles what would be expected in situations of iodine deficiency (14, 17). However, the disappearance curve of ^{131}I rules out a lower iodine intake as the only explanation. In iodine deficiency the biological half-line is lower than that found in normals (14), which was not the case here. The high uptake at 24 hours accompanied by a delayed disappearance of ^{131}I suggests that the clearance of the isotope from the blood is diminished; this seems to be the case with the high-altitude natives. The decrease in the renal excretion of iodine could be the reason why the iodine remains longer in its space, and this would cause secondarily a greater percentual thyroidal uptake.

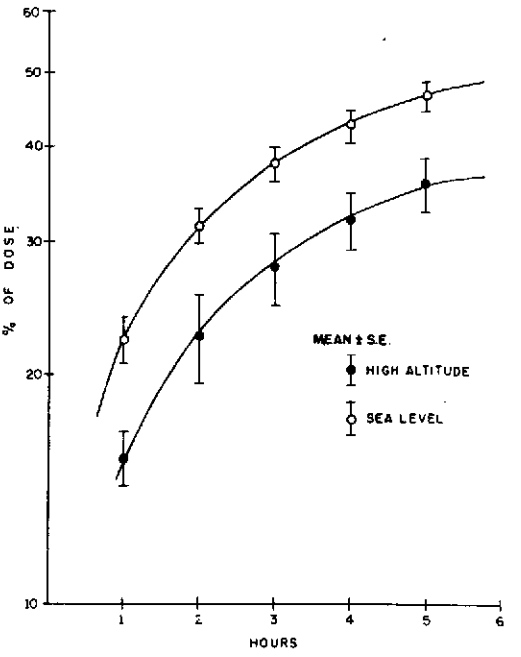


Figure 3. URINE ^{131}I ACCUMULATED EXCRETION—INTRAVENOUS INJECTION

The lower renal excretion is not easy to explain. It is likely that the lower renal plasma flow described in high-altitude natives (1, 8) may be one cause; another possibility might be that the red blood cells, which we know are increased in high-altitude natives (22), act as iodine reservoirs. A third interpretation may be a slower diffusion of iodine from plasma to the extra- and intracellular fluids. Even though our results do not allow us to disregard completely the lack of iodine as one factor to

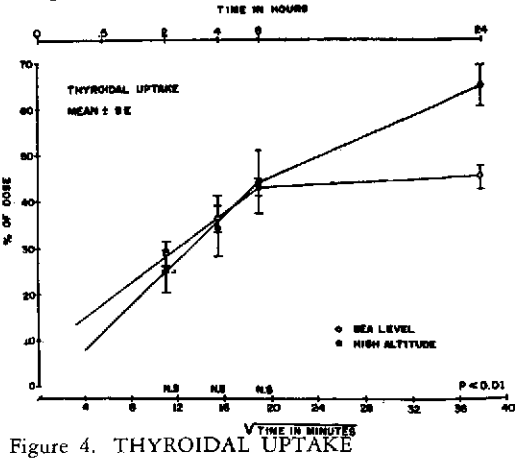


Figure 4. THYROIDAL UPTAKE

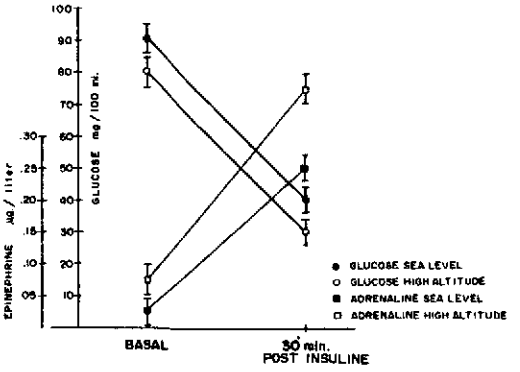


Figure 5. PLASMA ADRENALIN IN FASTING AND HYPOGLYCEMIA IN HIGH-ALTITUDE AND SEA-LEVEL NATIVES

explain our findings in high-altitude natives, one is tempted to speculate that either deficient elimination or slow diffusion of iodine would result in lower requirements for the element (14); if so, this might be an explanation for the lower incidence of endemic goiter at the highest altitudes (2, 4, 9).

Gonads

Not many studies have been made of gonadal function in high-altitude natives. Guerra-García *et al.* (5) reported that the urinary excretion of testosterone in men was 96.5 μg/24 hrs, very similar to the 99.8 μg/24 hrs value found in sea-level natives. Sobrevilla *et al.* have reported no differences in total urinary gonadotrophins (16). However, Guerra-García's results (personal communication) with the urinary excretion of testosterone under stimulation with human chorionic gonadotrophins indicate a smaller and shorter increase in the high-altitude natives, resembling what happens with the corticoid response to ACTH stimulation.

Catecholamines

The plasma levels of adrenalin and noradrenalin have been found, in fasting conditions, to be 0.07 μg/l and 0.36 μg/l in high-altitude natives as compared with 0.03 μg/ and 0.33 μg/l in sea-level natives (10). The differences were not statistically significant. Under hypoglycemia caused by insulin injection, a rise in adrenalin is observed in both populations—significantly higher, however, for the high-altitude natives (see Figure 4). The glycemic recovery starts from a lower concentration in high-altitude natives but is of the same magnitude as in sea-level natives. The more intense hypoglycemia would explain the greater adrenalin concentrations, but the fact that the recovery was the same despite the higher adrenalin concentration may be interpreted as some sort of "resistance" to adrenalin. A decreased action of adrenalin under hypoxia has been described by other investigators (19, 21).

Summary

The results presented indicate that most of the endocrine indexes are within normal range in high-altitude natives. However, there is evidence that under certain circumstances their response to several hormones is lower.

PHYSIOLIGICAL PATTERNS: ENZYMATIC CHANGES

Baltazar Reynafarje

Life in general depends upon the inherited ability of each organism to extract and utilize the energy contained in a wide variety of sources. With man such a source is his foodstuffs. To extract and make use of their chemical energy he requires the presence of adequate amounts of oxygen and proper enzyme systems. The following expression will clarify this concept:

$$\text{Foodstuffs} + O_2 \xrightarrow{\text{Enzymes}} \text{Useful energy} + CO_2 + H_2O$$

When foodstuffs and the activity of the enzymes are not the limiting factors, the amount of useful energy extracted is apparently a simple and direct function of oxygen concentration at tissue level. When this becomes too low, as during exhausting work, physical fatigue ensues because metabolites are not completely oxidized.

In the high-altitude native, however, despite the low concentration of oxygen in the inspired air, physical fatigue is delayed (1) and the accumulation of lactate and pyruvate in peripheral blood at the end of exercise is far below the level observed in the sea-level resident (1, 2). Such striking physiological and biochemical differences cannot be explained merely in terms of improved oxygen transport systems. To account for this behavior there must also be important changes at tissue level in the high-altitude native.

Data confirming this supposition will be presented in this paper.

The Reserves of Chemical Energy

The rate of energy expenditure during the performance of a given task is constant from beginning to end. The rate of oxygen consumption, however, is not constant but is an exponential function of time. At the beginning of the exercise, therefore, the energy derived from the oxidation of substrates is negligible in comparison with the energy expenditure; during this period the reserves of chemical energy must be used.

Figure 1 illustrates this concept. On the left is represented a mitochondria and on the right the contractile apparatus of the myofibril. When work is performed, chemical energy, constituted by ATP, is transformed into mechanical energy. This thermodynamic transformation results in muscular contraction and ADP formation. ADP then diffuses toward the mitochondria, where in the presence of oxygen, it is regenerated by oxidative phosphorylation. The newly formed ATP diffuses toward the myofibril to provide it with the energy needed for ensuring its contraction. Since this type of energy generation is negligible at the beginning of exercise, the cell must resort to its reserves of chemical energy, which consist mainly of phosphocreatine and ADP. For the reserves to be used, specific phosphotransferases must be present. Cazorla has recently shown that the activity of these enzymes is significantly higher in two skeletal muscles of the high-altitude-native guinea pig (3). Some years ago we determined the total

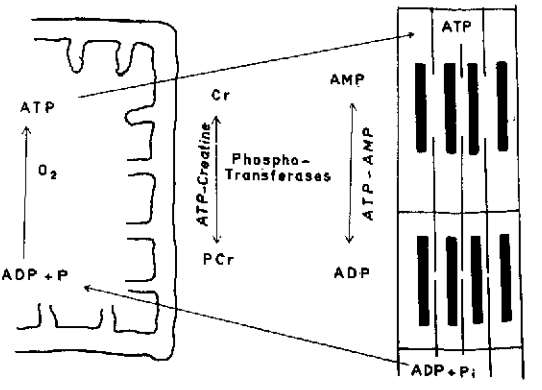


Figure 1. THE TRANSFORMATION OF CHEMICAL ENERGY INTO MECHANICAL ENERGY

TABLE 1. Effects of Altitude on Adenosinetriphosphatase and High-Energy Phosphates CRP

TISSUE	ADENOSINETRIPHOSPHATASE μM P LIBERATED/MG TISSUE/15 MIN		HIGH ENERGY PHOSPHATE (CRP, ATP, ADP), μM P/GM	
	SEA LEVEL (13) *	ALTITUDE (14)	SEA LEVEL (12)	ALTITUDE (9)
Heart	5.43 ± .47	7.40 ± 52 †	9.35 ± .86	8.25 ± .88
Diaphragm	7.89 ± .31	8.57 ± .50		
Rectus femoris			22.14 ± 1.15	26.63 ± 2.31
Red	12.44 ± .59	12.31 ± .47		
White	13.87 ± .54	13.49 ± .62		
Biceps femoris			23.72 ± 1.07	27.07 ± .95 †
Psoas	13.52 ± .62	14.24 ± .83	19.95 ± 1.23	24.68 ± 1.29 ‡
Sartorius	13.74 ± .76	11.70 ± .54 ‡	15.56 ± 1.02	21.00 ± .91 †
Liver	3.38 ± .24	4.98 ± .40 †	7.01 ± 1.08	7.03 ± .62
Kidney	3.53 ± .30	5.01 ± .45 ‡	4.86 ± .53	5.21 ± .48

* Number of determinations

†, ‡ Significantly different from sea-level values—P $<$ .01 and $<$.05, respectively

concentration of high-energy phosphate bonds in various muscles of the animal (4); the results are shown in Table 1. All tissues except heart exhibit a larger concentration of these energy-rich phosphates, although significant differences were found only in biceps femoris, psoas and sartorius. The activity of adenosinetriphosphatase, the enzyme that hydrolyzes ATP, is significantly higher in the heart of the altitude guinea pig, which suggests that although the concentration of energy-rich phosphates is not much larger their turnover may be faster in heart and other tissues. We have no data on the magnitude of the energy reserves in man. However, study of the kinetics of oxygen consumption during the period of recovery from exercise can give us indirectly an idea of this magnitude.

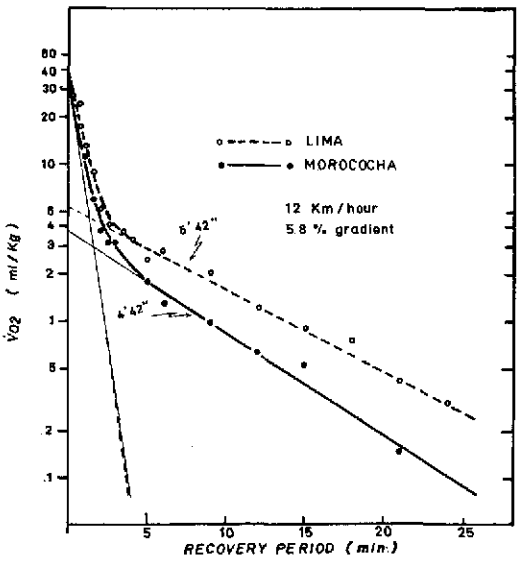


Figure 2. RATE OF PAYMENT OF THE OXYGEN DEBT

Figure 2 shows the rate of payment of the oxygen debt during a 10-minute run, at 12 km/h, in subjects from sea level and from high altitudes. The oxygen debt has been broken down into its so-called alactacid and lactacid components. The alactacid oxygen debt, the area under the steeper lines, would represent the oxygen consumed in order to restore the reserves of energy depleted at the beginning of exercise. It is clear that the area is approximately the same in both groups, which indicates that the energy reserves are of about the same magnitude. Agreeing with this is the previous showing that the alactacid debt does not change either with the intensity of work or with the oxygen tension in the inspired air (5).

Anaerobic Pathways of Carbohydrate Metabolism

Proteins and fats, to produce energy, must first enter into aerobic metabolic pathways. Carbohydrates, however, can produce a certain amount of energy during its anaerobic or glycolytic breakdown. Figure 3 illustrates the two main pathways for carbohydrate metabolism. On the left is the pentose or phosphogluconate pathway, with its end products fructose-6-P, glyceraldehyde-3-P, CO_2, and TPNH. The first two are also intermediary products of the Embden-Meyerhof pathway, which is represented on the right, with pyruvate as the end product. The circle represents oxidative pathways.

The advantage in using the pentose pathway appears to derive from the fact that no additional ATP is required to generate glyceraldehyde-3-P, as is necessary in the Embden-Meyerhof pathway. This would be one of the mechanisms employed by the altitude-adapted organism to save energy—that is, to produce more chemical energy with the same oxygen consumption. Furthermore, the use of this pathway renders TPNH instead of the DPNH of the other pathway. Although it is not clear whether ATP is efficiently generated by the oxidation of TPNH, the use of the transhydrogenase pathway may produce three moles of ATP per mole of TPNH formed. We shall see later that the transhydrogenase pathway is significantly more active in human high-altitude natives.

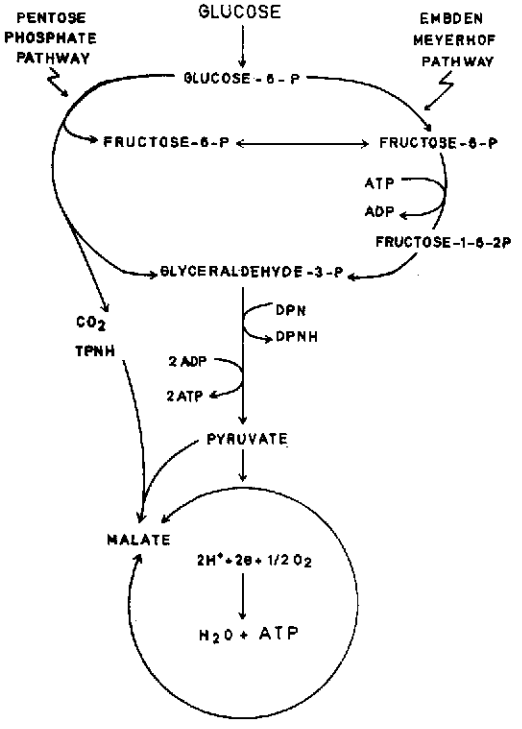


Figure 3. PATHWAYS FOR CARBOHYDRATE METABOLISM

Another important advantage of using the pentose pathway would be the formation of substrates for the Krebs cycle. By the action of Ochoa's malic enzyme, the CO_2 produced can be added to pyruvate to form malic acid, using TPNH as cosubstrate. Malate is an important source of energy in the citric acid cycle. It would be in this way that CO_2 is saved to produce energy. The preferential operation of the pentose pathway would be of great importance during work because more energy is produced with equivalent amounts of oxygen consumed; furthermore, because the rapid accumulation of lactate is prevented, fatigue will be delayed. Experiments carried out so far have shown that the enzyme activity in the Embden-Meyerhof pathway is not significantly different in subjects from sea level and from high altitudes (6, 7). The activity of the glucose-6-P dehydrogenase, an important enzyme in the pentose pathway, seems on the other hand to be higher in some of the tissues of the high-altitude guinea pig, which suggests that the pentose pathway may be more operative at high altitudes.

The study of fructose metabolism in humans, carried out first by Picón (8) and more recently by us, provides evidence that the preferred metabolic pathways of high-altitude natives are different from those of sea-level residents. In our experiments the metabolism of fructose in the liver and extrahepatic tissues was studied in healthy young sea-level and high-altitude natives. Figure 4 shows the kinetics of fructose disappearance in extrahepatic tissues. It appears that the hexose is metabolized at about the same speed at sea level and at high altitudes,

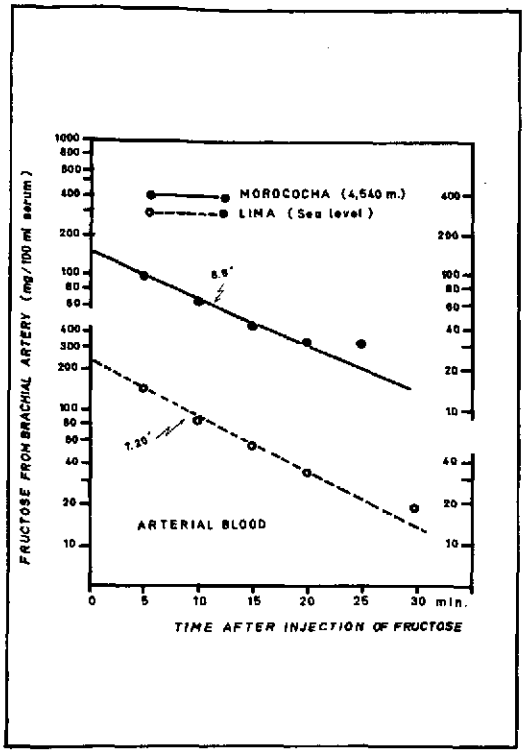


Figure 4. KINETICS OF FRUCTOSE DISAPPEARANCE IN EXTRAHEPATIC TISSUES

and most probably along only one major metabolic pathway, since the disappearance is apparently a simple exponential function of time. Figure 5 shows what happens in the liver. As is apparent, the rate of disappearance is clearly different in the two groups of subjects. Whereas at sea level fructose is apparently metabolized following only one metabolic pathway, in the altitude native the metabolism of fructose in the liver follows two metabolic pathways, each with a clearly different rate, as is shown in the graph by the slope of the lighter lines.

The rate of accumulation of the products of fructose metabolism is also completely different. Figure 6 shows the rate of fructose conversion into glucose in the liver and extrahepatic tissues. At sea level, glucose concentration in the blood from the suprahepatic vein and from the artery increases considerably over the basal level after a lag of about ten minutes. In the high-altitude native, on the other hand, glucose concentration in both the suprahepatic vein and the artery

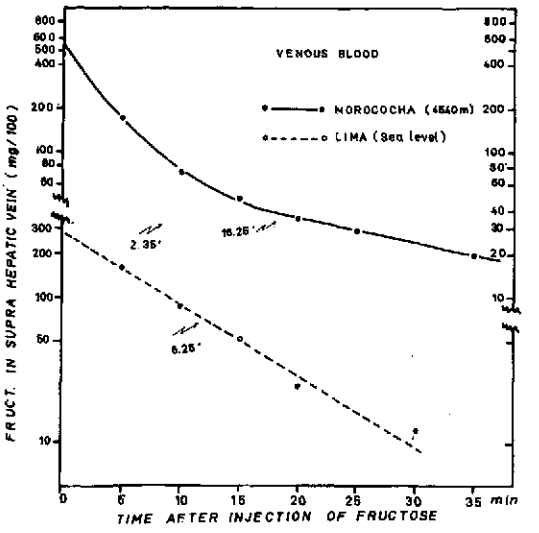


Figure 5. KINETICS OF FRUCTOSE DISAPPEARANCE IN LIVER

tends to decrease continuously for at least thirty-five minutes. Furthermore, it is interesting to note that while at sea level the concentration of the newly formed glucose is always higher in the suprahepatic vein than in the artery, the reverse is true at high altitudes.

Lactate and pyruvate are formed from fructose in both groups of subjects, but always to a lesser extent in the altitude group. It may be observed in Figure 7 that lactic acid is formed almost immediately after the injection of fructose and that its concentration is already decreasing at high altitudes at a time when it is still increas-

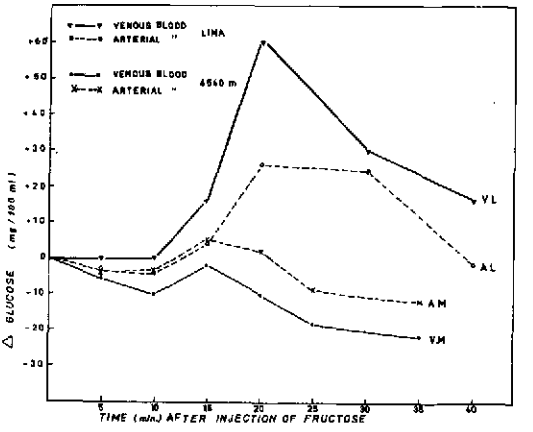


Figure 6. RATE OF FRUCTOSE CONVERSION INTO GLUCOSE

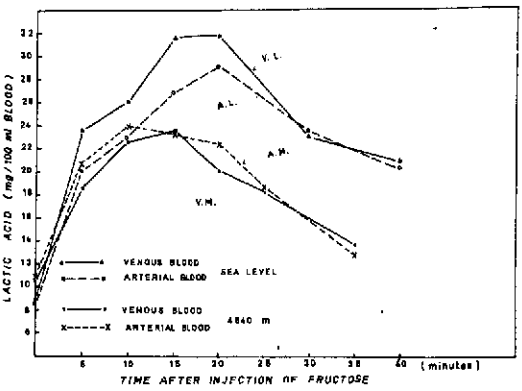


Figure 7. THE RATE OF LACTIC ACID FORMATION FROM FRUCTOSE

ing at sea level. This suggests a faster rate of combustion, probably through more efficient oxidative pathways.

Respiratory Pathways

There is a variety of evidence that the activity of oxidative enzymes is greater in the tissues from high-altitude natives. It is well known that the larger proportion of energy formation occurs during the oxidation of DPNH in the respiratory chain. The various enzymes involved in this oxidation were studied in the so-called DPNH-oxidase system. The results are shown in Table 2. In the homogenate of the whole cell the DPNH-oxidase system is significantly more active in the altitude native. In the mitochondria, where energy is produced, the enzyme DPNH-cytochrome c reductase, which is only part of that system, is not significantly higher at altitudes, but evidently this enzyme is not a limiting step in the oxidation of DPNH. The TPNH-cytochrome c reductase and the transhydrogenase, on the other hand, are significantly more active in the high-altitude than in the sea-level subject. This would be in accordance with the hypothesis that the pentose phosphate pathway is used to a greater extent at high altitude than at sea level. If this is true, the resulting TPNH would induce the formation of larger amounts of enzymes concerned with its oxidation. It would then be by action of the transhydrogenase that TPNH would generate chemical energy; otherwise the direct oxidation of TPNH would use oxygen without forming the same amount of energy.

Recent findings suggesting that the concentration of myoglobin in heart may be related to the amount of work performed by this organ indicate that the respiratory pigments play an equally important role in the process of adaptation to high altitude, since this and other pigments have been shown to exist in larger amounts in high-altitude natives.

TABLE 2. Specific Activity of Some Enzymes and Enzyme Systems in Sartorius Muscles of Subjects Native to Sea Level and High Altitudes

ENZYMES	SEA LEVEL	HIGH ALTITUDE	P <
	Whole homogenate		
DPNH-oxidase	41.38 ± 2.79 (8)	52.09 ± 11.86 (9)	.05
	Mitochondrial Fraction		
DPNH-cyt. c r.	57.86 ± 16.37 (9)	65.66 ± 10.15 (7)	N.S.
TPNH-cyt. c r.	0.83 ± 0.29 (8)	1.48 ± 0.39 (7)	.01
Transhydrogenase	1.46 ± 0.61 (8)	2.59 ± 0.97 (9)	.05
	Supernatant Fraction (S_1)		
DPNH-cyt. c r.	97.85 ± 36.55 (8)	104.10 ± 16.71 (7)	N.S.
TPN-ICD	10.99 ± 2.78 (8)	14.78 ± 4.65 (9)	N.S.
LD	1358.14 ± 79.90 (7)	1321.10 ± 143.10 (9)	N.S.

Values are means ± S.D. Figures in parentheses indicate number of cases
Cyt. c r. = cytochrome "c" reductase; ICD = isocitric dehydrogenase; LD = lactic dehydrogenase

Moderator: Until not very long ago, discussions on high altitude were almost exclusively concerned with physiological aspects. But work in the last few years shows that there is a gold mine yet to be explored from a clinical standpoint. Our next presentation therefore deals with clinical conditions at high altitudes.

Monge: To make a shorter presentation, I plan to concentrate on chronic mountain sickness.

NATURAL ACCLIMATIZATION TO HIGH ALTITUDES: CLINICAL CONDITIONS

Carlos Monge C.

The distribution of human life on the high mountains of the world poses two main problems to the clinician interested in human health at high altitudes. One is concerned with the modifications of clinical conditions known at sea level when they occur in a hypoxic environment; the other refers to conditions inherent to high-altitude life.

The first group includes a large variety of clinical conditions. In 1937 Loewy and Whittkower (1) collected a large body of information on the influence of high-altitude climate on a wide variety of diseases. It is unfortunate that there is no contemporary publication comparable to this fine work. Nevertheless, there is a group of diseases that has received careful study in recent years, and they will be briefly described here.

Pneumoconiosis is known to cause respiratory insufficiency at sea level, and it has great significance when it occurs at high altitudes. A reduction in vital capacity without reduction of residual air volume has been found by Hurtado (2). Monge M. (3) has pointed out the difficulties in differential diagnosis between this disease, when it occurs at high altitudes, and the clinical picture for chronic mountain sickness, which will be described later.

The higher incidence of patent ductus arteriosus at high altitudes was first reported in 1952 by Alzamora-Castro *et al.* (4). In a recent paper Peñaloza *et al.* (5) describe a parabolic relationship between this condition and altitude.

Pulmonary edema of high altitude may occur either in acclimatized dwellers returning to a high altitude after a stay at sea level or in newcomers to a high altitude. In both cases, exercise has usually preceded the onset of the clinical picture. Its occurrence was first pointed out by Hurtado (6). Marticorena *et al.* (7) have recently made a detailed description of this disease in thirty-six cases. Arias-Stella and Kruger (8) have described, in two adult cases studied at autopsy, the occurrence of pulmonary hyaline membrane similar to that found in newborn cases at sea level.

Patients with sickle-cell disease who are asymptomatic at sea level may develop splenic infarction when traveling at high altitudes. Aste-Salazar (9) has studied several patients with this condition. This disease is important to countries like Peru, where a fairly large Negro population lives at sea level but within easy reach of high-altitude places.

Among the clinical pictures inherent to life at high altitudes, acute and chronic mountain sickness are important. Acute mountain sickness develops frequently during ascent to a hypoxic environment. It may occur at all ages and is difficult to predict, since it may occur with no apparent precipitating cause in travelers who have often been in high places before. It is usually brought on or aggravated by exercise. Its duration is short and is usually followed by a sense of well-being as acclimatization ensues.

Chronic mountain sickness was described by Monge M. (10) in 1928. It is characterized by congestive symptoms, reduction of the arterial oxygen hemoglobin concentration below physiological levels, and excessive polycythemia. Hurtado (11) considers hypoventilation the causative factor. This disease may not be an isolated clinical picture but rather one affecting a considerable portion of the high-altitude population. Its incidence would increase as a function of altitude. Whether or not there is a certain altitude below which it does not occur is unknown.

A statistical study of the hematocrit distribution at high altitudes shows that the hema-

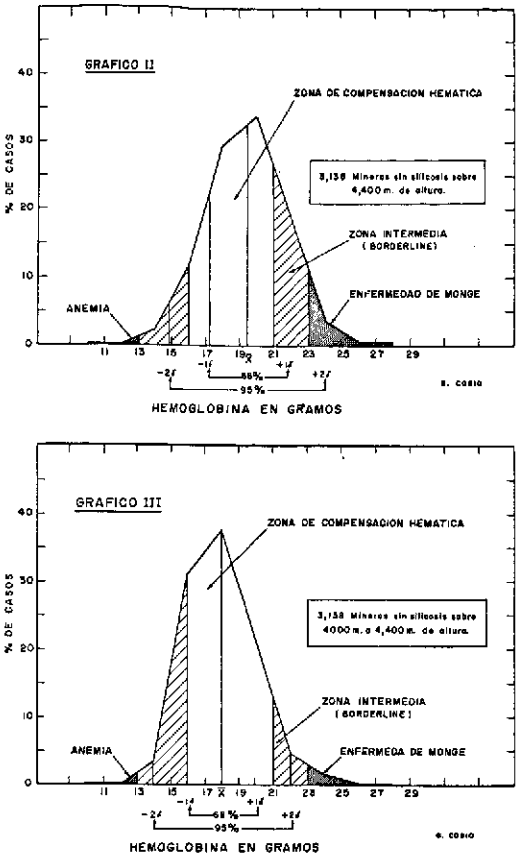


Figure 1. NORMAL DISTRIBUTION CURVE OF BLOOD HEMOGLOBIN CONCENTRATION BETWEEN 4,000 AND 4,400 M ABOVE SEA LEVEL, LOWER FIGURE, AND ABOVE 4,400, UPPER FIGURE. Note that the value of 23 g% taken arbitrarily as the sole diagnostic criterion of chronic mountain sickness is above the figure corresponding to two standards deviations above the mean in the lower figure. In contrast, the area considered chronic mountain sickness in the upper figure overlaps the area contained by two standard deviations above the mean. Therefore the hematological criterion cannot be taken by itself as a diagnostic tool since it does not differentiate between the normal and the abnormal population. (Figure reproduced by permission of the Instituto de Salud Ocupacional, Lima)

tological criterion when used alone in diagnosis of this disease is not valid. Thus, Figure 1, taken from an official publication of the Institute of Occupational Health of Peru (12) gives normal distribution curves for hemoglobin in two selected populations of apparently normal people. A hemoglobin concentration of 23 per cent or higher was arbitrarily considered diagnostic of chronic mountain sickness. It may be seen that the normal statistical area does not include this figure when the altitude is between four thousand and forty-four hundred meters (bottom figure). When the altitude is above that, the area considered as including chronic mountain sickness overlaps the one included in two standard deviations above the mean. Therefore, the hematological criterion cannot be used as a diagnostic tool, since by itself it does not make a differentiation between the normal and the abnormal population.

Lower-than-normal oxygen hemoglobin saturation is also taken as a diagnostic criterion. However, the normal variation of oxygen saturation is large and its correlation with polycythemia is poor (see Figure 2). The ventilation rate of the high-altitude native is lower than that of the newcomer. Thus the hypoventilation of chronic mountain sickness is only an accentuation of that encountered in the normal population.

This paper emphasizes how difficult it is to distinguish normal high-altitude physiology from

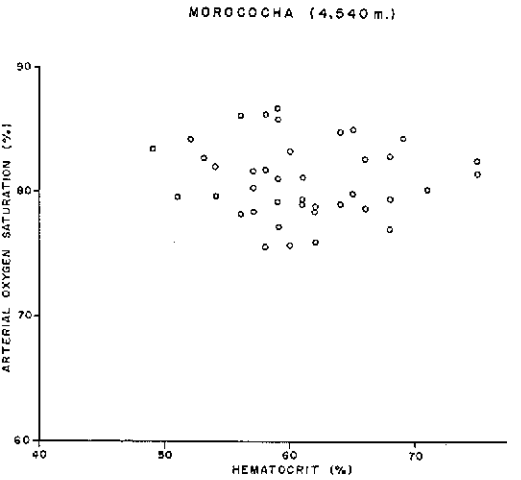


Figure 2. CORRELATION BETWEEN HEMATOCRIT AND ARTERIAL OXYGEN SATURATION AT 4,540 M ABOVE SEA LEVEL. The correlation is poor. The figure shows that marked polycythemia may occur in the presence of a physiological arterial blood unsaturation

the pathophysiology of chronic mountain sickness. Therefore the diagnosis of this disease should depend on symptoms of intolerance to high altitude. On the other hand, if the hematological criterion proved to be diagnositic or predictive of the disease, then it must be accepted that a large portion of the high-altitude population is affected by chronic mountain sickness and has lost its acclimatization.

The book *High Altitude Disease, Mechanism and Management* (12), by Monge M. and Monge C., surveys the old and recent literature on the subject.

The relationship between acclimatization to high altitude and chronic mountain sickness is of great importance in a mountainous country where low barometric pressure becomes a fundamental parameter in public health policy.

DISCUSSION: NATURAL ACCLIMATIZATION TO HIGH ALTITUDES

Moderator: I should now like to invite comments and questions about the subjects that have been presented so far.

Roche: I have just a minor comment about Dr. Moncloa's data on iodine metabolism at high altitudes. Sea-level inhabitants have served as control for high-altitude inhabitants; but in these two groups we have at least two variable parameters—altitude, which is the object of our study, and iodine intake, which is probably much higher near the sea. I suggest that a better control group for iodine clearances would have been a group living in a goitrous area at a moderate altitude. Perhaps this has been studied, in which case I should like to hear about it.

Moncloa: No, we have no controls at intermediate altitudes.

Caldeyro-Barcia: A question for Dr. Ceśar Reynafarje: What is the dissociation curve like in the llama?

C. Reynafarje: There are few experiments on this. I think only two llamas have been studied by Hall and some other people. The dissociation curve of hemoglobin is on the left compared with that of man.

Caldeyro-Barcia: Dr. Mithoefer, under what conditions was the pO_2 of 20 mm Hg for fetal blood obtained?

Mithoefer: That is a conservative estimate made by Dawes as a result of his survey of the literature on the subject. Actually, the literature gives a wide distribution of values for umbilical artery oxygen tension. Some people have said it was as low as 10 mm. For that graph I went by Dr. Dawes' opinion that probably the true value was between 20 and 25 to 30 mm. Measurement is difficult because of problems of anesthesia, of constriction of the cord at the time of birth; I don't think that the data permit anything but an intelligent estimate.

Caldeyro-Barcia: In the nonanesthetized human fetus in utero we have found pO_2 to be higher—20 to 35 mm Hg. This is in the blood of the cutaneous capillaries of the scalp.

Velásquez: Dr. Mithoefer has said that the oxygen drive of ventilation is absent in natives. We have studied the ventilatory response to oxygen given 100 per cent, 60 per cent, and 36 per cent, in all cases using both continuous administration and the De Jours oxygen test, and we found a depression of ventilation of about 25 to 30 per cent. So there does seem to be an oxygen drive in the ventilation of natives.

Mithoefer: I did not mean to imply that an oxygen drive could not be demonstrated—I think Dr. de Jours has shown it. My point was that low ambient oxygen tension is not responsible for the sustained hyperventilation at high altitude. In other words, although a potential oxygen hypoxic drive can be demonstrated, it does not necessarily imply that the ambient oxygen tension is what is sustaining the hyperventilation.

Neel: Are there any observations on serum uric acid levels in these groups? A related question: has an increase in clinical gout in acclimatized populations been observed?

Monge: I don't know about uric acid determinations done by good techniques; I don't really trust the chemical techniques used. They show no differences between high-altitude people and normal people at sea level. But I myself have seen typical cases of gouty arthritis not in normal natives but in cases of chronic mountain sickness with tremendous polycythemia. The last case I saw was a very young fellow who had a hematocrit close to 80 per cent; he had typical symptoms of gouty arthritis. Unfortunately, I was isolated and could not do a uric acid determination. Since the man was about to leave the hospital, I made a urinary collection as a simple test and put it in the refrigerator. The amount

* Dr. Moisés Behar, Director, Institute of Nutrition of Central America and Panama.

of urates in that urine was enormous, so I suspect that this was a typical case.

Behar*: In the data on blood pressure presented by Dr. Peñaloza it was evident that diastolic blood pressure did not increase with age in the high-altitude natives but did so in the foreigners living at high altitudes. He mentioned that they were of two different socioeconomic groups and had different diets. Among Indians in Guatemala living at what for this purpose can be considered a low altitude—only fifteen to eighteen hundred meters—diastolic pressures do not increase with age. This we think has to do with diet. Here is a factor that should be distinguished. It might also affect other parameters that have been measured in comparisons between residents and nonresidents of high altitudes.

Lahiri*: I think all of us agree that a given altitude the altitude resident will ventilate less than the recently acclimatized sea-level man, or, in other words, that sea-level man will hyperventilate more. We confirmed this on Sir Edmund Hillary's Himalayan expedition in 1964. We looked for the reason why the altitude residents ventilate less. The main conclusion is that their sensitivity to hypoxia is much less than that of the recent arrivals.

If I may show one or two slides, I think the point will be made clear at once.

In Figure 1 you see plotted the well-known CO_2 response curve: ventilation against pCO_2. On each line is a number indicating the oxygen pressure. This experiment was done at sixteen thousand feet. The upper family of curves shows the response of a lowlander recently acclimatized to that altitude; the lower one shows the response curves of a high-altitude resident (Sherpa). You see clearly that in spite of the variation in oxygen pressure from 33 to 200 mm Hg the ventilation response was much less in the case of the Sherpa subject.

These curves are analyzed in Figure 2 by plotting slopes of these lines against the corresponding pO_2. The lower curve, with the dots, repre-

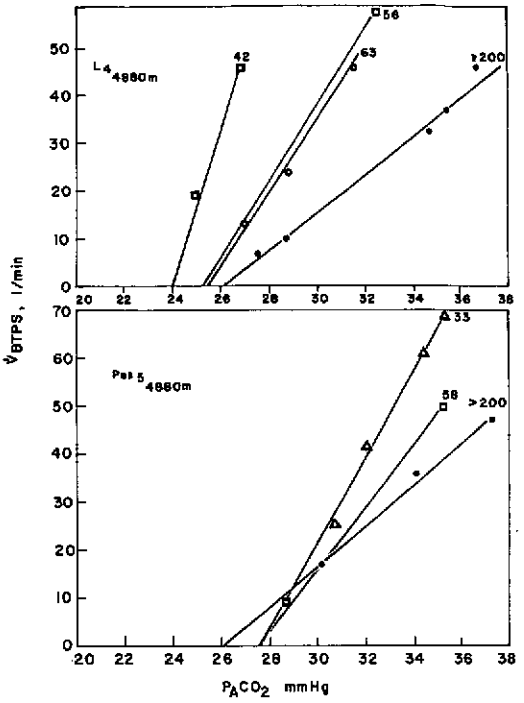


Figure 1. VENTILATORY RESPONSE TO HYPOXIA AND CARBON DIOXIDE IN ACCLIMATIZED SHERPA ALTITUDE RESIDENT (PEN_5) AND SEA-LEVEL RESIDENT (L_4) AT 4880 M. Note closed appearance of response lines in Sherpa indicating relative insensitivity to hypoxia

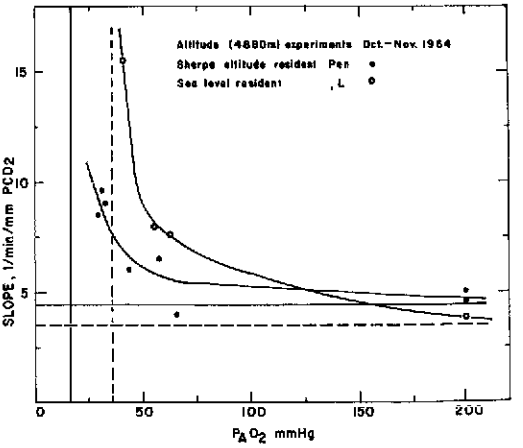


Figure 2. RELATIONSHIP BETWEEN pAO_2 AND SLOPES OF THE v-$pACO_2$ LINES IN SHERPA (PEN) AND SEA-LEVEL RESIDENT (L) AT 4880 M. This brings out altitude resident's greater tolerance of and low sensitivity to hypoxia

sents the response of the Sherpa subject, the highlander; the upper one, with the open circles, pO_2—let us say about 200 mm Hg—the slopes

* Dr. S. Lahiri, visiting lecturer, Downstate Medical Center of the State University of New York, Brooklyn, U.S.A.

that of the acclimatized lowlander. At high of the lines for Sherpa and lowlander are similar. If anything, this Sherpa slope shows a slightly smaller value. This means that the CO_2 response of the Sherpas may be slightly lower but not significantly different. But the other part of the curve shows the Sherpa subjects' response to hypoxia to be less in terms of both sensitivity and tolerance. In summary, therefore, one can say that the Sherpa subject's sensitivity to low oxygen is significantly different from, significantly smaller than, that of the recently acclimatized man. I should like to add that when one of the Sherpa highlanders came down to Calcutta (sea level) and was studied again, he maintained this characteristic of low response to hypoxia.

Mithoefer: I should like to ask Dr. Moncloa a question about his very interesting observations on the difference in responsiveness to an injected dose of catecholamine or adrenal cortical steroid. We know that the blood volume of high-altitude residents is considerably higher than that of sea-level residents. I wonder if this is taken into account in arriving at the dose —is a correction made for it, to see whether the epinephrine injected into high-altitude residents is actually being diluted by a larger pool of blood, or is the dose based on body weight, or what?

Moncloa: In the instantaneous intravenous injections of ACTH, we injected on a body-weight basis. The so-called standard ACTH test is an eight-hour infusion. I am not aware of any report that ACTH goes into the red cells. On the other hand, the plasma volume is normal at high altitude. In regard to the epinephrine, this is endogenous epinephrine induced by hypoglycemia, and certainly the insulin dose was on a body-weight basis.

Chiodi: I want to make a short comment on what Dr. Mithoefer said about our study on the CO_2 sensitivity of the respiratory center in two high-altitude residents. Our first publication dealt with three residents, two at 4,000 m and one at 4,515 m. In later publications we presented twenty long-term residents at different altitudes in whom no increased CO_2 sensitivity of the respiratory center was found. This result seems to be confirmed by the findings of Severinghaus in his study on the pH of the CSF in high-altitude natives.

Moderator: I must say that our findings are not similar to Dr. Chiodi's. In many observations, we have found in the native an increased sensitivity of the respiratory center to CO_2. The response of newcomers is much higher, but in the native it is higher than in the man at sea level. At least, that has been our experience.

Rahn: I was very much interested in Dr. Monge's analysis of chronic mountain sickness. From his presentation I would take it that pCO_2 of the blood might be as good a criterion as any other. Is that correct?

Monge: Yes, it is. I think that pCO_2 is a good criterion in diagnosis—because it checks, first, with Dr. Hurtado's demonstration that cases of chronic mountain sickness hypoventilate and should have a higher pCO_2, and also with Dr. Severinghaus' recent studies showing the same thing.

Just a few days ago we posed the following problem to the computer at Johns Hopkins: which is more sensitive, pCO_2 or arterial oxygen saturation? The answer was that the diagnostic approach can be varied according to the ventilatory rate; in other words, it was in the form of curves that move along with the ventilatory rate. So I am not yet sure whether pCO_2 is ideal. But the pCO_2 electrode seems to me much easier to use and more to be trusted than the pO_2 electrode. It is very simple to do an arterial puncture, or use capillary blood, and do a pCO_2 measurement with the microelectrodes now available. Perhaps this would be a nice tool to give us laboratory parameter in addition to a clinical parameter.

Our average pCO_2 for chronic mountain sickness is 40 mm Hg—exactly the same as for Lima, at sea level—as against 30 or 32 for the normal native. That would mean that these cases are not ventilating much, just keeping the same pCO_2.

Moderator: I am glad Dr. Rahn asked this question because I agree with Dr. Monge that there are many other criteria besides the hematological one of polycythemia for diagnosing chronic mountain sickness. As he said, we find no hyperventilation in most cases of chronic mountain sickness. Their ventilation is the same as that found at sea level, and when we give them CO_2 we find as a rule a ventilatory response much lower than is found in the healthy native; they respond almost the same as at sea level. It seems to me that something is happening to the respiratory center. Perhaps the chain of events is as follows: the respiratory center fails; there is hypoventilation; when there is hypoventilation at such an altitude the degree of hypoxia is greatly increased; the stimulus to the bone marrow, consequently, is increased. This, in a way, is the whole picture for chronic mountain sickness. However, I agree that sometimes we have difficulty in making a correct diagnosis; I believe that too many people have been wrongly diagnosed as having chronic mountain sickness.

Chiodi: I think that a definition based on a few parameters, as proposed here, will not include many cases of what I consider true chronic mountain sickness. My own case might be a good example. Fifteen years ago, after living for twenty-six months at 4,000 m, I had a meningeal hemorrhage; six months later I had a right hemiparesis. My alveolar pCO_2 was around 28 mm Hg (the average alveolar pCO_2 in old residents was 34 mm Hg), because of a rather high hyperventilation with increased sensitivity of the respiratory center to CO_2. The hemoglobin values were not above normal for that altitude. Since then I have lived in lowlands with no hemorrhagic accident, but the few times I have tried to go back to a high altitude the symptoms started again.

To avoid some of the confusion created by the present definition of chronic mountain sickness, I think it would be better, until we know more about chronic hypoxia intolerance, to classify as chronic mountain sickness all cases that show signs and symptoms of a progressive intolerance to chronic hypoxia but in which, for reason of rather short residence (months or a few years), a previous process of complete acclimatization could not be clearly established. The name *Monge's disease* or *Monge syndrome* should be reserved for cases of chronic hypoxia intolerance in which a previous complete acclimatization could be fairly assumed. It is perhaps the existence of this long previous acclimatization that gives Monge's disease such particular symptoms as exaggerated polycythemia, decreased CO_2 sensitivity of the respiratory center, and increased alveolar pCO_2.

Moderator: I think it must be remembered that at high altitudes we are dealing with human organisms, just as at sea level; many pathological processes go on at high altitudes that are not dependent on the environment but may impair adaptation to it because they mean a breaking down of the physiological condition. A case of anemia at high altitude has a good many symptoms that are not found in anemia at sea level. But, at least in my opinion, this is not chronic mountain sickness. I think the term *chronic mountain sickness* or *Monge's disease* must be restricted to clinical cases in which the whole syndrome is due or related to the environment as an etiological factor.

Chiodi: Cerebral blood-flow measurements showed that my cerebral vessels are not very sensitive to the dilating effect of hypoxia and respond normally to the vasoconstrictor action of hypocapnia. The lack of compensation for the hypocapnic vasoconstriction would enhance brain hypoxia. Cerebral angiography showed no anatomical abnormality in my brain vessels. The fact that while living at low altitudes I had no trouble at all for fourteen years, after two cerebral hemorrhages in six months at a high altitude, and the recurrence of the symptoms every time I tried to go back are in favor of the hypothesis that I had a chronic mountain sickness caused by my own particular trait—a low sensitivity of the cerebral vessels to oxygen lack.

Moderator: May I now invite Dr. von Muralt to give his paper, which is on acquired acclimatization to high altitudes, and then Dr. Velásquez to speak on acquired acclimatization to sea level. Dr. Kellogg will then discuss the regulation of breathing in acquired acclimatization.

ACQUIRED ACCLIMATIZATION: TO HIGH ALTITUDES

Alexander von Muralt

Mountain climbing became a challenge to sportsmen in the middle of the last century. Whymper's first ascent of the Matterhorn in 1866 opened up a general campaign to climb all the peaks in the Alps, the Himalaya and Karakorum, the Andes of South America, and the Rocky Mountains of North America. Mountain sickness was rarely reported by these climbers, because in climbing the body has time to acccommodate itself to the gradual decrease of partial pressure of oxygen with altitude (hypoxia). Father José de Acosta, however, encountered mountain sickness in South America as far back as 1596 and described it vividly. Only in 1878 was the real reason for this phenomenon discovered by Paul Bert (1), who clearly explained the discomfort as due to oxygen lack. The first reliable observation of physiological changes at high altitudes was made in 1890 by Viault (2), who measured the increase in red blood cells in man during his expedition to the Andes. The present paper deals with the normal adaptive reaction to high altitude, which we call acclimatization.

There is a marked difference in acclimatization between a subject who reaches a high altitude passively by transportation and one who does so actively by mountain climbing. In considering body adjustments to the hypoxia of high altitude it is advisable to distinguish three adaptive processes: accommodation, acquired acclimatization, and natural acclimatization (3, 4).

The clearest picture of the sequence of the first two of these processes is obtained by bringing a subject to high altitude passively and keeping him there for at least ten days at rest or with only very moderate exercise. Fleisch and Von Muralt (5), aided by a group of researchers, have done this with several hundred subjects during four years under standard conditions. The immediate responses of the body to the exposure are regulatory reactions, such as can be observed under heavy exercise or any other stress. For these reactions, which have a tendency to disappear with a prolonged stay at high altitude, the term *accommodation* to hypoxia was proposed. At some time during exposure a new set of phenomena set in and "take over"—an increase in the production of red blood cells, a decrease of buffer base in the blood, a shift in the respiratory regulation to a new equilibrium, a shift in the dissociation curve of hemoglobin, and so on. These changes, specific reactions of the body to a permanent hypoxia, develop slowly at high altitudes and are called acquired acclimatization (4). It is obvious that accommodation is a first step toward acquired acclimatization, in which the individual feels no effects of altitude at rest or during moderate exercise. But if it comes to heavy exercise or maximal performance, he is unable to achieve the same performance as at sea level. Comparison demonstrates clearly that an altitude native has a higher degree of acclimatization. This is why Hurtado (4) insists on the distinction between acquired and natural acclimatization. (The term *adaptation to high altitude* should be avoided because it is reserved for genetically transmitted milieu adaptations.)

The following effects accompany passive transportation to high altitude and a sojourn of at least ten days at rest or under moderate exercise. They are listed in order of their appearance in man:

The first symptom, observed even during the ascent, is hypocapnia (loss of CO_2) in the blood. At 3,500 m the partial pressure of CO_2 in the alveolar air and in the blood drops from a normal value of about 40 torr. (1 torr. = 1 mm Hg) to 29 torr., which results in a respiratory alkalosis of the blood and an alkaline shift in the cerebrospinal fluid. The pH of the plasma increases slightly. The minute volume $\dot{v}T$ of respiration is somewhat increased at rest and

rises more rapidly with exercise compared to the same performance at sea level. The driving force of CO_2 on respiration is obviously increased during ascent and upon arrival at high altitude, with the result that the relation between $\dot{v}T$ and $pACO_2$ is changed. This relation can be described by the following formula (6):

$$\dot{v}T = S(pACO_2 - B)$$

The relation between $\dot{v}T$ and $pACO_2$ for a given pAO_2 (partial alveolar pressure of oxygen) is linear. But at a given point of $pACO_2$ this linear function stops and a "shoulder" or "dogleg" appears (see Figure 1), which will be discussed below. Extrapolation of the linear function to the abscissa yields the intercept or the value for B; S is the slope of the linear function. Figure 1 shows that with a decrease of pAO_2 this slope increases and that there is at the same time a shift of the intercept to the left. There is unanimity that, in hypoxia, S immediately increases; as for B, some authors maintain that it remains unchanged and others

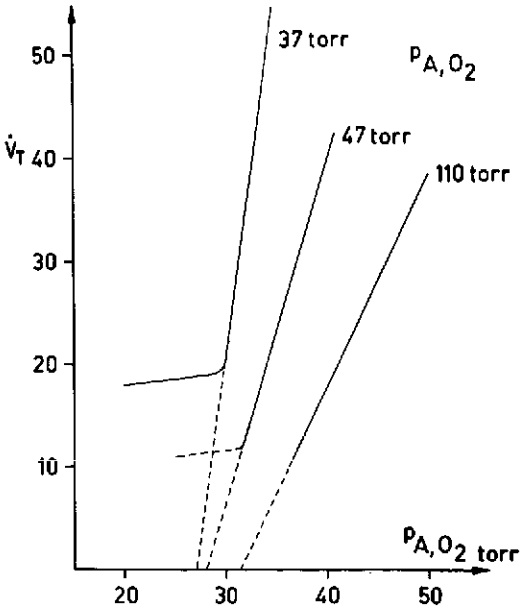
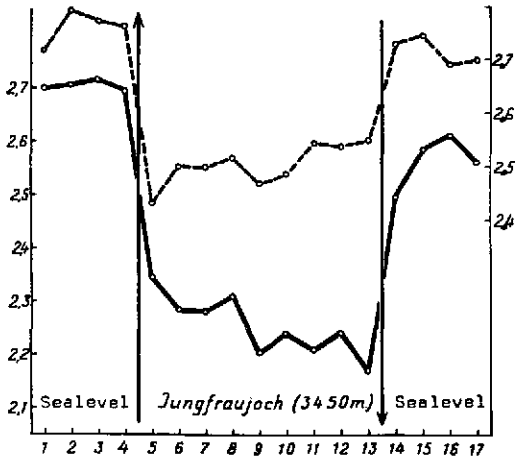


Figure 1. SCHEMATIC REPRESENTATION OF NIELSEN AND SMITH (7) FINDINGS ON RELATION BETWEEN VENTILATION RATE, v_T, AND PARTIAL PRESSURE OF CO_2 IN ALVEOLAR AIR, p_{ACO_2} AT 3 CONSTANT PRESSURES OF ALVEOLAR O_2, p_AO_2

that it becomes smaller. Our experience on Jungfraujoch (3,500 m) has been that B shifts markedly but slowly toward a value of 25 torr. CO_2, reaching an end value after seven to ten days at high altitude (8). Cunningham, Patrick, and Lloyd (6), in their experiments with Oxford students breathing hypoxic gas mixtures, found that B remains unchanged at a value of 37.7 ± 2.8 torr. CO_2. This explains the differences in opinion: at high altitudes a shift of B to the left (smaller values) occurs slowly, as a sign of acquired acclimatization; in short-term experiments with gas mixtures there is only the increase of S, as a sign of accommodation to hypoxia. This example shows how useful it is to separate the two terms.

As can be seen from Figure 1, the level of the shoulder or dogleg ($\dot{v}T$) rises in hypoxia. To describe these shifts in physiological terms, it may be said that at high altitude the excitability of the CO_2 receptors increases, the threshold for the CO_2 stimulus decreases, and at rest ("shoulder") the driving force of CO_2 on respiration is also increased.

From our point of view all these changes are due to a general change in the response of the autonomic and central nervous system to external stimuli, which is a general phenomenon of accommodation and acclimatization to hypoxia at high altitudes. Fleisch and his coworkers (Grandjean, Posternak, Waridel, and Zwahlen) and Von Muralt and his group (Plüss, Sommer, Tschirren, Werner, and Wiesinger) have found the following changes in the nervous response (5, 9): Upon the arrival of the subjects at Jungfraujoch there immediately appears a general lowering—between 25 and 40 per cent—of the thresholds for all external stimuli, such as CO_2, touch, pain-producing stimuli, light, and stimuli affecting taste and smell. Studies on patellar reflex and pupillar reflexes showed a drop in threshold, a shortening of reflex time, and an increased response. Optical reaction time is shortened. All these effects disappeared when oxygen was administered. The amplitude of equilibratory movements is diminished. Measurements of adapta-



Ordinate left: threshold of reflex (log.)
Ordinate right: threshold for touch (log.)
- - - - average of threshold for touch, 32 subjects
——— average of threshold for patellar reflex, 26 subjects

Figure 2. CHANGE OF THRESHOLD FOR TOUCH AND FOR PATELLAR REFLEX AT HIGH ALTITUDE. After Grandjean (9)

tion to the dark showed a lowering of threshold due to increased visual sensitivity, which also produces a smaller pupillary diameter under standard illumination. The rhythmical diurnal and short-period oscillations of the pupil disappear in the first days at high altitude and reappear with acclimatization. We feel that this rapid increase in response of all nervous functions so far examined is the primary process of accommodation of the body to the new environment and that all the other changes might be secondary. This hypothesis needs further verification, especially with regard to the shifts that occur between accommodation and acquired acclimatization. Figures 2 to 4 give some examples of these very marked effects.

The question arises, What is the adaptive value of the increase in ventilation rate at high altitudes? On this point I should like to quote Arthur B. Otis (10): "The hyperventilation which occurs in residents at altitude is clearly of adaptive value. The higher the ventilations the less is the amount of oxygen removed from each volume of inspired air. Thus, an increased ventilation raises the pO_2 in alveolar gas and, as a result, the pO_2 and oxygen content of arterial blood are increased."

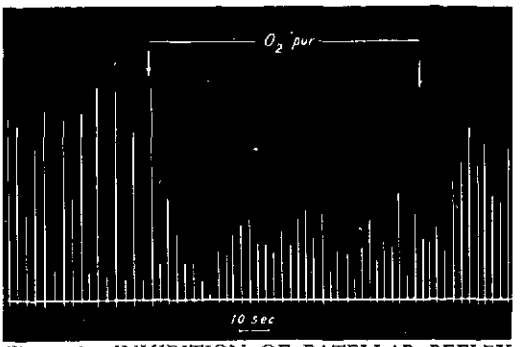
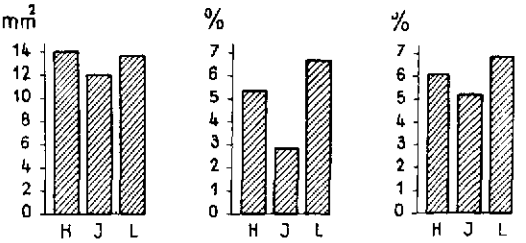


Figure 3. INHIBITION OF PATELLAR REFLEX DURING INHALATION OF OXYGEN AT HIGH ALTITUDE. After Grandjean (9)

As a result of this hyperventilation, respiratory alkalosis develops and the pH of blood plasma increases slightly. This is only temporary, because the kidney immediately regulates this tendency by a reduction in the excretion of ammonia and acids, an increase in the excretion of buffer base, an increase of pH in urine, and diuresis.*

This alkalosis reduces gastric secretion with regard to HCl production, amount of gastric juice, but the pH remains in the acid region. In the blood whole buffer base decreases, and as a result the pH of plasma returns to almost normal values.

* For the literature see Grandjean (9) and (all in 5) Stämpfli and Eberle, Schönholzer and Cottier, Schönholzer and Gross, and Schönholzer, Gross, and Marthaler.



Left: pupillary diameter in mm² near sea-level (H and L) and on Jungfraujoch (J), average of 10 subjects
Middle: pupillary diurnal oscillations, average of 10 subjects in % deviation of average diameter
Right: pupillary rapid oscillations, average of 10 subjects in % of average diameter

Figure 4. PUPILLARY DIAMETER, PUPILLARY DIURNAL OSCILLATIONS AND PUPILLARY RAPID OSCILLATIONS AT HIGH ALTITUDE (J). After Wiesinger and Werner (5)

There is a marked difference between the apparent increase in ventilation and the oxygen uptake. Whereas ventilation in exercise increases notably at high altitude, the oxygen uptake for the same amount of exercise does not vary (see Figure 5)—an old finding regularly confirmed by recent work.

As was pointed out at the beginning, the increase in the number of red blood cells is one of the most striking regulations of acquired acclimatization. Figure 6 illustrates the data available in the literature. At the same time the number of reticulocytes in blood and in the bone marrow increases, leveling off according to the altitude. A higher rate of iron utilization and iron turnover rate in plasma and red cells has been observed (4). There is an increase in platelets, a transient increase in eosinophils, and a decrease in lymphocytes, which corresponds to the observed increase in ACTH in the blood (12, 13, 14).

One of the great problems of today is the nature and mode of action of the erythropoietins in blood. There seem to be a thermostable and a thermolabile fraction, both probably elaborated in the kidney, acting directly on the bone marrow. One stimulates the production of hemoglobin, and the other an increase in red blood cells. Since they have very little or no effect on man at sea level, it looks as if the erythropoietins could act efficiently only on a sensitized (by hypoxia?) bone marrow. There

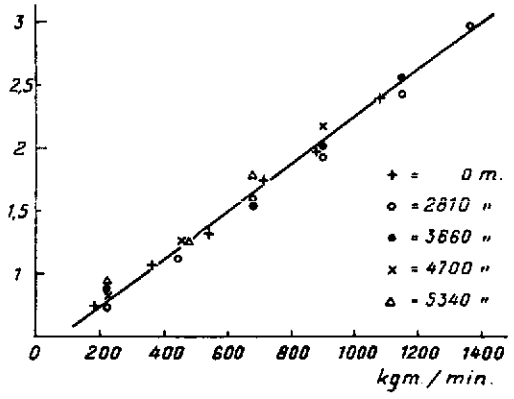
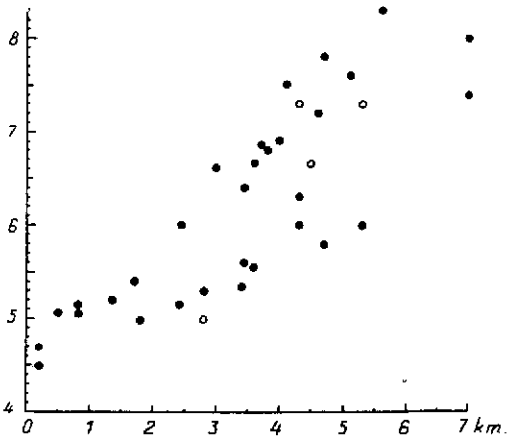


Figure 5. OXYGEN UPTAKE AS A FUNCTION OF WORK PERFORMED AT VARIOUS ALTITUDES. After Christensen (11)



● data from tourists after several days of sojourn
○ data from natives of high altitude

Figure 6. INCREASE OF RBC AT VARIOUS ALTITUDES. After Grandjean (9)

is no doubt that the maximum of erythropoietins in the blood is found in man after three to four days at a high altitude (15). The results of these adaptive regulations are manifold: increase in oxygen capacity of the blood (from 20 ml O_2/100 ml blood to 33.5 ml O_2/100 ml blood), increase in total and circulating blood volume, increase in total blood hemoglobin.

A very interesting observation is the drastic reduction of the alveolar gradient for oxygen, which may be illustrated by a series of figures obtained by Hurtado (4):

	pAO_2	paO_2	pvO_2	Diff. A—V
Lima	96 torr.	87 torr.	42 torr.	54 torr.
Morococha	46 torr.	45 torr.	34.8 torr.	10.2 torr.

The gradient between alveolar oxygen tension and arterial oxygen tension, which at Lima is 9 torr., is only 1 torr. at high altitude. Thus, the oxygen tension drops in the alveoli at a ratio of 2.08, but in the arterial blood at only a ratio of 1.93. There are many other changes due to acquired acclimatization, which will be discussed by other speakers in this symposium. In concluding, I should like to point out an

aspect of general physiology that I consider of special interest.

In 1927 L. J. Henderson published a book entitled *The Fitness of the Environment* (16), in which he showed that oxygen was unique in its behavior. The essence of his thesis was this: not only has life adapted itself to the environment, by the survival of the fittest, but the environment itself is fitted for life. Oxygen in the atmosphere of the earth is a key unlocking the stores of energy in the living body. This environment of oxygen in our atmosphere is dealt with by almost all living beings by means of regulating mechanisms that lead to equilibria, which Walter Cannon (17) called homeostasis. Within certain limits these can balance off changes in the outside world. Human beings are able to accommodate to changes in oxygen partial pressure from 150 torr. downward to 90 torr. and upward to 800 torr. When the limits are passed, body homeostasis is endangered—at the lower end by oxygen lack and dysfunction, at the upper end by inhibition of many enzymes (oxygen poisoning). Since the atmosphere of our earth does not provide high oxygen tensions, all processes of accommodation are directed toward balancing the immediate effects of low oxygen tension or hypoxia. There is a remarkable range in the regulation of oxygen uptake between rest and heavy exercise—from 250 ml to 5000 ml per minute, probably the greatest range to be found in any of the homeostatic mechanisms. The oxygen demand of the tissues is the regulating factor. It is monitored by a system of information that which flows into the regulatory centers controlling respiration, heart activity, blood flow, blood production, and many other functions. It seems to me very interesting that the first reaction of the autonomic and central nervous system, which is extremely sensitive to oxygen lack, to a not-too-pronounced hypoxia is increased excitability and responsiveness. I consider this an "emergency reaction" in Cannon's sense (18) or, in W. R. Hess's terminology, an "ergotropic reaction" (19). Acquired acclimatization is a defense against an imminent danger, which a normal human body can fight successfully if it is not too great.

ACQUIRED ACCLIMATIZATION: TO SEA LEVEL

Tulio Velásquez

It would be particularly rewarding to figure out how a high-altitude-born physiologist would describe a recently discovered sea-level man. Take, for instance, the very well known fact that systemic blood pressure is around 100 or 110 mm Hg in altitude natives. What would our physiologist think of the higher blood pressure of sea-level man? How would he judge the tendency of this pressure to increase with age and eventually, for unknown reasons, to develop pathological states leading to heart failure and death? Would he consider sea-level systemic blood pressure as being normal, or would he call it hypertension?

It is possible that small animals exposed in chambers to high oxygen pressures do not feel the same anguish and distress as the ones exposed to hypoxia; it is even possible that they feel quite all right. But they die just the same. The lack of symptomatology in high-altitude people transported to sea level may merely conceal some aspects of the process of adaptation in which the physiological changes imposed on the body by the environment would cause a lowering of physical and physiological capabilities and decreased resistance to disease.

This idea was advanced by Monge in 1934 (1). He reported to the IX Pan American Sanitary Conference, held in Buenos Aires, that altitude natives transported to the coast for army service developed tuberculosis more easily than sea-level men from similar rural places.

It is well known that altitude natives will develop anemia after some time at sea level. Donoso (2) reported in 1947 that his Bolivian altitude athletes were unable to repeat at sea level their previous performances—which had usually been in La Paz, at 12,240 feet—especially in events calling for strenuous effort.

There is also almost general agreement among observers who go back and forth between low and high altitudes that a more or less accentuated feeling of tiredness, nervous excitability, and emotional instability exists during the first few hours after descent from a high altitude.

Scientific literature on the subject is very scarce, especially in relation to altitude natives. Some work has been published on sea-level men previously adapted, for different but always short periods, to high altitudes. In 1928, Hurtado (3) reported on changes in the pulmonary capacity of altitude and sea-level natives living at high altitudes when they were transported to lowlands. In 1948, we published an investigation made under the direction of Monge (4). The subjects, whose homeland was at 10,170 feet, were transported to 14,900 feet and kept there for two weeks before being taken to sea level, where they were studied for eight weeks. Prominent changes in heart activity (EKG, pulse rate) and in the organ's size and position were reported. C. Reynafarje (5) has published data on blood morphology during adaptation to sea level. He found hematological changes still taking place eight months after arrival at the coast.

In the hope of eventually finding the basic differences, if any, between sea-level and altitude natives, we are studying some physiological parameters of the process of adaptation of altitude-adapted persons—either natives of the highlands or sea-level-born subjects sojourning for long periods in the mountains—to the coastal environment. This report deals with two groups of subjects: altitude natives and sea-level natives previously adapted to altitude for varying lengths of time.

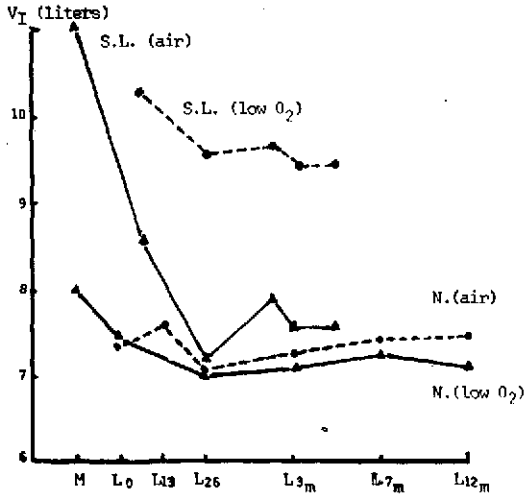
The altitude studies were done in Morococha, at 14,900 feet; the sea-level studies in Lima, at 450 feet. Every subject was first studied in his own evironment, then was transported passively to the other. Some of the lowlanders

sojourned in Morococha twenty and thirty-five days, others for eight months. At sea level, they were followed for periods ranging from the very first hours to one year. All the subjects were young and healthy, with definite physiological characteristics belonging to their places of origin. In many of the tests, oxygen mixtures were used to simulate at either altitude the conditions of the other with respect to inspired pO2.

Figure 1 shows resting ventilation in both groups. Resting ventilation at Morococha is much higher in lowlanders after eight months of adaptation than in altitude natives. This difference persists at Lima: two days after arrival it is 19 per cent higher. With time, the difference becomes smaller.

If room air is replaced by a low O_2 mixture (11.8 per cent), ventilation increases very little in natives, while in sea-level subjects it is 36 per cent higher than the values for natives. This is a marked difference.

Respiratory response to CO_2 in twenty-eight altitude natives is represented in Figure 2. Each point on the graph represents the average of the last three minutes of a fifteen-minute period of breathing a mixture giving an inspired pCO_2 of 37.5 mm Hg. The individual differences are so great that the average has no statistical significance. The group has therefore been divided into three subgroups—depending on intensity of response—whose average is statistically significant. The first subgroup has a ventilatory response 350 per cent higher than the resting value, the second, between 350 and 500 per cent; and the third more than 500 per cent. The difference between groups persisted at sea level, though both the absolute and the relative values tended to diminish.



M = Morococha
L = Lima
0, 13, 26 = days at sea level
3m, 7m, 12m = months at sea level

Figure 1. RESTING VENTILATION AT DIFFERENT PERIODS OF ADAPTATION TO SEA LEVEL

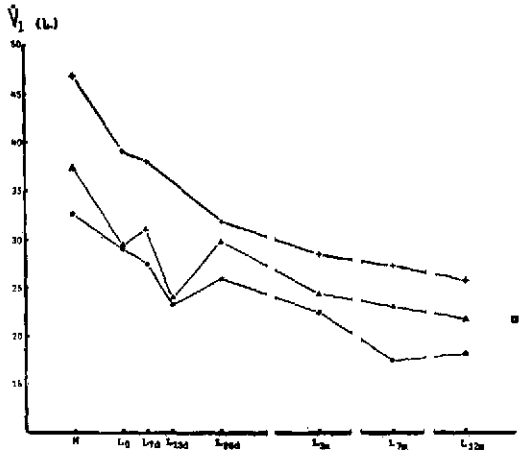


Figure 2. VENTILATORY RESPONSE TO CO_2 IN THREE GROUPS OF ALTITUDE NATIVES DURING ADAPTATION TO SEA LEVEL. Volumes in liters (BTPS). Small square at right represents data on sea-level natives

When the inspired gas at Morococha is CO_2 + high O_2, the ventilatory response is lower (which should mean the elimination of the hypoxic drive). As Figure 3 shows, CO_2 + low O_2 mixture in Lima produces no definite reaction but follows the trend of the response to CO_2 and air.

Figure 4 represents the ventilatory response to CO_2 of sea-level subjects previously adapted to altitude. They were divided into two groups, also on the basis of intensity of response to CO_2 when tested at Morococha; the same difference even before ascending is easily seen.

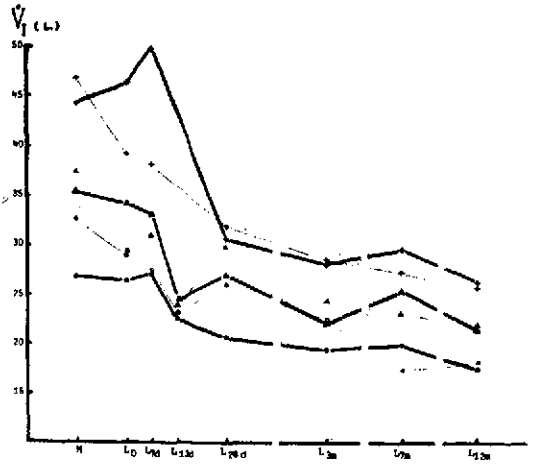
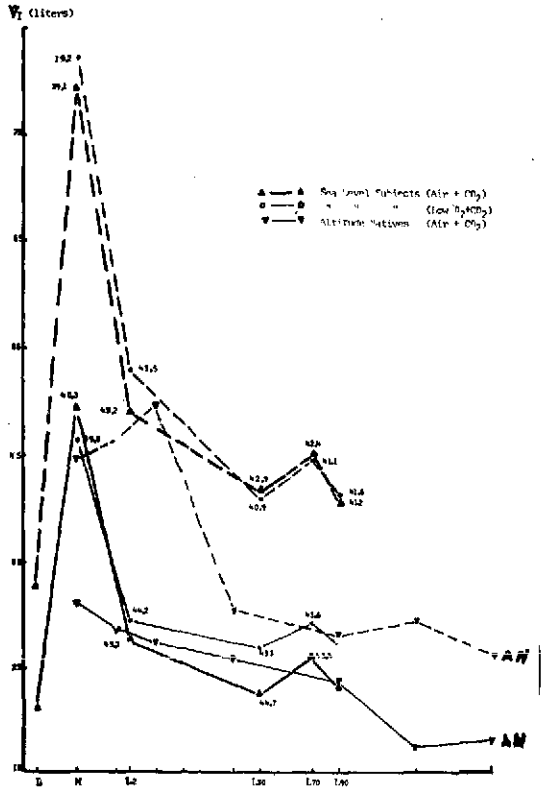


Figure 3. VENTILATORY RESPONSE TO CO_2 IN ALTITUDE NATIVES BREATHING MIXTURE CONTAINING LOW OXYGEN AND CO_2. Volumes in liters (BTPS). Light lines are those in Figure 2



AN = 2 groups of altitude natives, presented for comparison

Figure 4. VENTILATORY RESPONSE TO CO_2 IN SEA-LEVEL SUBJECTS BEFORE ASCENDING, AFTER 8 MONTHS AT 4,540 METERS, AND DURING READAPTATION TO SEA LEVEL

When both groups are compared with similar ones of natives, the difference is very large. One group, even after three months at Lima, gives a response higher than before ascending.

The pO_2 is given at any particular point; it is certainly not responsible for the difference. It is important to notice that the differences between groups (and between individuals) in response to CO_2 is very large; some sea-level groups have a higher response than altitude subjects, others the opposite. Both results have been reported in the literature and discrepancies still exist.

MBC in altitude natives is of the same order of magnitude as in sea-level subjects, especially in view of the smaller body size of altitude natives, as may be seen in Figure 5. In both groups, highlanders and lowlanders, MBC decreases immediately after descending from the mountains and later tends to recover. At al-

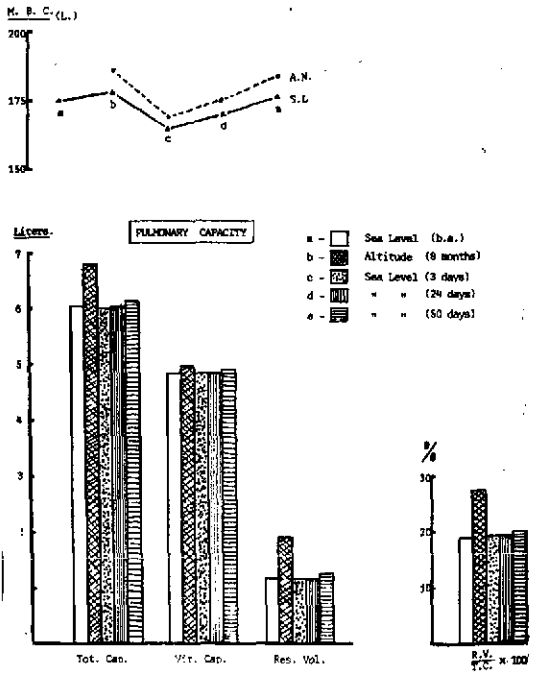


Figure 5. ABOVE: MAXIMUM BREATHING CAPACITY IN LITERS (BTPS). BELOW: CHANGES IN TOTAL PULMONARY CAPACITY AND ITS COMPONENTS OF SEA-LEVEL SUBJECTS BEFORE ASCENDING, AFTER 8 MONTHS AT 4,540 METERS, AND DURING READAPTATION TO SEA LEVEL

titude, two factors work in opposite directions to help or to counteract the respiratory muscular effort: diminished density of the air and the probable increase in lung stiffness due to congestion. Just after descending, only the second remains, and it could be a factor in the reduction of MBC. The graph also shows the variations in pulmonary capacity of the sea-level subjects before ascending, after eight months at Morococha, and in Lima during readaptation.

Altitude causes a definite increase in total capacity due mainly to an increment of residual volume, although in three cases out of ten there was also an increase in vital capacity. The increase in residual volume could be explained by an increase in the tonus of respiratory muscles or a diminution of the elastic force of the lungs or both, but the changes in total capacity are difficult to explain in the same way.

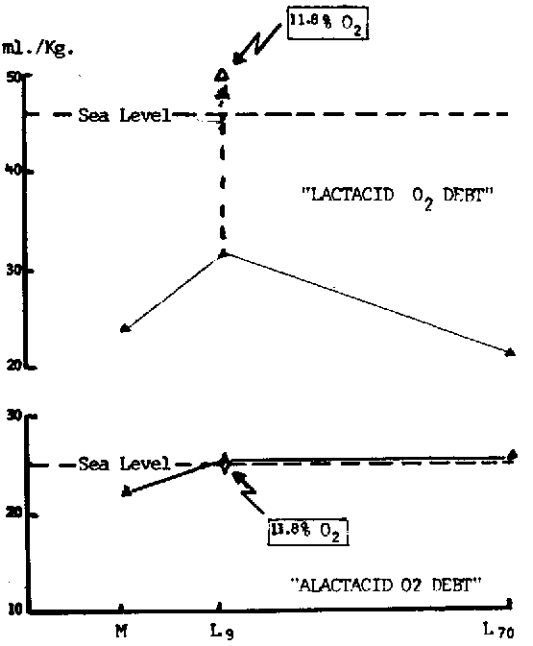


Figure 6. OXYGEN DEBT IN SUBMAXIMAL EXERCISE PERFORMED AT MOROCOCHA AND AT SEA LEVEL BY HIGH-ALTITUDE NATIVES. Dotted horizontal line represents oxygen debt in sea-level subjects performing at Lima

Physical Activity

Some of the physiological aspects of muscular activity are being investigated in altitude natives during their adaptation to sea level.

Two types of exercise have been used: submaximal (running at 12 km/hour on a 5.8 per cent ascending grade) and maximal (running at 15.6 km/hour on a 14.5 per cent grade).

Figure 6 shows, in submaximal exercise, the two components—alactacid and lactacid—of the oxygen debt. The distinction is based on the use made of O_2 at recovery: in the latter instance oxidation acid; in the former, other oxidative processes.

The alactacid debt increases very little after the descent to Lima and does not change even when the inspired pO_2 is diminished on the tenth day. It is of the same magnitude as in sea-level subjects. The lactacid debt is much lower in altitude natives performing at Morococha than in lowlanders performing at Lima. The total oxygen debt is thus lower also, because of the similarity of the alactacid components at both altitudes. The lactacid debt has increased by the tenth day at sea level but is still far below sea-level values; by the seventieth day, the difference is even greater. The debt increases when, on the tenth day, the subjects perform while breathing low oxygen, which seems logical.

Table 1 shows the data on submaximal exercise. The oxygen uptake is 40 ml/kg/min, which is lower than the found value for sea-level men performing at Lima (42.35 ml/kg/min); the difference is small but consistent. By the tenth day at Lima, the O_2 uptake is a bit higher when breathing air but definitely smaller with low O_2 mixture. At the seventieth day, the O_2 uptake is lower than at altitude and significantly lower than in sea-level subjects. The rate of payment of the two components of the oxygen debt is given in terms of half the time for debt disappearance. The

TABLE 1. Oxygen Debt in Altitude Natives During Acclimatization to Sea Level: Submaximal Exercise (12 km/hour—5.8 per cent gradient)

ITEM	ALTITUDE	SEA LEVEL		
		After 10 days		After 70 days
	Air	Air	Low O_2	Air
Alactacid Debt (ml/kg)	22.45	25.60	24.70	23.90
Lactacid Debt (ml/kg)	24.00	31.60	49.60	20.41
Total Debt (ml/kg)	46.45	57.20	74.30	49.31
½ ADP (min.)	0.45	0.46	0.67	0.45
½ LDP (min.)	4.94	6.82	5.25	5.61
vO_2 (last min. exercise)	39.98	41.29	35.32	37.96
Hemoglobin (grs. %)	18.9	17.5		14.3

ADP: alactacid debt payment
LDP: lactacid debt payment
(vO_2 sea-level subjects: 42.35 ml/kg)

speed with which the alactacid debt disappears is the same at both altitudes and the same as in sea-level subjects, but decreases significantly (49 per cent) when low O_2 mixture is breathed ten days after arrival at Lima.

The rate of payment of the lactacid debt is faster in Morococha than it is in Lima for natives, but in altitude subjects transported to Lima it slows down on the tenth day (−38 per cent) and later increases again. It is important to note that if low oxygen is breathed the lactacid debt payment speeds up, approaching the figures obtained at altitude.

Lactate in venous blood taken at the end of the exercise is lower in altitude natives performing at Morococha than in sea-level subjects performing at Lima, as is shown in Figure 7. When highlanders perform in Lima, lactate tends to be the same or a little lower. It is significant that it is lower still when the performance is done while breathing low O_2 mixture, which is contrary to the changes in lactic acid.

Maximal Exercise

High-altitude natives performing in Morococha showed values for maximal oxygen consumption similar to those reported by us (6) and by Elsner (7), but definitely higher than the values found by Balke (8) in the same type of subjects (see Table 2). The average was 51.2 ml/kg/min, which compares quite well with sea-level values for untrained subjects. When the natives breath high oxygen mixtures (36.5 per cent), the oxygen uptake increased to 59.8 ml/kg/min; in one subject, it went from 54.1 ml to 68.3 ml. Maximum

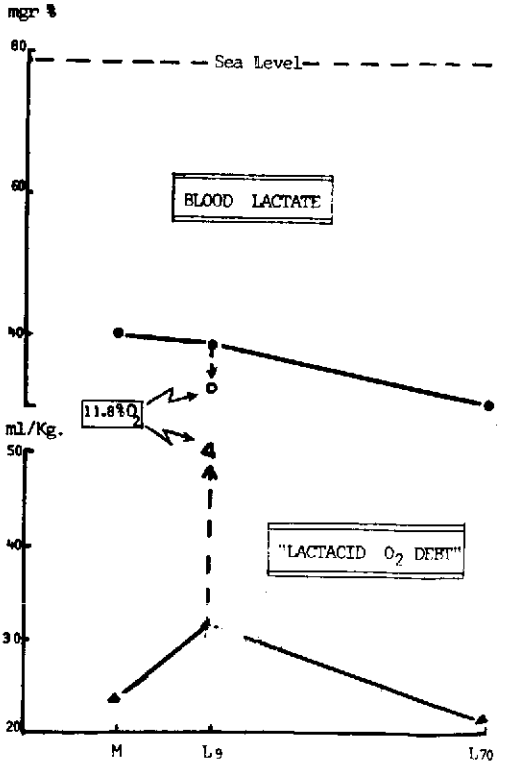


Figure 7. BLOOD LACTATE IN SUBMAXIMAL EXERCISE. Upper line is for altitude natives at Morococha and at Lima. Dotted horizontal line represents lactate values in sea-level subjects performing the same exercise at Lima

TABLE 2. Altitude Natives During Acclimatization To Sea Level: Maximal Exercise

VARIABLE MEASURED	ALTITUDE		SEA LEVEL		
			Air		
	Air	36.5% O_2	2 days	10 days	70 days
vO_2 (lts/min.)	2.92	3.53	3.36	3.24	3.10
vO_2 (ml/kg)	51.2	59.8	55.3	56.2	53.2
Pulse	188	182	182	190	186
vO_2/Pulse	15.5	19.4	18.4	17.0	16.7
Hb (grs. %)	18.9		17.5	17.1	14.3

vO^2 decreases at Lima two days after arrival, very definitely in two of the subjects. One week later the data show random changes; but at the seventieth day the maximum oxygen uptake moves downward, approaching sea-level values in three of the subjects.

Figure 8 relates ventilation to maximum O_2 consumption. At Morococha the subjects attained their maximum O_2 uptake using quite scattered ventilations. When high O_2 is given, ventilation falls in two subjects and changes very little in the others; ventilation seems to have been taxed in the first two subjects during the performance while breathing air, which should be one of the limiting factors. Two days after arrival, ventilation decreases in all cases at the same time as O_2 uptake. Later it increases in all, though in some there is a decrease in O_2 uptake.

This report is certainly very incomplete. However, it shows two things: First, even after seven months of exposure to sea level, the high-altitude natives retain some characteristics that make them different from lowlanders; in blood lactate in exercise and oxygen debt, whose behavior depends in some way upon intimate cellular processes, there is a definite difference between altitude and sea-level natives that has no tendency to disappear even when hemoglobin has decreased to sea-level values. Second, sea-level subjects returning to the lowlands after eight months' exposure to altitude do not exhibit the same characteristics as altitude natives. Whether the differences eventually disappear is something the present data do not show.

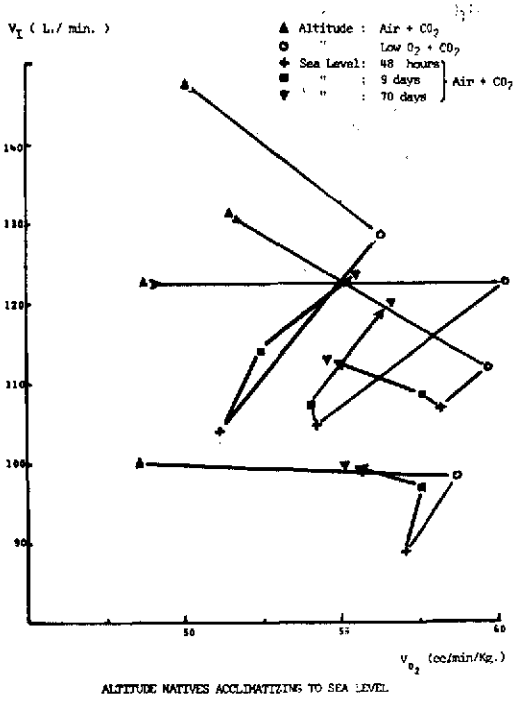


Figure 8. RELATIONSHIP BETWEEN VENTILATION AND OXYGEN UPTAKE IN MAXIMAL EXERCISE. Lines represents individual values in each of four altitude natives

ACQUIRED ACCLIMATIZATION: REGULATION OF BREATHING

Ralph H. Kellogg

The papers presented this morning dealt mainly with differences between natives of high altitude and sea-level residents; attention was focused on acclimatization as a set of attributes that some people have and other people do not have. This afternoon the emphasis has shifted to the changes that occur in sea-level residents after they have moved to a high-altitude environment or vice versa; here the focus was on acclimatization as a physiological process or a collection of physiological responses that progress with time. If we are to understand these processes and how they may relate to the very long-term end result in the high-altitude native, I think we should look at the very beginnings of the process of acclimatization, for at that stage we have a chance to analyze the sequence of physiological mechanisms by which any particular aspect of acclimatization is produced. With this in mind, I have been interested in the changes in the regulation of breathing that accompany a change of altitude.

When a person first goes to a high altitude or is otherwise made hypoxic, his breathing increases within a few seconds—which, as everybody knows, is attributable to stimulation of the respiratory center by nerve impulses arising from the chemoreceptors in the carotid and aortic bodies. This is a desirable adaptive response, because the extra breathing raises the alveolar and arterial oxygen pressure (pO_2) closer to that of the inspired air; but nobody would call it acclimatization, for it is too rapid. We think of acclimatization as something that is slowly acquired over an appreciable period of time.

On the other hand, it is well known that when a person remains exposed to a particular low oxygen pressure for several days or weeks, his breathing increases progressively beyond the level achieved through simple chemoreceptor stimulation in acute hypoxia. We consider this progressive increase to be one aspect of the process of acclimatization. Moreover, the restoration of normal oxygen pressure after such acclimatization has occurred does not immediately return the breathing to the control level, although there my be a slight, immediate decrease as the effect of chemoreceptor stimulation is shut off. The persistence of hyperventilation, which may outlast the hypoxia by days or weeks, is still another evidence of acclimatization because it too is a slow response, in this case taking a long time to stop rather than to start. Or one can look at it the other way around and say that it may take a long time to acclimatize to sea level.

Dr. von Muralt's paper pointed out that different aspects of acclimatization proceed at very different rates. I submit that there is no sharp line between acclimatization and the immediate response to hypoxia. Even the reflex hyperventilation that occurs initially from chemoreceptor stimulation takes a few seconds, and the slower, progressive increase in breathing may start rather promptly even if it takes a long time to become complete. In summary, I look at acclimatization as a collection of physiological responses differing only in time from the quicker responses of everyday laboratory experiments, and I should like to summarize for you how we have been attempting to analyze the ventilatory aspects of acclimatization in this way. To do this intelligibly, I must first summarize what some other people have been doing.

Over half a century ago Hasselbalch and Lindhard (2) measured their ventilatory responses to CO_2 inhalation while they were acclimatizing to an altitude of 3,290 meters in the Alps. They found that they became sensi-

tized to lower alveolar CO_2 pressures (pCO_2) and that stimulation from their metabolic CO_2 kept them hyperventilating even when they breathed oxygen to eliminate their hypoxia temporarily. The recent discovery by Mitchell, Loeschcke, and others (4) of medullary chemoreceptors responsible for much of the ventilatory stimulation from CO_2 helps us understand this better. They have found that a region rather superficially located in the ventrolateral part of the medulla oblongata greatly stimulates breathing in proportion to the hydrogen ion concentration of its immediate environment. The pH in its interstitial fluid is quickly changed by changes in the blood pCO_2 and is slowly changed by slow changes in the bicarbonate concentration of the cerebrospinal fluid (CSF) overlying this region. The CSF bicarbonate seems to equilibrate rapidly with that of the interstitial fluid in this region, while blood bicarbonate seems to be somewhat isolated from it by the "blood-brain barrier." Thus we should attempt to interpret Hasselbalch and Lindhard's findings of sensitization to CO_2 during acclimatization in terms of its effect on the pH of these medullary chemoreceptors, although the effect of CO_2 on the pH of blood may also play a role. But I think I should stress that the mechanisms that tend to return the blood pH toward normal during the early stages of acclimatization have been somewhat overemphasized in the past. I think it is now clear from the work of several investigators that during the first few weeks at high altitude the respiratory alkalosis produced by the hyperventilation is inadequately compensated and the arterial pH remains slightly elevated.

When some of our experiments at the White Mountain Research Station (3) called attention to the fact that the well-known renal excretion of bicarbonate from the plasma upon ascent to high altitude was insufficient to account for the altered regulation of breathing in terms of the then known stimuli, arterial pH, pCO_2 and pO_2, my neighbor John Severinghaus and his associates undertook to investigate whether a more rapid, active removal of bicarbonate from the CSF might account for the altered regulation of breathing in acclimatization. This led to a series of rather heroic experiments, and indeed they are up at White Mountain right now tapping each other's lumbar spinal fluid, jugular bulb blood, and so on. They have already found (5) that bicarbonate in the CSF does fall at altitude before it falls in blood plasma. This lowers the medullary chemoreceptor pH associated with any given pCO_2. In effect, it resets the level at which arterial pCO_2 is regulated by changing its relation to medullary chemoreceptor pH, without requiring any change in the chemoreceptor response to hydrogen ion concentration. Severinghaus has postulated that the primary effect of hypoxia is to stimulate breathing via the carotid and aortic chemoreceptors. This leads to a fall in pCO_2 and a generalized respiratory alkalosis, as we all know. He postulates a homeostatic mechanism that restores the brain's pH toward normal by actively removing bicarbonate from its interstitial fluid and from the CSF whenever the brain's pH remains too high. This would automatically reset the regulation of pCO_2 in the observed manner.

A logical deduction from this reasonable hypothesis would be that sensitization to pCO_2 at altitude should occur only if the hypoxia is allowed to produce a respiratory alkalosis. Hypoxia without a fall in pCO_2 should not change the brain's pH and thus should not stimulate an active change in its bicarbonate. We have begun to test this hypothesis in a series of experiments in which we reduce the oxygen or the carbon dioxide separately as well as in their normal combination. Dr. Eger reported our results to the American Physiological Society this past April (1), and a more detailed manuscript is in preparation, so I need only outline the important features here. In our earlier experiments on CO_2 sensitization at altitude (3), we had found that the alveolar pCO_2 required to produce a given degree of ventilatory stimulation decreased during three weeks of residence at 4,340 meters by about 14 mm Hg, but about two-thirds of this sen-

sitization occurred within the first day. In our recent experiments, lowering the alveolar pO_2 to 45-50 mm Hg by simply diluting our inspired air with nitrogen in the laboratory at sea level, we have found we can produce a CO_2 sensitization of 7 or 8 mm Hg in only eight hours. By that I mean that the pCO_2 required to stimulate the breathing to an arbitrary level, 15 liters per minute per square meter of body surface area, is lower by about 7 or 8 mm Hg than it was before this period of hypoxia. This is only half as much as occurs in three weeks, but it makes possible repeated analytical experiments without going to the mountains or even using a decompression chamber. (I must admit that I miss the fringe benefits of my previous mountain trips.)

By controlling the oxygen and carbon dioxide in the inspired gas, we have kept our alveolar pO_2 between 45 and 50 mm Hg while simultaneously preventing our pCO_2 from falling despite the strong ventilatory stimulation. When we did this, we found that hypoxia no longer produced sensitization to CO_2, evaluated by measuring our ventilatory response to CO_2 after the hypoxia had been terminated by extra oxygen. Conversely, if we hyperventilated (either voluntarily or with a Bird Respirator) to lower our alveolar pCO_2 while our oxygen pressure was kept normal, CO_2 sensitization did occur. Thus we agree with the hypothesis that the essential stimulus for this particular aspect of altitude acclimatization is the secondary lowering of pCO_2 rather than the hypoxia itself.

To see whether the hypoxia plays any direct role at all, we have produced the same degree of hypocapnia (alveolar pCO_2 about 10 mm Hg below normal) with the oxygen kept normal and with the oxygen kept at 45-50 mm Hg. We found that the CO_2 sensitization was about twice as great when the subject had also been hypoxic during the eight hours as it was when the oxygen had been kept normal. In other words, although hypoxia does not cause persistent sensitization to CO_2 by itself, it does greatly enhance the CO_2 sensitization produced by eight hours of hypocapnia, such as that normally brought about by hypoxic stimulation of the carotid and aortic bodies. Obviously, we now need to find out by what mechanism a low pCO_2 or respiratory alkalosis slowly changes the CSF bicarbonate and how hypoxia accelerates that slow change.

It is interesting to try to relate these findings to the well-known fact that high-altitude natives do not hyperventilate as much as sea-level residents sojourning at the same altitude. Drs. Severinghaus and Carcelén (6) have reported that the CSF bicarbonate in high-altitude Peruvian natives is such as to make their CSF pH normal at their pCO_2 levels. They supposed that this might indicate an abnormally weak ventilatory stimulus from the hypoxia in their carotid and aortic bodies. Another possibility might be that the further progress of some other aspect of acclimatization had so improved the oxygenation at the point where hypoxia accentuates the effect of respiratory alkalosis on CSF bicarbonate that this accentuation was no longer so pronounced. But of course all such suggestions are merely speculative and become useful only to the extent that they point to further experiments.

Moderator: In opening the discussion, I want to start with Dr. Chiodi, who was specially invited as a discussant.

DISCUSSION: ACQUIRED ACCLIMATIZATION TO HIGH ALTITUDE

Hugo Chiodi

Are there at the present time enough data on which to base a clear-cut distinction between natural and acquired acclimatization?

According to Hurtado (1), "the investigation of man at altitudes which are compatible with a high degree of mental and physical activities, at least in the subject born and raised in such environment, gives a useful knowledge of true acclimatization." This has been taken as a definition of natural acclimatization. Monge, in his book *Acclimatization in the Andes* (2), says that the indigenous races became acclimatized to high altitudes through an age-long process and that "the Man of the Andes possesses biological characteristics distinct from those of sea-level man."

What are these biological characteristics that make a "Man of the Andes" different from a sea-level native? So far as I know, there are few data on permanent biological features that would differentiate an Andean man from his sea-level peer.

The persistence of the fetal structural pattern of the pulmonary artery to adulthood has been described in recent years in high-altitude natives (3). Is the persistence of this fetal pattern an indication of a greater capacity to acclimatize, acquired over generations by natural selection or some other genetic mechanism? Or is it the accidental consequence of high pulmonary blood pressure due to the fact that the newborn is living in a hypoxic environment? Like the abnormally high incidence of patent ductus in subjects born at high altitudes, it could be an example of the inhibiting effect of hypoxia on some of the mechanisms triggered at birth. Perhaps the question could be answered by studying subjects born at high altitudes to sea-level parents with a rather short residence there.

It is relevant to mention that even conspicuous morphological changes like high-altitude polycythemia (4) or cardiac hypertrophy (5) will disappear in time with lowland residence.

Are the enzyme tissue changes described by B. Reynafarje (6) a biological characteristic of the Man of the Andes or a feature acquired through a given subject's long residence at high altitudes? Here again, a comparative study of high-altitude natives and lowlanders who have lived for a long time at high altitudes is necessary before any valid conclusions can be reached.

I shall close this part of my discussion with another question that, when answered, will also answer the question of natural and acquired acclimatization. Can a sea-level man (without any peculiarity that might render him abnormally sensitive to chronic hypoxia) reach a degree of acclimatization similar to that of a native who is the product of many generations at high altitudes? Elsewhere in the same book Monge (2) says: "The Spaniard evidently attained biological acclimatization and came to equal the native. All the story of the conquest and of the colonial period show this. Thus Montesinos, speaking of Carbajal and referring to the swiftness with which Gonzalo Pizarro's Captain General and Master of the Field carried the provisions from Quito to Guamanga, says: 'So this minister of Satan, for all his eighty years, walked [sic] the leagues which lie between Quito and Guamanga over the rough roads in a little more than two months and a half."

Is the marked difference in acclimatization mentioned by Professor von Muralt, depending on whether the high altitude has been reached by passive transportation or active mountain climbing, only a quantitative one or is there also a qualitative difference in the process?

Has the physical fitness of a subject prior to the ascent anything to do with a faster and/or more complete acclimatization? At a

recent meeting in Alaska it was reported that, at least at moderate altitudes, well-trained sea-level athletes can compete successfully, a few days after their arrival, with native athletes trained at that altitude.

Professor von Muralt states that the driving force of CO_2 on respiration grows steadily every day, reaching a maximum after about ten days at high altitude. In my experience (7), CO_2 sensitivity of the respiratory center has already reached a maximum after twenty-four hours at a high altitude and from then on appears to decline to a level similar to that of sea-level residents. How long it takes to reach this level remains obscure.

A pH and pCO_2 sensory receptor in the medulla has been described by Mitchell *et al.* (8). The short time (a few hours) it apparently takes for the pH and the CSF to come back to its sea-level value after the subject has been exposed to high-altitude hypoxia is difficult to reconcile with a long period of increasing CO_2 sensitivity of the respiratory center as postulated by Professor von Muralt.

The last point I should like to discuss concerns the part played by the chemoreceptors in the process of acclimatization. Today it is a well-accepted fact that high-altitude hyperventilation in man is sustained at least in part by chemoreceptor driving. Experimental studies in dogs seem to show that in this species chemoreceptors are of paramount importance in high-altitude hyperventilation. But in man things look more complicated.

Our early studies (9), confirmed by Bainton *et al.* (10), showed that chemoreceptors in long-term residents at high altitudes are less active or sensitive than those of newcomers or subjects acclimatized for a short period. Chemoreceptors seemed more active between two and three thousand meters than at four thousand to forty-five hundred—a rather surprising finding.

Moderator: Before we go on with the discussion, Drs. Waterlow and Caldeyro-Barcia have asked to present some comments on the papers that have been discussed. But first allow me to say just a few words about Dr. Chiodi's remarks. If I understood him correctly, Dr. Chiodi has great doubt about whether we are correct in saying that there are a natural and an acquired acclimatization. I understood him to say that we do not have enough evidence to make this distinction.

I don't agree. I think we have a number of observations—some of them not yet published—to prove the idea. I believe there is a definite difference between natural and acquired acclimatization.

Between a high-altitude native and a man originally from sea level who has been at high altitudes for some time, there are some definite differences. For about a year we made a monthly study of a large group of men from sea level. We also had the opportunity to study some U.S. employees of mining companies who were living at a high altitude. We found many differences between these two groups of people—in the level of ventilation, in the sensitivity to inhaled CO_2, in the affinity of hemoglobin for oxygen, and in the position of the oxygen dissociation curve. I suspect that tissue chemistry factors will prove to be decisive and that studies of tissue chemistry will be of tremendous value in explaining the high degree of acclimatization shown by the altitude native.

We found a very definite difference between the two groups when we subjected them to the additional stress of physical activity. We observed that no matter how long a man from sea level stays at a high altitude, his efficiency and his tolerance for maximal work were a great deal lower. Actually, we found that the altitude native's average length of tolerance for given types of exercise was greater than among people living at sea level.

I think we (and by "we" I do not mean myself alone but a large group of investigators) are partly to blame for this doubt because we have not yet published our observations. I hope that, when we do publish, Dr. Chiodi may change his mind.

Von Muralt: May I say something on this point, too? In the experience of every single European who has worked with Sherpas in the Himalayas, under any given conditions the Sherpa is superior to the European member of the party in physical performance except at the end; he fails, to a certain extent, at the very high peak. But this is a different thing—it is a question of stamina, and of course the leaders of an expedition have ambition and other motives that keep them going in the face of storms, cold, and other conditions. So far as withstanding hypoxia is concerned, I believe everybody admits that the Sherpa is superior to any European mountaineer.

In Switzerland too I think this fact can be corroborated. We have a group that we call Mountain Guides, the grandsons of the famous mountain guides who took Whymper and others up in the pioneer times of Alpine discovery. My personal experience with these men is that, under extreme conditions, their performance and resistance not only to hypoxia but also to cold and other difficulties are far superior to what any sportsman can exhibit.

Arias-Stella: Dr. Chiodi raised the question that perhaps a genetic factor may play a role in some of the differences in the characteristics of the pulmonary vessels found in people at high altitudes. We have a few well-documented cases of autopsies on children of Americans living at Cerro de Pasco. In these children who were born and lived at high altitudes, we have found just the same histological changes that we see in the natives.

Waterlow: The Moderator has very kindly allowed me five minutes to present some new data. I was very much pleased when Dr. Hurtado made the point that many of the phenomena of adaptation to altitude are relevant to situations in clinical medicine. This is the reason, apart from fondness for mountains, for my interest in this subject. The general point I should like to make is this: there has been much mention today of changes in pH, bicarbonate, pCO_2 and so on, in tissues and body fluids, but we know from clinical medicine that one can never consider these changes without also thinking of changes in amounts and transport rates of other electrolytes. These have not been mentioned.

I am interested in the problem of adaptation to altitude from the standpoint of what happens *before* a man has adapted—in other words, during the period of mountain sickness. It is very well known that the symptoms of mountain sickness, which can be very severe, are quite variable, both as between individuals and in the same individual at different times. They have nothing to do with physical fitness, and some of the finest climbers have been most prone to them.

Usually, in biological questions, great variability means that several factors are at work. I had the idea that a vicious circle might arise in the following way: It is well known that, physiologically, part of the response to a respiratory alkalosis is excretion of potassium as well as of sodium; it is also very well known in clinical medicine that in a metabolic alkalosis there may be potassium loss. Therefore the question arose, Could there be potassium depletion preventing proper compensation of the alkalosis that occurs on first exposure to high altitude?

We studied this problem on three expeditions to the Sierra Nevada de Santa Marta, in Colombia. The subjects had to climb to nearly forty-five hundred meters, marching about fifty miles in three days and carrying loads. This was hard physical work. The subjects were on a low potassium intake, but some had potassium supplements. Complete balance studies were done for periods up to twenty-four days, with measurements of pH, titratable acidity, and bicarbonate. There is no time for details.

The results were as follows: First, there was no question whatever that clinically, from the point of view of symptoms and performance, those who had supplementary potassium did better. I myself on one expedition received the low potassium intake. After three days at 14,500 feet I became comatose with general-

ized edema, but without evidence of cardiac or renal failure. After three days of potassium treatment I was perfectly all right again.

We were not able to establish the existence of potassium depletion in the sense of persisting cumulative negative balances, but the unsupplemented subjects had very significantly lower serum potassium levels. I consider it perfectly reasonable, from other evidence, to think in terms of a *functional* potassium deficit, even without a massive loss of total body potassium.

Second, evidence was obtained that the subjects without the potassium supplement retained sodium and water; the clinical edema was one aspect of this.

Third, there was no difference between the two groups in blood pH, so far as we could measure it, or in plasma bicarbonate. Both groups excreted acid urine throughout, quite contrary to the theory, but this is probably because of the relatively severe level of exertion plus rather low food intakes. The fact that the urine was acid is not, I believe, evidence of failure of adaptation, because the urines were even more acid in those who were fit, showed the best performance, and received the potassium supplements.

I think it can be argued that during the phase of incomplete adaptation there is an intracellular acidosis, accompanied perhaps by an extracellular alkalosis, and that this carries with it changes in the movements and amounts of other electrolytes. This is an aspect that I suggest needs more study.

Finally, it is interesting to remember that Whymper, in his 1879 book, *Travels in the High Andes of the Equator,* mentioned that his physician recommended potassium chlorate to him as an antidote to mountain sickness, from which even Whymper, one of the giants, suffered extremely severely.

Moderator: Dr. Caldeyro-Barcia.

Caldeyro-Barcia: Figure 1 illustrates the record of fetal heart rate (FHR) and amniotic pressure obtained from a parturient woman in Mexico City, at twenty-four hundred meters above sea level. When the mother is breathing

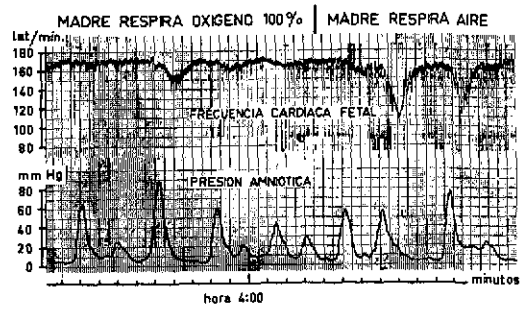


Figure 1. FETAL HEART RATE AND AMNIOTIC PRESSURE, MEXICO CITY (2400 M), IN PARTURIENT WOMAN BREATHING AIR (right) AND OXYGEN

room air, each uterine contraction causes a transient fall in FHR; the bottom of each fall is recorded about thirty to forty seconds after the peak of the corresponding uterine contraction. These falls have been designated "Type II dips". When the mother breathes 100 per cent oxygen the amplitude of the FHR falls diminishes significantly. If she resumes breathing room air, the initial conditions are restored.

In Figure 2 the amplitude of each Type II dip has been plotted against the amniotic pressure recorded at the peak of the corresponding uterine contraction; the two variables bear a direct linear relationship. There is a significant difference between the slope of the regression lines fitted to the experimental points obtained when the mother is breathing air and those obtained when she is breathing 100 per cent oxygen.

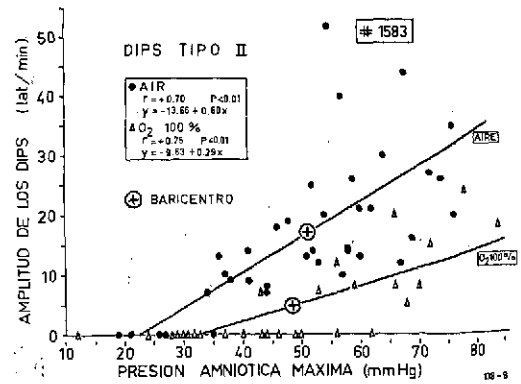


Figure 2. TYPE II DIPS PLOTTED AGAINST AMNIOTIC PRESSURE

These results indicate that the administration of 100 per cent oxygen to the mother reduces markedly the amplitude of these transient falls in FHR which follow each uterine contraction.

There is much evidence to support the view that Type II dips are the sign of a transient aggravation of fetal hypoxia. The uterine contraction aggravates the hypoxia by compressing the intramyometrial part of the uterine blood vessels supplying the maternal blood to the intervillous space.

At sea level, Type II dips appear only in abnormal conditions in which the metabolic exchange between the mother and the fetus is reduced below normal ranges. The blood of these fetuses is hypoxic (saturation $<30\%$) and acidotic (pH <7.20). Both respiratory and metabolic acidosis are present. Under these conditions, the administration of oxygen to the mother has an effect similar to (but less marked than) that illustrated in Figures 1 and 2; at twenty-four hundred meters the effect on FHR of O_2 administration to the mother is much more striking.

Neel: Yesterday when we discussed the International Biological Program, particularly that part of it concerned with the study of human adaptability, I noted that that there were two types of adaptability that would be considered, genetic adaptability and acquired physiological adaptability. I think the presentations today illustrate the difficulties we may have in disentangling the two. We have heard a great deal here about the adapted adult. I wonder what we know about the adapted child. Are there detailed observations on children, Indian and Caucasian, who have grown up side by side at these altitudes and under relatively similar nutritional circumstances? Such observations would be useful in deciding how much of the Indian adult's remarkable adjustment to high altitudes is genetic and how much physiological.

Moderator: We have made no observations in childhood; I do not know whether anyone else has. But I always have the impression that the newborn at high altitude is a newcomer to that environment. He has very little polycythemia. This does not start developing until some time after birth. Balderon and Huckabee, who were in Peru for some time making a study of fetal physiology, came to the conclusion that during fetal life there are many compensating and adaptive mechanisms. The hypoxia is no more severe than is usually found at sea level.

Moncloa: I should like to show three slides that give some results of observations made in ten sea-level natives who were taken up to Cerro de Pasco (fourteen thousand feet) by train.

In Figure 1 we have the radioactivity over the neck in percentages of a single tracer dose of ^{131}I. The black dots represent the results obtained at sea level prior to the trip. The open circles correspond to the results obtained in the same group of subjects when the tracer was given thirty-six hours after arrival at the high altitude. It can be seen that the exposure results in an increase in the thyroidal uptake of radioiodine and also in a faster turnover of the intrathyroidal iodine.

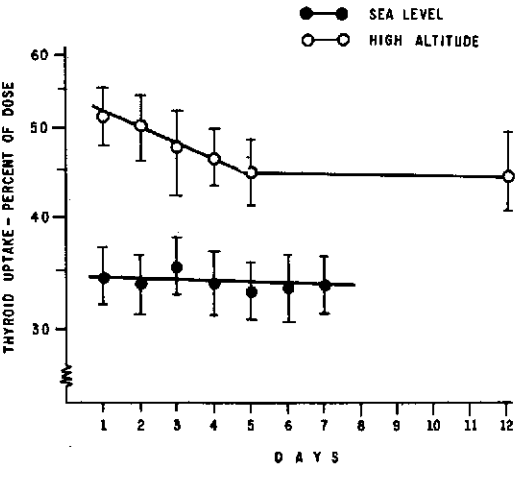


Figure 1. RADIOACTIVITY OVER THE NECK AFTER A SINGLE TRACER DOSE OF ^{131}I IN TEN SEA-LEVEL NATIVES EXPOSED TO 4,240 METERS. (Moncloa *et al., J. Clin. Endocrinol.,* in press)

In Figure 2 we have the results obtained in the same group of subjects in terms of urinary steroids and cortisol secretion rates. The changes were transitory, and two weeks were enough for a return to normal values. During the day of descent there were no changes in these indexes.

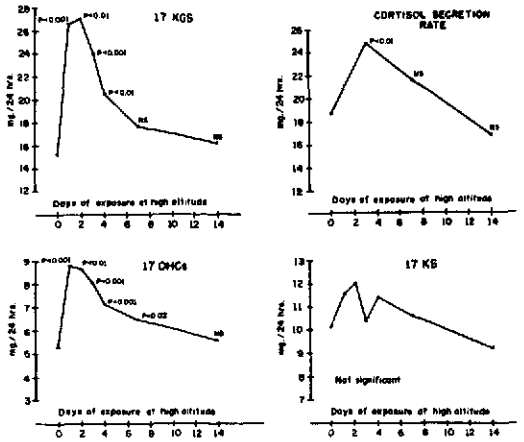


Figure 2. CORTISOL SECRETION RATE AND URINARY EXCRETION OF 17 OHCs, 17 Ks, AND 17 KGS IN TEN SEA-LEVEL NATIVES TAKEN TO 4,240 METERS FOR TWO WEEKS (Moncloa *et al., J. Clin. Endocrinol.*, 25:1640, 1965)

It may be of interest to note that the increase in 17-hydroxycorticosteroids parallels the results shown by Dr. C. Reynafarje in regard to erythropoietin. Whether the increase in the cortisol secretion rate plays any role in acquired acclimatization we do not know; nor do we know whether this increase is due to hypoxia *per se* or to alkalosis or to some of the other changes caused by acute exposure to hypoxia.

Figure 3 gives the results of ACTH stimulation in terms of urinary 17-hydroxycorticoids in sea-level natives. It may be observed that acute exposure to high altitude does not produce a maximal response of the adrenal cortex. High altitude causes an increase similar to that obtained with 1 U of ACTH. The other group of sea-level subjects were injected with ACTH

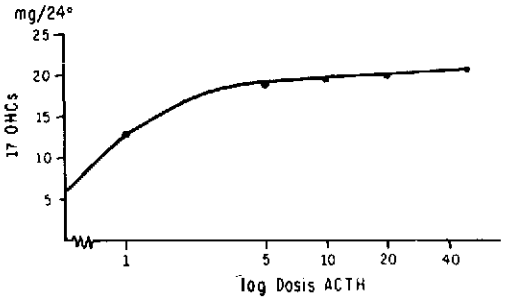


Figure 3. URINARY 17 OHCS AFTER DIFFERENT DOSES OF INTRAVENOUSLY INFUSED ACTH. (Moncloa *et al., Steroids*, 1:437, 1963)

on the train during the trip to the high altitude; we have found that a further increase in adrenal function is possible. Therefore, hypoxia is not stimulating the adrenal gland to its capacity. On the other hand, it is also possible to inhibit the so-called stress of hypoxia, in terms of adrenal secretion of hydrocortisone, by administering dexamethasone the day prior to the trip to a high altitude.

Peñaloza: To supplement Dr. Velásquez's presentation on acquired acclimatization to sea level, I should like to mention some observations on pulmonary circulation in eleven high-altitude subjects after two years of residence at sea level.

By the end of this period the pulmonary artery pressure has become normal. This means that the effect of a prolonged residence at sea level on the pulmonary pressure is more accentuated than the acute administration of 100 per cent oxygen at a high altitude. Releasing of precapillary vasoconstriction by oxygen is a common response to both conditions. Therefore, the difference may be due to a gradual regression of structural changes in the pulmonary vasculature during the prolonged residence at sea level. Gradual disappearance of hypervolemia and polycythemia may be contributing factors.

Despite a complete regression of the pulmonary pressure values, we obtained only a partial regression of the right ventricular hypertrophy as appreciated by the electrocardiogram and vectorcardiogram. Perhaps we need more prolonged observations at sea level to obtain a complete regression of the right ventricular hypertrophy. It should be remembered that after surgical treatment of cardiac diseases with right ventricular hypertrophy, the anatomic changes occur slowly and are preceeded by hemodynamic improvement.

Mithoefer: Professor von Muralt emphasized the reduction in the alveolar arterial oxygen gradient in high-altitude residents as an important mechanism of adaptation. I think this question calls for further study, because it would be disloyal to my colleagues for me not to present the data that Dr. Kroutzer, Dr.

Tenney, Dr. Remberton, and I collected at Morococha a few years ago. We measured alveolar arterial oxygen gradients in native residents at Morococha, at three levels of oxygenation, with the subjects in a supine position and the arterial tensions measured by direct polarography. On ambient air the AA gradients in our studies were equal at sea level and at high altitude, but when the inspired oxygen tension was lowered at sea level to values equivalent to that of a high altitude, there was a higher gradient in native residents. This suggests that the diffusing capacity for oxygen may not be decreased in native residents—it may, in fact, be increased.

When the inspired oxygen concentration is raised at high altitude to a value equivalent to that existing in the ambient air at sea level, there is a significantly greater gradient among the high-altitude residents, which suggests that their ventilation and perfusion are more unequal than those of sea-level residents.

Finally, when native residents are given high inspired oxygen concentrations to breathe, they have—or had in our studies—a very much larger gradient, which suggests that the true veno-arterial shunt is greater at high altitudes. If this is true, high-altitude residents are surviving in spite of an increased disproportion between ventilation and perfusion and in spite of an increased veno-arterial shunt. I think it is very important that further studies of this sort be carried out to try to settle this question.

Moderator: As Dr. Mithoefer has just said, there is a discrepancy between these findings and ours. There is nothing more stimulating in research than to find different data. I think further studies will be of great value.

The next presentation will be that of Dr. Donayre.

POPULATION GROWTH AND FERTILITY AT HIGH ALTITUDE

José Donayre

Population Growth

The present report refers only to the Peruvian population at high altitudes, but these observations may probably be extended to the rest of the Andean countries.

From 1961 census data it has been estimated that Peru's population reached the twelve-million mark in the period 1965-1966. This was the result of an annual growth rate of 3 per cent derived from a high birth rate nearing 45 per cent combined with a rapidly decreasing mortality rate estimated at about 15 per thousand.

A very important characteristic of our demographic phenomenon is the spatial distribution of the population. Peru, crossed longitudinally by the Andes has three natural regions—the coast, the highlands, and the so-called jungle. Mostajo (1) has studied the evolution of the Peruvian population by departments. A first approximation can be obtained grouping departmental data according to the natural regions. We see that the region with the highest growth rate in the country is the jungle, with an annual increase of 37.53 per cent in the intercensus period 1940-1961. The jungle is followed by the coast with an annual 28.11 per cent increase. Last comes the highlands, with 15.92 per cent annually. The departments with the highest growth rate, according to these figures, are Madre de Dios for the jungle, Lima-Callao for the coast, and Pasco—a department east of Lima— for the highlands.

However, the political division of the country into departments does not coincide with altitude. Many coastal departments have districts on the Andean slopes. To examine demographic phenomena related to altitude, therefore, the inhabited areas should be classified according to elevation. Such a study has been reported by Monge (2), who finds that in 1940 the population living above 1,750 meters came to 66 per cent of the total and that by 1961 this percentage had been reduced to 55 per cent whereas the coastal population below 500 meters increased from 28 to 40 per cent in the same period. Between 1,750 and 500 meters, a stable population represented 6 and 5 per cent respectively for 1940 and 1961.

This phenomenon of a declining population in the Andean plateaus is another expression of the current flight from rural areas to the cities. The high-altitude rural population, engaged mostly in agriculture, migrates in increasing numbers to the coast, especially to the Lima-Callao metropolitan area.

Although the results of a study on internal migration in Peru are not yet available, it is possible to suggest that a high birth rate in an area where modern and effective contraception is not practiced and where criminal abortion as a means of controlling fertility does not seem common is one of the main stimuli to migration. This factor, combined with deteriorating social and working conditions under feudalistic land-tenure systems, could explain the increasing trend toward migration to the coast. It is hoped that a timid agrarian reform now under way may help to improve the general situation in the rural areas and permit the highland population to stabilize.

The attraction exerted by the semi-industrialized urban areas of the coast on the Andean population, a phenomenon common to underdeveloped countries in rapid population expansions, should not be ignored but, in view of the factors mentioned above, may be secondary.

Fertility

Infertility in man at high altitudes was recorded by chroniclers and historians (3) during the Spanish settlement and was later observed by Monge (4) in certain couples arriving at high

altitudes from sea level. Corresponding reports of animal fertility impairment go back as far as 1639 in the chronicles of the Conquest (5). This phenomenon has been observed and commented on up to our days (3, 6).

Sexual cyclicity in animals has been found to be altered by exposure to hypoxia (4), although data on the extent of the damage and the species differences are meager. Regarding ovulation—a most sensitive step in the accurate chain of reproductive events—under simulated, intermittent conditions of cold and hypoxia, depression has been observed (7) by the indirect method of Slechta *et al.* (8). Atland (6, 9), San Martín (10), and Fernández-Cano (7) reported on embryonic reabsorption and death and reduced size of embryos in animals exposed, findings that correlate with descriptions of placental modifications in high-altitude mammals (11). These findings indicate that both early stages of fertilization and the mechanism of implantation might be affected.

Later Guerra-García (12) showed that the exposure of guinea pigs born and bred at sea level to an altitude of 14,300 feet for two weeks produces profound alterations in the epithelium of the seminiferous tubules with a marked decrease of all cellular types. Pituitary-to-body-weight ratio was found elevated, with an increase in the basophilic cells, which are probably the gonadotrophin-producing cells in this species.

Despite all these indications of reproductive failure on exposure to high altitude, Moore and Price, in their 1948 study (13) of the effects of altitude on the reproduction, growth, and sexual maturity of small mammals, failed to demonstrate any significant change. In autopsies performed after thirty, sixty, and ninety days of exposure at four different levels of altitude (6,000, 7,500,9,600, and 14,000 feet above sea level) no alterations in body weights, reproductive organ weights, or endocrine sex glands were found. The reproductive performance seemed unimpaired, although litter numbers and average litter size were smaller at the 14,260-feet station. Strikingly low survival and subnormal growth of young prevailed, and the authors attributed this to cannibalism and faulty lactation. In this study the time of the first autopsy is set at thirty days, which suggests that by this date the acute changes had probably been reversed. In summary, despite excellent care of the animals and proper control of feeding and temperature, litter size was reduced, cannibalism was high (suggesting dead or weak offspring), and failure to grow adequately to weaning was evident.

In an effort to understand the mechanisms involved in fertility impairment at high altitudes and to locate the damage in the reproductive performance, we have studied animals exposed to high altitude and a group of young men originally from sea level who were transported to and kept at 14,300 feet for fifteen days. Preliminary results are reviewed.

Animal Studies

Estrous cycle (Figure 1)

In the animal studies we have tried to dissociate the effects of hypoxia and altitude cold (the temperature fluctuates between 15° and 8°C daily). We followed a total of ninety rats, in three groups of thirty each, with vaginal smears for three months. The usual incidence of estrous days in our colony at sea level is 35.378 per cent, a figure that correlates well with the data in the literature. During the first ten days of observation rats exposed to altitude cold revealed a significantly lower incidence of estrous days (10.7 per cent), which tends to recover in the succeeding twenty days (30.1 per cent, 24.1 per cent), whereas nonsignificant variations

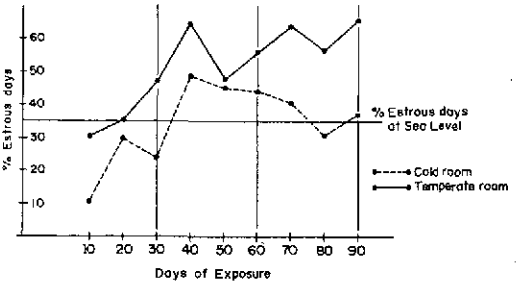


Figure 1. ESTROUS CYCLE IN RATS EXPOSED TO HIGH ALTITUDE

are observed in animals exposed in a temperature room at 24° ± 1°C for the first twenty days. However, the latter group, after twenty and thirty days of exposure, show a markedly increased incidence of estrous days. While animals exposed to altitude cold had 48.8, 45, and 44.3 per cent estrous days, animals exposed to hypoxia in temperature rooms increased to 64.6, 48, and 56 per cent—a trend that continued into the sixty-to-ninety day period (63.88, 56.66, and 65.66 per cent). In the same period the frequency of estrous days in the other group of animals went down to about the normal range (40.62, 30.62, 36.78 per cent).

This experiment tends to indicate that exposure to high altitude markedly affects the estrous cycle sequence, producing mainly sustained estrus. The added exposure to cold seems to bring about different initial effects characterized by varying degrees of anestrus.

Ovulation (Figure 2)

This important step in the chain of events has been studied in immature mice by the superovulation technique adapted from Purshottam *et al.* (14) and using doses of 2IU of PMS and 1IU of HCG. One typical experiment will serve to illustrate the findings.

With the technique used, control mice at sea level give a total shedding of 41.32 ± 3.068 eggs. When these animals were exposed to high altitude under two temperature conditions, a marked and gradual alteration of ovulation was observed. Gonadotrophin administered to animals exposed for an increasing length of time

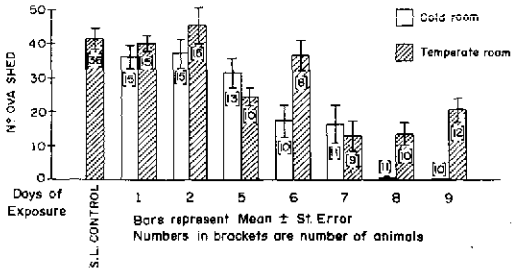


Figure 2. SUPEROVULATION ON EXPOSURE TO HIGH ALTITUDE

seemed to elicit a gradually diminishing response. In the group of animals exposed to high altitude under adequate temperature control, significant depression of ovulation occurred from the fifth day on. More profound impairment of ovulation was observed in the group exposed to cold, since values at the sixth and eighth days were significantly lower than in animals exposed in a temperature room. At the ninth day of this experiment none of the animals in the cold room ovulated.

These results would indicate either that the ovary under these conditions becomes refractory to gonadotrophins or that exogenous gonadotrophins at high altitudes have a diminished half-life that prevents them from exerting their normal effects. Such "resistance" has previously been observed for small doses of ACTH and for glucagon at high altitudes. On the other hand, these results correlate closely with the observed effects of HCG on males that will be summarized below.

The effects of different doses of gonadotrophins is being explored to help toward an understanding of the mechanism involved in this phenomenon.

Human Studies

Survey of Newcomers to High Altitude

A small sample of twenty-nine couples originally from low levels and now residing at 14,300 feet was surveyed for information on reproductive capacity in order to establish clearly the incidence of altitude infertility (unpublished observations). The only common complaint was related to menstrual disturbances: 58.6 per cent of the women mentioned marked dismenorrhea, increased menstrual flow, moderate alterations in menstrual cyclicity, and noticeable alterations in the duration of flow. Only limited conclusions can be obtained from this survey since 65.5 per cent of the women were using contraceptive measures, owing to fear of pregnancy at the high altitude. Only three cases of possible high-altitude infertility are being followed.

Total Urinary Gonadotrophins

Using the kaolin-acetone extraction and the bioassay in the immature mouse uterus, two groups of subjects were studied by Sobrevilla *et al.* (16). The first group consists of eight natives of high altitudes living at 14,300 feet in whom the total gonadotrophin levels were found similar to those of the sea-level natives (1.25 vs. 1.14 mg/24 NIH-HPG-UPM-1). The second group is composed of ten men acutely exposed to a similar altitude. In this group total gonadotrophins did not vary significantly when assayed the second, third, seventh, and fourteenth day of exposure.

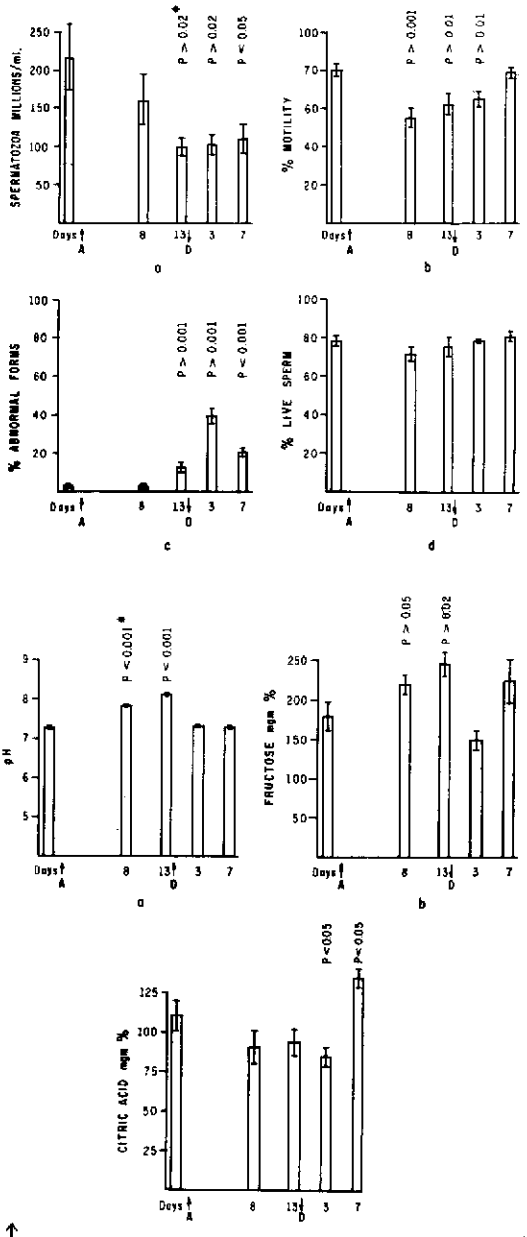
The author concludes that the high-altitude native living under chronic hypoxic conditions does not require an increase in gonadotrophin excretion for adaptation and that the fourteenth-day exposure to altitude in men does not cause detectable changes in gonadotrophin excretion. However, it will be necessary to explore the possibility of modification in the ratio, FSH/LH, which could explain the presence of the variations in the seminal characteristics (20) and urinary testosterone reported for these same subjects (17).

Urinary Testosterone

Guerra-García *et al.* (17), using Ibayashi's method (18), assayed twenty-four-hour urinary excretion of testosterone in the same group of subjects during the third, seventh, and fourteenth day of exposure to 14,300 feet. A significant decrease was found at the third day of exposure (47.1 ± 3.66 μg) as compared with controls before ascent (99.8 ± 14.3 μg). On days 7 and 14 of exposure the values returned to normal. High-altitude natives had a value of 96.5 ± 10.16 μg, similar to sea-level natives (19).

Seminal Changes (Figure 3)

In the same group of subjects we have studied the effects of high-altitude exposure on seminal characteristics (20).



↑ A = Day of Ascent
↓ D = Day of descent

Figure 3. SEMINAL CHANGES IN MEN AFTER ACUTE EXPOSURE TO HIGH ALTITUDE

A marked decrease in sperm count, dropping from a mean of 216.2 million/ml to 98.2 million/ml, a decrease of motile forms to 55.2 per cent, and an increase in abnormal forms to 39.3 per cent were found. At the same time the

pH was elevated to slight alkalinity (8.11) with no alteration in the percentage of live sperm, revealing the presence of metabolic disturbances. In this connection the levels of fructose were found to increase, probably owing to lack of utilization by the nonmotile spermatoza, and citric acid was found to decrease, which explains in part the alterations in pH.

In all cases, return to sea level initiated or produced a total recovery, which indicated that the damage incurred during two weeks of exposure was mild and reversible.

From this and the previous study, we could conclude that both the seminiferous epithelium and the interstitial tissue are reversibly damaged by exposure to hypoxic conditions.

Since the seminiferous cycle in man averages seventy-two days, it will be necessary to follow the histologic damage either directly by obtaining testicular biopsies or by observing subjects exposed for a longer period of time.

Effects of HCG on testicular function

Guerra-García (unpublished observations) studied the effect of 2,500 I.U. of HCG injected i.m. on testicular function in groups of subjects at sea level and at high altitude (see table). The response, measured in twenty-four-hour urinary excretion of testosterone, indicated again that high-altitude natives had values (79.2 ± 7.12 μg/24h) similar to those obtained for sea-level natives (97.6 ± 20.5 μg/24h). However, one, two, and five days after the administration of HCG, high-altitude natives showed a significantly lower urinary excretion than sea-level subjects. Only during the third day after HCG injection were values significantly higher in high-altitude subjects, whereas from the first day on the figures for sea-level subjects were significantly higher than their basal ones.

These findings tend to indicate that in hypoxic conditions there exists a diminished response to HCG, a phenomenon similar to those described for ACTH and glucagon and for a PMS-HCG combination in immature mice, referred to above.

Excretion of Urinary Testosterone (μg/24 hrs) after HCG (2,500 I.U.)

	BASAL	DAY 2	DAY 3	DAY 5
Sea level	97.6 ±20.5	154.1 ±12.4	301.4 ±47.5	286.6 ±30.4
P	—	0.01	0.001	0.001
Altitude	79.24 ± 7.12	93.20 ±15.97	133.56 ±11.07	95.06 ±29.04
P	—	0.30	0.001	0.01
P	0.30	0.001	0.060	0.001

Appearance of Menarche and Pregnanediol Excretion (Figures 4 and 5)

In a survey of one hundred school-age girls at Cerro de Pasco (14,300 feet), Moncloa (unpublished observations) found that menarche is delayed in comparison to a similar population from the coast. At all age levels the incidence of menarche was lower in the high-altitude sample, the difference being largest at

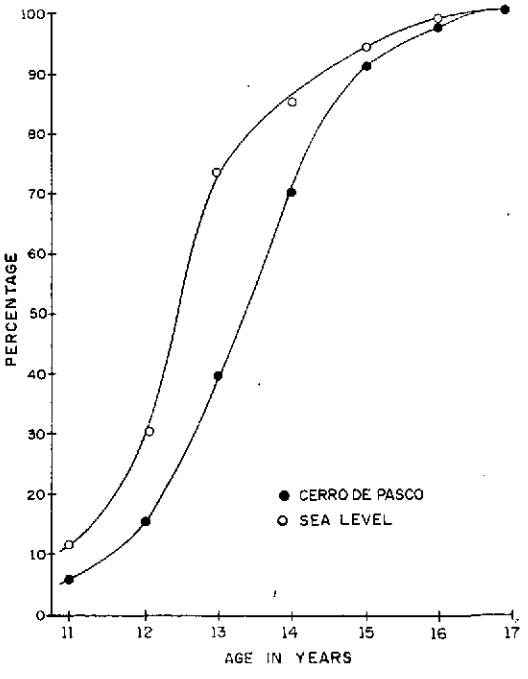


Figure 4. APPEARANCE OF MENARCHE BY AGE AT HIGH ALTITUDE AND SEA LEVEL

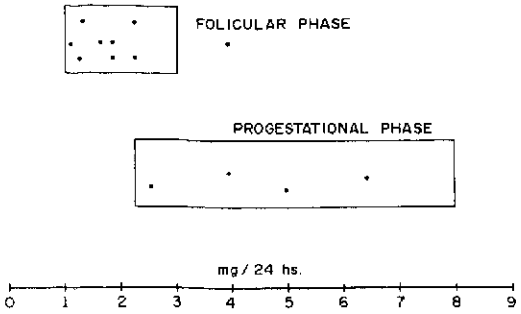


Figure 5. PREGNANEDIOL EXCRETION DURING THE MENSTRUAL CYCLE AT HIGH ALTITUDE

thirteen years of age. At that level 73 per cent of sea-level girls had presented their menarche whereas only 38 per cent of the high-altitude girls had. These results could indicate a difference in maturation of the hypothalamic-pituitary-gonadal axis.

Moncloa (unpublished observations) has also studied urinary pregnanediol; he finds no difference between sea-level and altitude women in either phase of the cycle.

Moncloa: I should like to make just a brief comment in reference to altitude and population. This subject was examined in a symposium held at our university about a year ago, and we have distributed the proceedings.* As medical people we were interested mainly in getting auxiliary or laboratory data from people in other fields to help in the diagnosis of our population problem. The data that impressed us most were those on income distribution. In general the per-capita income in our country is on the order of three hundred dollars. If we divide the population into the poor 50 per cent and the rich 50 per cent, we see from the distribution curve that the high-altitude population is among the poorest. Assuming for the sake of simplicity that the population grows exponentially (which is not precisely true) and that economic growth were to follow the same pattern, it would take a century for the poor 50 per cent to approach the present U.S. per-capita income. If population growth decreased from the present 3 per cent per annum to 1 per cent, it would take only sixty-four years—a saving of thirty-six years.

Moderator: It seems to be my turn now.

* L. A. Sobrevilla, J. Donayre, F. Moncloa, and R. Guerra-García, *Población y Altitud,* Imp. Seasator, Lima, 1965.

NEEDS FOR FURTHER RESEARCH

Alberto Hurtado

High-altitude research has characteristics common to all types of research with very few, if any, exceptions. Significant contributions have been made by numerous investigators in many countries, and considerable knowledge has been gained of some of the processes responsible for tolerance and for acclimatization to the hypoxia of such environments. Something is also known about the factors that play a role in the appearance of symptoms during early exposure, or that cause loss of acclimatization after a prolonged residence or even after having been born and brought up under the constant influence of low ambient pressure. We still lack complete understanding, however, of many aspects and phenomena, and some of the data reported have given rise to questions as yet unanswered. During this session an attempt has been made to single out the main gaps in knowledge and to indicate the most urgent or interesting problems for investigation.

Hypoxia, or oxygen deficiency, has been considered the most important factor in high-altitude environments. But there are other factors whose influence on type and quality of body responses has not been adequately investigated. Some of these are hypocapnia, low temperatures, low air density, decreased humidity, and perhaps increased radioactivity even at the level of the more populated areas.

A great deal is known about the symptomatology observed in newcomers to high altitudes, but little or nothing is known to help explain the tremendous variability among individuals in their early response and in the degree and nature of the changes frequently seen or why the same individual may be asymptomatic during a given exposure and show severe disturbances during a later one. Whether a healthy subject will respond well or poorly when taken suddenly to low ambient pressures is difficult to predict. Many observations have been made on young people before ascent, but no studies with well-defined criteria have been conducted. General impressions have been reported, such as a greater incidence of acute mountain sickness among people of nervous and unstable temperaments than among phlegmatic people, but here too the reports are conflicting.

It may be correct to assume that men born and brought up at a high altitude exhibit the highest degree of acclimatization to the environment in which they live. Some of these characteristics have been discussed during this session, and important adaptive mechanisms have been described. In most cases, bases exist for understanding why these mechanisms are thought to be compensatory in nature and how they tend to counteract the harmful consequences of hypoxia. But frequently there is no corresponding knowledge on how they originate. For example, it is well known that hyperventilation is present at rest and during physical activity in most, if not all, residents of high altitudes. There is some evidence of change in the sensitivity of the respiratory center to the chemical stimulus of blood carbon dioxide, but there is a lack of understanding of how important other factors—such as acid-base balance, the chemistry of the cerebrospinal fluid, modified nervous impulses and reflexes, and hypoxia —may be in this process. The mechanical aspects of the breathing process at high altitudes still await investigation. The lower density of the air, the greater volume of the blood and its higher viscosity due to the elevated hematocrit, the changes in the anatomical structure of the vascular tree, the dilatation of the alveoli and the thickening of their walls, the low position of the diaphragm, and the changes in the rhythm and volume of respiration are all of special interest to respiratory physiology from the point of view of its mechanics. It would be also of value to investigate the interrelationship of fac-

tors that influence the diffusion of gases through the alveolar membrane.

It is now well known that people living at high altitudes show a constant degree of moderate pulmonary hypertension. It is also known that anatomical changes in the pulmonary vascular tree play an important role in the pathogenesis of this condition. There are, nevertheless, unknowns in the significance of the additional contribution of functional factors. It is worth mentioning that the study of high-altitude pulmonary hypertension may contribute to a better understanding of this condition in cases observed at sea level.

Although known since the last century, the polycythemia of high altitudes still presents interesting aspects for study. The relation of hypoxia to erythropoietin in the increased production of red cells and hemoglobin under a variety of circumstances, the exact level of hypoxia at which a depressing rather than a stimulating action is exerted, the observation that a high-altitude resident develops moderate anemia after being brought down to sea level, the fact that a definite polycythemia is only evident some time after birth, the increased tendency to bleed after surgical operations—these are only a few of the many important problems that deserve additional investigation.

Significant work, some aspects of which have been discussed in this session, has already been done on endocrine activity at high altitudes. There is little doubt that more such studies will be valuable. Thyroid function, steroid metabolism, sexual regulation, the possible contribution of the adrenal to early tolerance, and carbohydrate metabolism are, among many others, excellent areas for further research.

Special emphasis should be given to the possibilities opened by the chemical and enzymatic investigations at the tissue level in chronic hypoxic conditions. The demonstration, years ago, that during the stress of severe physical activity the high-altitude native releases into the blood an amount of lactate much lower than that observed at sea level under a similarly increased metabolic demand raises very interesting and fundamental questions. This repeatedly confirmed observation indicates that, in high-altitude environments, actively working muscles paradoxically have a larger supply of oxygen, a better way to utilize it, or both. Contraction follows more an aerobic than an anaerobic pathway. In recent years, fundamental studies have been carried out indicating the existence of qualitative and quantitative changes in the chemical and morphological characteristics of pathways and energy production. There are some fundamental and exciting possibilities in the field of tissue chemistry and metabolism concerned with the effectiveness of the tolerance developed in the face of a constant difficulty with oxygen supply and utilization. It is likely that here may be found an effective answer to the intriguing question of how to explain the evident differences between natural and acquired acclimatization. Biological research generally is more and more approaching the cellular and molecular level; high-altitude problems are no exceptions to the trend.

Before I leave the subject of natural acclimatization, the complete lack of genetic investigations in this field is worth mentioning. Some years ago, in the high Andean regions of Peru, human skeletons were discovered that were estimated, by means of radioactive carbon studies, to be about nine thousand years old. This finding gave an indication of how many successive generations have been subjected to these same environmental influences. Genetic factors must play a role in the development of the high degree of acclimatization shown by permanent dwellers, but these aspects still need investigation. Although some interesting observations have already been made on fetal physiology, there is, in this regard, an attractive and important field for research.

Up to a relatively short time ago, all high-altitude research was oriented toward better understanding of acclimatization and its physiological background. But there is an awareness now that there are also pathological and physiopathological problems directly related to the factors operating in such an environment. Ac-

climatization, natural or acquired, may be lost and the affected person may have to be transferred to sea level. This syndrome, characterized by a symptomatology chiefly neural in nature, is called chronic mountain sickness, or Monge's disease, in honor of the investigator who originally described it. There is evidence that this disturbance is fundamentally a hypoventilation process with changes in the sensitivity of the respiratory center to chemical stimulation, although the responsible factor or factors are unknown. Further investigation is needed. Circulatory or chemical variables, or both, may be involved in the pathogenesis of this interesting clinical condition.

In recent years numerous cases of pulmonary edema occurring upon arrival to high altitudes or shortly thereafter have been described. The original report appeared in 1937. The symptoms usually develop in otherwise healthy natives of high altitudes who have spent a short time at sea level and have returned to the elevated zones while they still had a moderate pulmonary hypertension and some degree of polycythemia. Oxygen administration usually relieves the symptoms. Although many clinical and some anatomical studies exist, a clear concept of the pathogenic mechanisms immediately responsible for the occurrence of the edema is unavailable. The study of these cases may throw some light on a condition that, even at sea level, is still obscure.

Although systematic clinical studies at high altitudes have not been conducted so far, the incidence and evolution of certain diseases may have patterns not found at sea level. Hospital statistics reveal that certain types of cardiovascular pathology are much less frequent in high places. Systemic hypertension and coronary episodes, such as thrombosis and infarct, are only occasionally observed at high elevations. It will be of great interest to have detailed studies on the anatomical characteristics of the vascular tree and on the frequency of sclerotic lesions associated with age and senile degeneration. Fortunately, an active program of investigation by a group of pathologists is now under way in Peru.

The epidemiology of cancer at high altitudes also offers attractive problems for study. Apparently the incidence of certain types of the disease is no different from that at sea level. On the other hand, it seems that leukemia is rather rare in man in a high environment, and there are some interesting supporting data on experimental animals.

Except for very few and isolated observations, the field of infectious diseases and immunology has not yet been studied. It is not known whether defense mechanisms against pathogenic bacteria and viruses are modified by the hypoxic condition, and what changes, if any, there are in the incidence, evolution, and prognosis of certain infectious diseases.

The high-altitude areas of Peru include many mining localities. Apparently some occupational diseases, such as pneumoconiosis, develop quite frequently and very rapidly. It would be important to study the role of hyperventilation—with more dust particles inhaled in a given time—and other factors such as lung congestion and lower air density. It appears possible that the safety limits for the concentration of dust particles in the inhaled air is not the same at high altitudes as at sea level.

In short, there are many physiological, clinical, and health aspects whose study will be significant, not only in relation to the environmental factor of high altitudes but also from the standpoint of a better interpretation of problems that have not been entirely solved at sea level. It is satisfying to know that at present there are laboratories and able investigators in many parts of the world engaged in this type of research. Research is no longer a matter of isolated personal work and dedication. To be fruitful and productive it requires collective efforts that know no international boundaries.

Now I shall ask Dr. Rahn to make a summary —a difficult problem, I know, but his ability and knowledge will solve it.

Rahn: After Dr. Hurtado's magnificent review, my summary of the meeting is obviously

quite superfluous. He covered splendidly not only this conference but also high-altitude research in general.

In anticipation I had carefully written out notes on all the excellent papers presented today. But to re-recite these would obviously be too monotonous, and I am sure that the Moderator would not give me another two hours to do a complete job. I have therefore torn up my summary and shall merely take a few minutes to tell you what my impressions have been. These I want to make very general.

As Dr. Hurtado first pointed out, we must distinguish between natural and acquired acclimatization. Perhaps in the years to come the distinction will disappear, but I should like to point out that most of what we knew up to twenty years ago was based on acquired acclimatization, and many of us—myself included—have made many errors in trying to interpret it in terms of natural acclimatization. There seems to be a difference. Eventually, when we understand acclimatization, these differences may disappear.

As Dr. von Muralt has pointed out, the reaction to low oxygen is probably one of the most fundamental defense mechanisms possessed by any kind of protoplasm, including man. Furthermore, the study of acclimatization is difficult, because we are dealing here not with a specific area but with integrated physiology—to me, the most difficult physiology. On the other hand, it does provide an incentive for us to keep working. Integration will always be the greatest challenge we shall have to face in our work.

What impressed me was the fact that many of you either said or implied that we are now looking not for more facts, necessarily, but for direction on how to interpret the facts. Facts alone will never provide an understanding.

I should like to dwell on one or two ideas presented by several of the speakers. First, is the fetus in utero probably the best-adapted of all mammalian organisms to the equivalent of high altitude or low oxygen tension?

It may be worth while to ask this question again and again. I remind you of Dr. Mithoefer's graph, with pO_2 on the ordinate and age or development on the abscissa. The fetus starts off with a very low oxygen tension. When it is delivered, it has two choices: if born at high altitude, it has to adapt itself to a relatively higher oxygen; if born at sea level, then it must adapt itself to a very high oxygen level. Let us restudy, with reference to the fetus, the various factors that have been brought out during this session. Let us look at what we learn about the fetus with what I call "high-altitude spectacles"; unless we do that, the facts alone will not enhance our understanding of acclimatization.

Now, if the fetus is the animal best acclimated to low O_2, after birth it must readapt itself either to a medium oxygen tension (high altitude) or to a very high oxygen tension (sea level).

Then there is another question: What are the so-called normal values? This point was raised by various speakers, particularly Dr. Monge and Dr. Velásquez, when comparing sea-level man with altitude man. But I should like to ask, What would the textbook of normal physiology look like it it were written by a fetus? What would it look like if it were written by the Incas, who had their empire and their major city at an altitude of ten thousand feet and regarded sea-level areas as places to which they banished the undesirable citizens?

It is easy to list what such a textbook would say about sea-level man. We would obviously be described as anemic; he would have a relatively high blood volume; he would be hypoventilating and exhibit a hypercarbia. Since his pH is the same as that of the man at Cuzco, he would be classified as a case of compensated respiratory acidosis.

Furthermore, the puniness of sea-level man would be easily seen in terms of his cardiovascular response. His blood-pressure response to exercise would increase much more for a given task at sea level than it does in the high-altitude native. More lactic acid would be found during

recovery from exercise. And, as Dr. Hurtado showed us years ago, the maximum amount of work that can be done at sea level by an equally trained man is often less.

Finally, the people at Cuzco would worry about the pulmonary hypotension of sea-level man. Their final message would be that man at altitude is apt to die of right heart failure. But those poor people at sea level die of left heart failure and arterial hypertension.

Without wishing to be facetious, I think we can sometimes learn by turning the tables and asking ourselves, as Dr. Monge has done so well, what normal values are. Without a proper standard we cannot interpret, we can only describe.

Lastly, let us ask other questions, about anoxia. Take the lower vertebrates. They are our ancestors, who taught us all the tricks that keep us alive today at altitude as well as at sea level and who can function surprisingly well when the oxygen tensions are reduced. Under such conditions they shift so easily into anaerobic metabolism that we call it normal behavior. But this is exactly what man has to relearn if he goes to altitude. I feel, therefore, that we must look further into enzyme modifications, pentose shift, and related phenomena, which Dr. B. Reynafarje discussed. This is an important and new way of looking at acclimatization.

We must ask the right questions. This may be the most important thing we can do, because facts alone may no longer be enough.

Moderator: To conclude this meeting, I should like to express our appreciation to the participants and to the audience. I am sure I speak for my Peruvian colleagues in expressing gratitude for the opportunity to talk to and learn from friends of other countries interested in the same problems.

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