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Pulmonary Hypertension and Pathology at High Altitudes

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Life at high altitudes has been a subject of scientific interest for more than a century. It is generally agreed that no contribution has exerted more influence in this field than Barcroft's landmark "Lessons from High Altitudes" in 1925.[1] There is a large body of literature on the subject, including recent monographs by Heath and Williams[2] and by Ward, Milledge, and West.[3] The latter should appeal, in particular, to those engaged in outdoor sports, such as mountain climbers and balloonists, and to people preparing for a sojourn at high altitudes.

A major impetus for the study of high-altitude problems has arisen from the need to ascertain the role of hypoxia in cardiorespiratory disease at sea level. Yet the opportunity for research has gone beyond the mechanisms of acquisition of O_2 from the rarefied high-altitude atmosphere; it encompasses transport and delivery of this gas to the tissues as well as intracellular metabolism in many organs. To be sure, life at high altitudes includes additional problems, including exposure to cold and radiation, but these are problems beyond the scope of the present review.

Millions of people throughout the world live at moderate altitudes (1515–3333 m or 5000–11,000 ft above sea level); large groups, exact numbers unknown, live at high altitudes (>3333 m or 11,000 ft above sea level), mainly in the South American Andes, the Himalayan regions, and the Tibetan plateau. Well-recognized pathologic manifestations of life at high altitudes include a higher prevalence of congenital heart disease (CHD; *e.g.*, patent ductus arteriosus [PDA])[4] and tumors of the carotid body.[5] Remarkably, these same pathologic manifestations occur in Mexico City (altitude, 2240 m or 7392 ft).[6,7] Large numbers of carotid body tumors have been noted in Bogota, Colombia (altitude, 2500 m or 8250 ft),[8] and another large series of these lesions originated in Colorado (1500–3000 m or 4950–9900 ft above sea level).[9] It seems, therefore, that pathologic manifestations are already evident at moderate altitudes; at high altitudes, the pathology is both more varied and dramatic and includes life-threatening conditions. They affect both well-acclimatized natives and newcomers to high altitudes (Display 24-1).

Recently, interest in high-altitude problems has been awakened by the popularity of sports such as mountain climbing, skiing, and trekking. To the hundreds of thousands of people involved in such pursuits, conditions such as acute mountain sickness (AMS) and high-altitude pulmonary edema (HAPE) have more than a passing interest. Because they can be life-threatening, they should be properly understood.

A basic and irrepressible trait of human nature is to conquer the environment, and this compulsion is vividly exemplified in mountain climbing. As a result of this activity, it has become possible to ascertain the hypoxic tolerance of humans to terrestrial altitudes. It appears limitless, as shown by the astonishing feat of Reinhold Messner and Peter Haveler, who climbed to the top of Mount Everest in 1978 (altitude, 8848 m or 29,198 ft) breathing ambient air.[10] Their feat has since been repeated by others.

HIGH-ALTITUDE PULMONARY HYPERTENSION

The discovery by Rotta and colleagues in 1956 of pulmonary arterial hypertension at high altitudes was not mere serendipity.[11] In 1946, von Euler and Liljestrand noted that the mean pulmonary artery pressure of cats rose significantly while breathing a

DISPLAY 24-1. PATHOLOGIC CONDITIONS THAT OCCUR AT HIGH ALTITUDES

High-altitude pulmonary hypertension
Congenital heart disease
Acute high-altitude pulmonary edema
Chronic mountain sickness (Monge disease)
Pathology of the carotid body and chemodectomas

10% mixture of oxygen in nitrogen.[12] This remarkable observation was soon followed by the demonstration by Motley and associates that the mean pulmonary artery pressure of man also rises while breathing reduced oxygen concentrations.[13]

It is well accepted that pulmonary hypertension at high altitudes is due to an increased vascular resistance.[14] Such striking response is noted in normal subjects exposed to acute hypoxia, in lowlanders acclimated to high altitudes, and in high-altitude natives. The pulmonary hypertension of acute hypoxia is relieved by breathing oxygen, but this is not the case in either the lowlander acclimated to high altitudes or in the high-altitude native. Such observations are consistent with the view that pulmonary hypertension during acute hypoxia is the result of vasoconstriction, whereas in the latter two groups, the response is fundamentally the result of structural changes in the pulmonary vessels.

In the lowlander who has acclimated to high altitude, the mean pulmonary arterial pressure rises from 12 to 18 mm Hg, on the average, after 1 year of residence at 4540 meters (altitude, 15,000 feet), and the resting pulmonary arterial pressure increases significantly during exercise. High-altitude natives show an even higher increment (26–60 mm Hg) in mean pulmonary arterial pressure during exercise, probably reflecting the severity of the vascular changes.[14]

Right Ventricular Hypertrophy

There are ample clinical and electrographic data indicating that the lowlander acclimated to high altitude develops right ventricular hypertrophy. As noted by Pugh, climbers returning from high altitudes show right heart enlargement on chest roentgenograms.[15] Pathologic evidence of right ventricular hypertrophy in children born between 3700 and 4260 meters (12,210–10,058 feet) in the Peruvian Andes was provided by Arias-Stella and Recavarren.[16] They showed that the ratio of left-to-right ventricular myocardium weight was, on average, 1.8 in the sea-level group and less than 1.3 in the high-altitude group, a highly statistical difference ($P < 0.001$) indicative of right ventricular hypertrophy (Fig. 24-1).

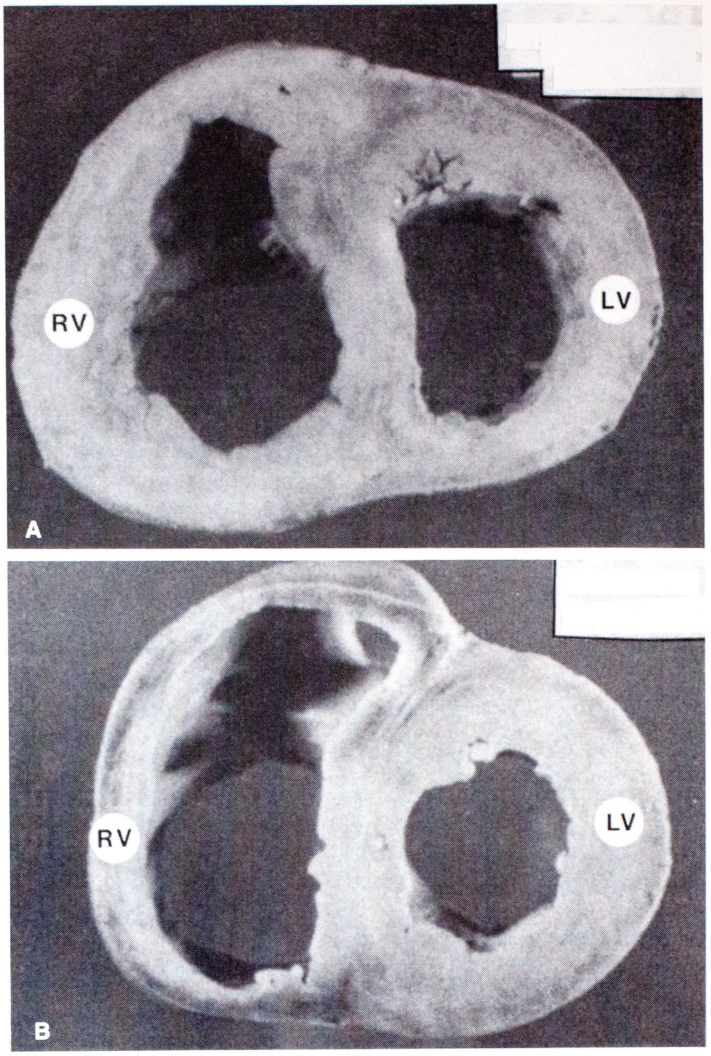

FIGURE 24-1. Transverse section of the ventricular mass in (**A**) a 2-year-old child born at an altitude of 4546 m (15,000 ft) and (**B**) a normal 3-month-old child born at sea level. In spite of the extreme degree of right ventricular hypertrophy, the child in (**A**) had no evidence of congenital heart disease or right ventricular failure and died as a result of an acute respiratory infection. (LV, left ventricle; RV, right ventricle; from Saldana M. Normal cardiopulmonary structure and function and related clinical conditions in people native to high altitudes. In: Liebow AA, Smith DE, eds. The lung. Baltimore: Williams & Wilkins, 1968:259.)

Elastic Configuration of the Pulmonary Trunk

We have studied the elastic configuration of the pulmonary trunk at sea level (Fig. 24-2) and at high altitudes (Figs. 24-3 and 24-4).[17,18] The results are summarized as follows.

An aortic configuration of the pulmonary trunk characterized by numerous long, uninterrupted elastic fibers was found at sea level only during the first 3 months of life; at high altitudes, it was commonly seen during the first decade of life (see Fig. 24-3).

In high-altitude natives, the normal transitional pattern noted at sea level between 25 days and 9 years of age and characterized by fragmentation of elastic fibers was rarely seen.

The persistent configuration of the pulmonary trunk characterized by a combination of long uninterrupted and fragmented fibers was seen in a minority of cases at sea level, mainly within the first 3 years of life. At high altitudes, it was the most common type of pulmonary artery throughout life (see Fig. 24-4).

Both the abnormal maintenance of the aortic type of pulmonary trunk during the first decade of life and its conversion to the persistent type at high altitudes are manifestations of pulmonary hypertension present since birth. Such phenomena are comparable to what occurs in sea-level children with CHD and pulmonary hypertension since birth. Evolution to an adult type of pulmonary trunk, which at sea level is seen already by 1 year of life, is almost never observed at high altitudes. Also reflecting chronic pulmo-

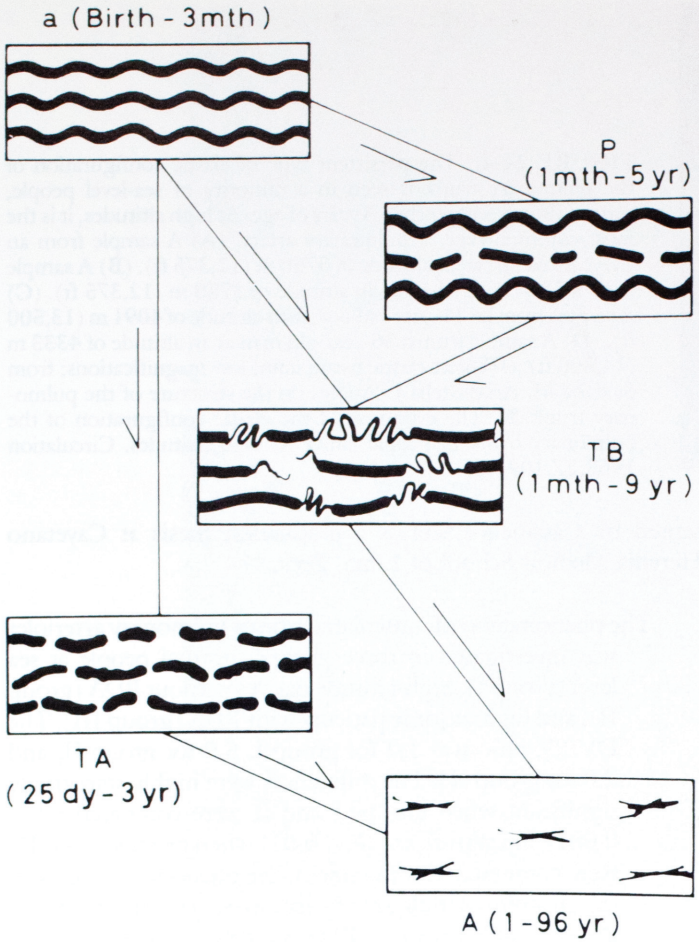

FIGURE 24-2. The evolution of the elastic configuration of the pulmonary trunk in normal people at sea level. The aortic pattern of the newborn (a) usually evolves to the adult pattern (A) through the transitional A pattern (TA) or less common, through the transitional B pattern (TB); a relatively uncommon pattern, designated as persistent (P), may also occur. (From Saldana M, Arias-Stella J. Studies on the structure of the pulmonary trunk. I. Normal changes in the elastic configuration of the human pulmonary trunk at different ages. Circulation 1963;27:1086.)

nary hypertension, the pulmonary trunk of the high-altitude native is significantly thicker than that of a person at sea level.[19]

Small Pulmonary Arteries and Arterioles

The cause of pulmonary hypertension at high altitude resides at the level of the small arteries and arterioles of the lung.[20] We studied 22 high-altitude natives ranging in age from 1 month to 76 years and compared them with a normal sea-level group matched by age. All high-altitude natives had been born at and resided at 3424 to 4333 m (11,300–14,300 ft) above sea level. All high-altitude natives and sea-level controls died of accidents or diseases unrelated to the cardiopulmonary system.

The muscular pulmonary vessels in both groups were classified into two groups according to the air channels they were associated with: proximal vessels (PV), which are located parallel to terminal bronchioles, and distal arteries (DV) or arterioles, which are located at the level of alveolar ducts and sacs. The average ratio of DV/PV was 1.24 at sea level and 5.66 at high altitudes ($P < 0.001$) during the first 2 years of life (Fig. 24-5). In a group aged 6 to 76 years, the DV/PV ratio was 1.18 at sea level and 4.36 at high altitudes ($P < 0.001$; Fig. 24-6). In the higher age group, medial hypertrophy of PV could also be demonstrated by morphometry.

The above findings are consistent with the view that at high altitude pulmonary hypertension is the result of a delay or incomplete involution of the fetal characteristics of the pulmonary arterial tree (*i.e.*, medial hypertrophy of arteries and arterioles, brought about by hypoxia acting from birth on).

We were unable to find intimal changes of significance involving pulmonary arteries or arterioles, and the findings have been confirmed by others (Fig. 24-7).[21,22] Specifically, we have never seen examples of hypertensive plexiform angiopathy. O'Neill and colleagues have provided an anecdotal report of an adolescent girl born to Scottish parents in the highlands of Peru; however, the changes in this case most likely represent coincidental primary pulmonary hypertension.[23]

The original proposition that pulmonary hypertension at high altitudes determines a more extensive perfusion of the alveolar capillary bed and thus contributes to the reduction in the alveolar-arterial O_2 gradient appears physiologically unsound.[14]

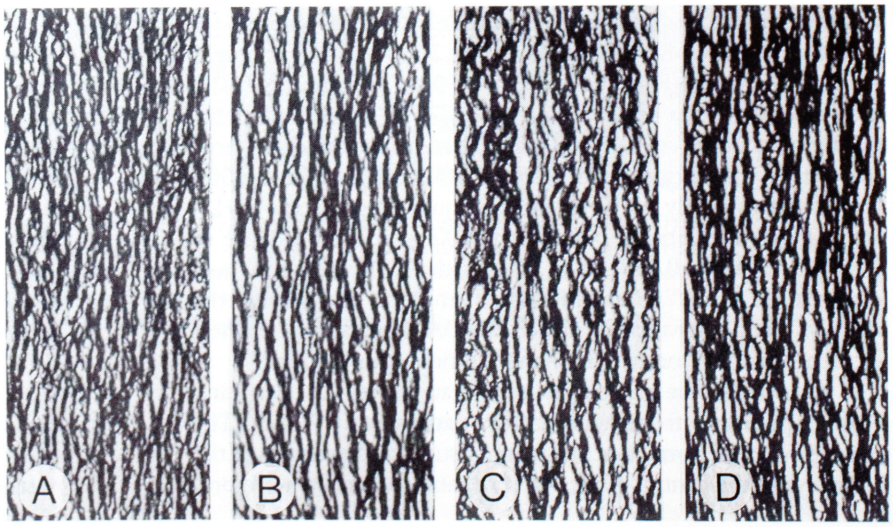

FIGURE 24-3. Maintenance of the aortic configuration of the pulmonary trunk occurs at high altitudes. (**A**) A sample from a 5-year-old boy at an altitude of 4079 m (13,460 ft). (**B**) A sample from an 8-year-old girl at an altitude of 4333 m (14,300 ft). (**C**) A sample from a 9-year-old boy at an altitude of 4333 m (14,300 ft). (**D**) The ascending aorta in (**C**), for comparison. (Weigert elastic tissue stain; low magnifications; from Saldana M, Arias-Stella J. Studies on the structure of the pulmonary trunk. II. The evolution of the elastic configuration of the pulmonary trunk in people native to high altitudes. Circulation 1963;27:1094.)

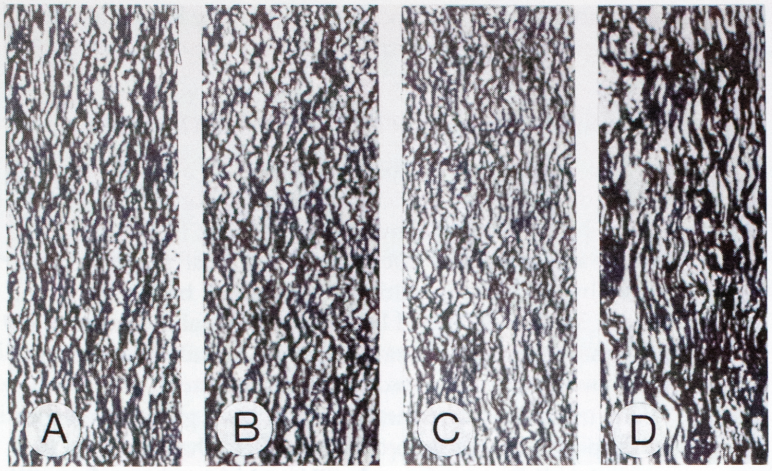

FIGURE 24-4. The persistent type of elastic configuration of the pulmonary trunk is seen in a minority of sea-level people, usually those younger than 3 years of age. At high altitudes, it is the most common type of pulmonary artery. (**A**) A sample from an 11-year-old girl at an altitude of 3750 m (12,375 ft). (**B**) A sample from a 28-year-old man at an altitude of 3750 m (12,375 ft). (**C**) A sample from an 11-year-old boy at an altitude of 4091 m (13,500 ft). (**D**) A sample from a 36-year-old man at an altitude of 4333 m (14,300 ft). (Weigert elastic tissue stain; low magnifications; from Saldana M, Arias-Stella J. Studies on the structure of the pulmonary trunk. II. The evolution of the elastic configuration of the pulmonary trunk in people native to high altitudes. Circulation 1963;27:1094.)

Instead, pulmonary hypertension is best interpreted as a vestigial type of phenomenon dating back to fetal life when pulmonary hypertension diverts blood to the aorta by way of the ductus arteriosus. If anything, pulmonary hypertension is an encumbrance in the process of acclimatization to high-altitude hypoxia, yet it is of little practical significance as a cause of disease. Indeed, it is a common observation in the highlands of Peru that natives engage in vigorous physical activities, particularly soccer games, and long-distance runners frequently excel in competition over their sea-level counterparts. One exception to the above statement is the condition of HAPE (see High-Altitude Pulmonary Edema).

CONGENITAL HEART DISEASE

In some animal species, even short periods of experimental hypoxia exert teratogenic effects on the cardiovascular system of the fetus.[24] It is therefore not surprising to find a higher incidence of CHD at high altitudes. Doubtless, high-altitude children born with cyanotic CHD (*i.e.*, tetralogy of Fallot, pulmonic stenosis, and certain forms of transposition of the great vessels) stand a low chance of survival. They probably die at birth or shortly afterward, and the prevalence of such anomalies goes unnoticed because of the lack of systematic autopsy investigations.

In sharp contrast to the above is the observation that PDA is the most common form of CHD, even at moderate altitudes such as Mexico City (altitude, 2240 m or 7392 ft).[4,7] This phenomenon was investigated by Marticorena and colleagues, who carried out screening cardiovascular investigations in 5000 children born and living at 3500 to 5000 m (11,550–16,500 ft) of altitude.[25] The incidence of PDA at high altitudes was 0.72%, which is 18 times greater than that at sea level (0.04%). The authors found a distinct correlation with altitude—at 4500 to 5000 m (14,850–16,500 ft), PDA was nearly 30 times more frequent than at sea level.

Among the Tibetan population of Xizang, the incidence of CHD varies from 0.51% to 2.25%, with PDA being the most common anomaly. As already noted in Peru, the greater the altitude, the higher the prevalence of PDA. Notably, the highest incidence of PDA occurred among Chinese immigrants.[26]

We carried out pathologic investigations on 27 open lung biopsy specimens from high-altitude natives with PDA.[27] The biopsies were performed at the time of surgical correction of the anomaly, in the central Andes of Peru, and the results were presented by Cassinelli-Ezeta as a graduation thesis at Cayetano Heredia Medical School of Lima, Peru.

- The phenomenon of muscularization of pulmonary arterioles was investigated in three groups: normal people at sea level (group I), high-altitude natives without PDA (group II), and high-altitude patients with PDA (group III). The DV/PV ratio was 1.2 for group I, 5.0 for group II, and 7.0 for group III. The differences were highly statistically significant when groups I and II were compared ($P < 0.001$) and significant ($P < 0.01$) when groups II and III were compared. Simply stated, the phenomenon of muscularization of pulmonary arterioles seen in the high-altitude dweller without PDA is even more accentuated in those having PDA (Fig. 24-8).
- The area of the media of small pulmonary arteries adjacent to terminal bronchioles (*i.e.*, PV) and arterioles (*i.e.*, DV) was carefully determined by planimetry and expressed as a percentage of the circle determined by the external elastic lamina in the same three groups. The values were identical for PV and DV within each group; they were 15%, 28%, and 33% for groups I, II, and III, respectively. The differences between these three groups were highly statistically significant ($P < 0.0001$). In other words, we confirmed the muscularization of arterioles and medial muscular hypertrophy of both arteries and arterioles in the high-altitude native, and the change was distinctly more accentuated in the presence of PDA (Fig. 24-9).
- Intimal changes such as fibrosis or fibroelastosis were minimal or nonexistent in this study. Of 27 patients with PDA, only 1 showed a lesion of minimal fibromuscular hyperplasia of the intima (Fig. 24-10). Pulmonary veins and venules were normal.
- In seven patients, 4 to 28 years of age (mean, 12 years), the ductus measured 9 mm in diameter (range, 3–18 mm). On average, the mean pulmonary arterial pressure for the group was 52 mm Hg and fell to 36 mm Hg after O_2 administration. The pulmonary blood flow increased by 145% and the pulmonary vascular resistance dropped by 50% after O_2 administration. These findings are consistent with the view that in high-altitude patients with PDA, pulmonary hypertension is due to a situation of vascular restriction caused by muscularization of pulmonary arte-

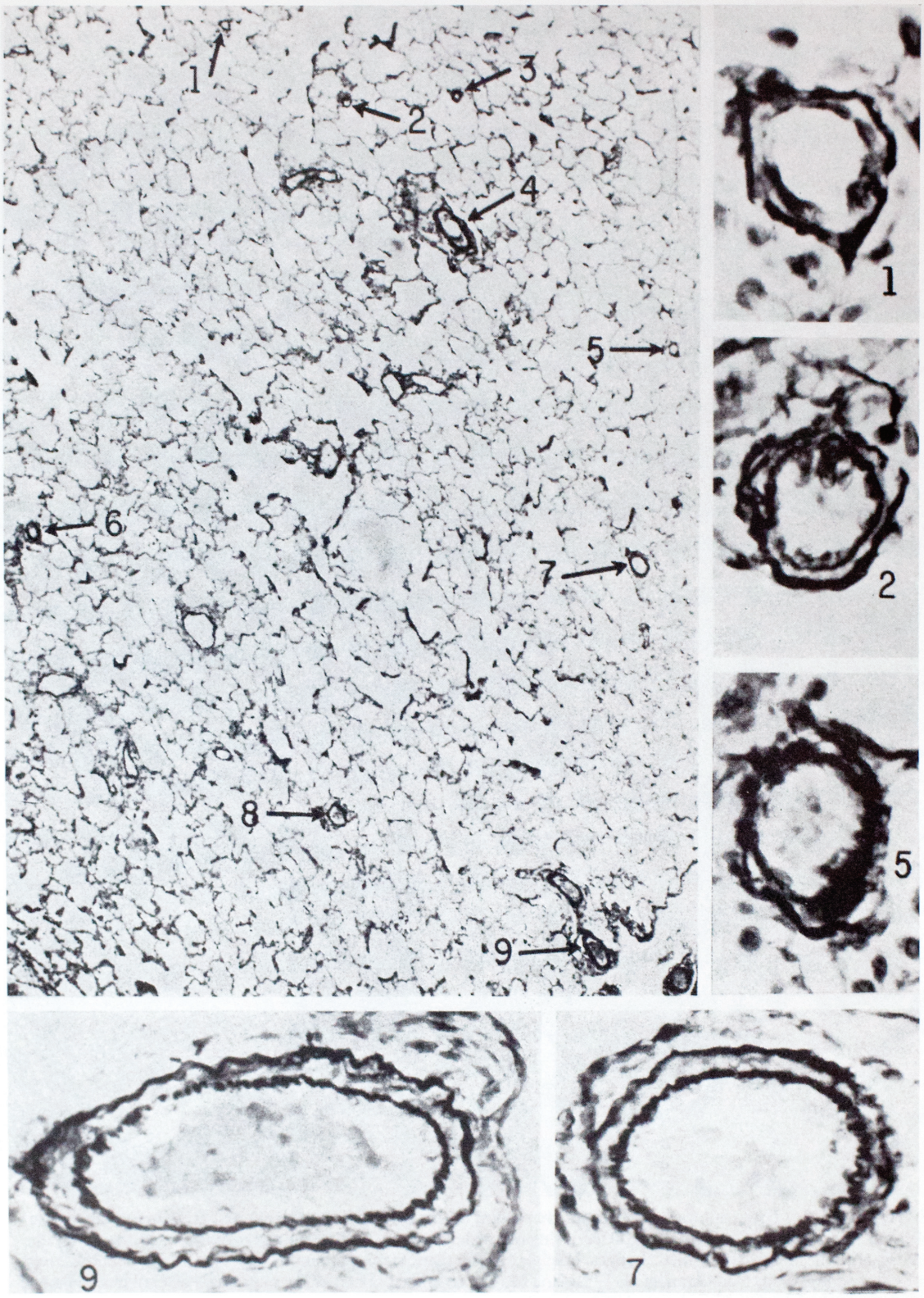

FIGURE 24-5. Lung tissue from an 8-year-old normal boy, born and living at an altitude of 4333 m (14,300 ft), who died as a result of a transit accident. Nine distal pulmonary vessels (*i.e.*, arterioles) can be seen in this field (numbered 1–9). Some of these are enlarged (*insets*) to demonstrate the distinct muscular media. (Weigert elastic tissue stain; panoramic view; low magnification; insets at high magnification; from Arias-Stella J, Saldana M. The terminal portion of the pulmonary arterial tree in people native to high altitudes. Circulation 1963;28:915.)

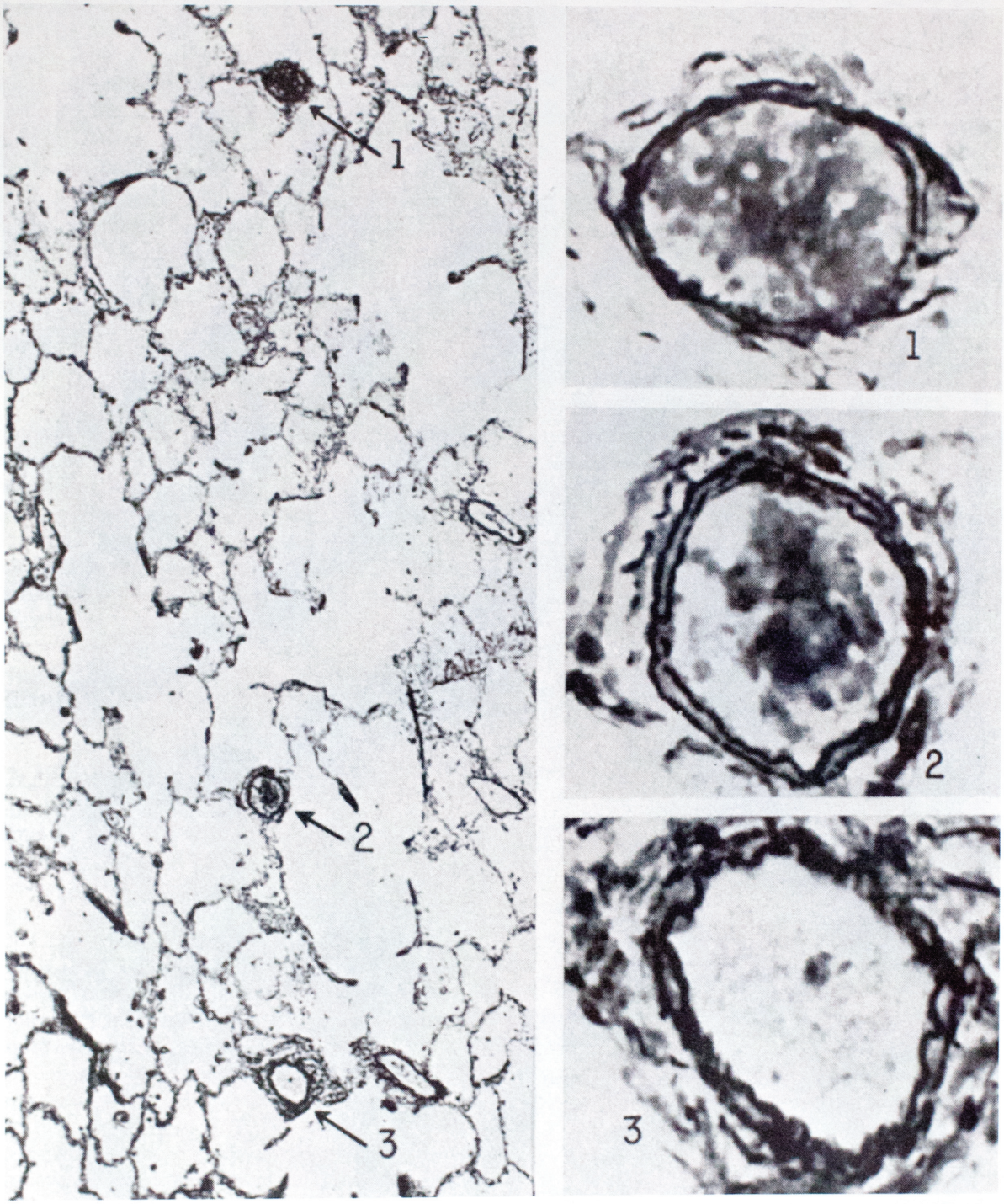

FIGURE 24-6. Three pulmonary arterioles are present in this field of view of lung tissue from a normal 33-year-old man at an altitude of 4433 m (14,300 feet). Enlargement (*insets*) shows that the arterioles have a distinct muscular media; note the absence of intimal changes. (Weigert elastic tissue stain; panoramic view; low magnification; insets at high magnification; from Arias-Stella J, Saldana M. The terminal portion of the pulmonary arterial tree in people native to high altitudes. Circulation 1963;28:915.)

rioles and hypertrophy of pulmonary arteries. This restriction is further aggravated by powerful vasoconstrictive.

Our observations also support the view that PDA at high altitudes has a very favorable evolution; we have never seen it progress to significant intimal proliferation of pulmonary vessels, and never has it progressed to plexogenic hypertensive arteriopathy. It should also be stressed that in our series of 27 cases, more than 50% of the patients were 10 years of age or older, including 3 patients 28, 29, and 34 years of age. As a result of these observations, Peruvian children with PDA at high altitudes undergo surgery during adolescence or later to avoid the surgical problems inherent to operations in very young infants and babies, as was the case before.

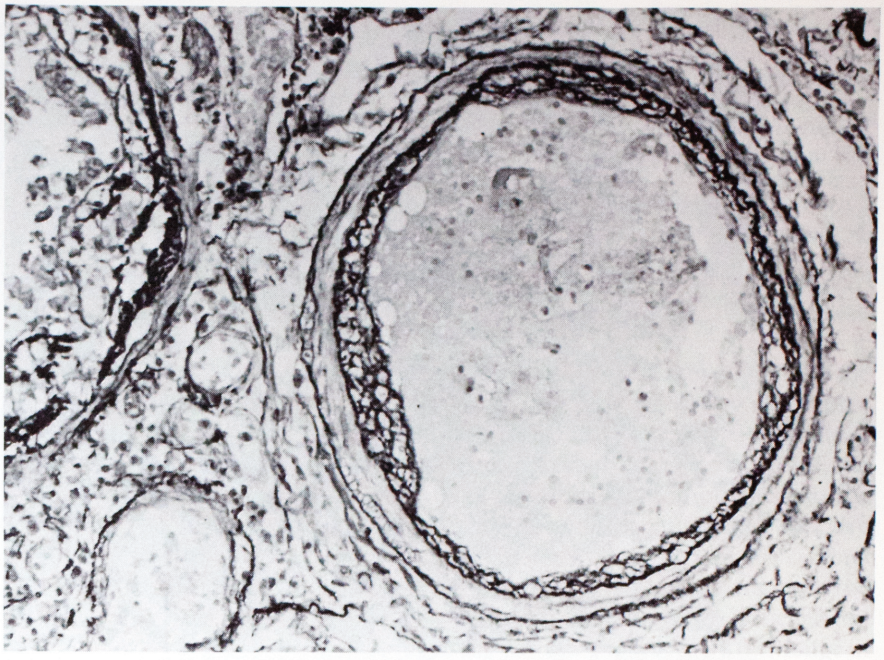

FIGURE 24-7. In this most unusual finding in a normal high-altitude native, there is proliferation of muscle and elastic tissue in the intima; however, no significant luminal occlusion is seen as the result of this change. There was no evidence of cardiopulmonary disease; the above change was focal and probably of no significance. (Weigert elastic tissue stain; intermediate magnification.)

HIGH-ALTITUDE PULMONARY EDEMA

A form of acute pulmonary edema can develop after ascension to high altitudes. In 1918, Ravenhill described three examples of what he designated "puna of the cardiac type," which most likely represent HAPE; he attributed these to cardiac failure.[28] Hurtado, in 1937, described his observations of the same disease.[29] The condition was rediscovered in the English literature by Houston, who, in 1960, published his landmark paper on "Acute Pulmonary Edema of High Altitudes."[30] Since the 1960s, there have been descriptions of hundreds of cases from every mountain area of the world. The Himalayan fighting of 1963 between China and India called attention to the frequent occurrence of the disease among the Indian troops.[31]

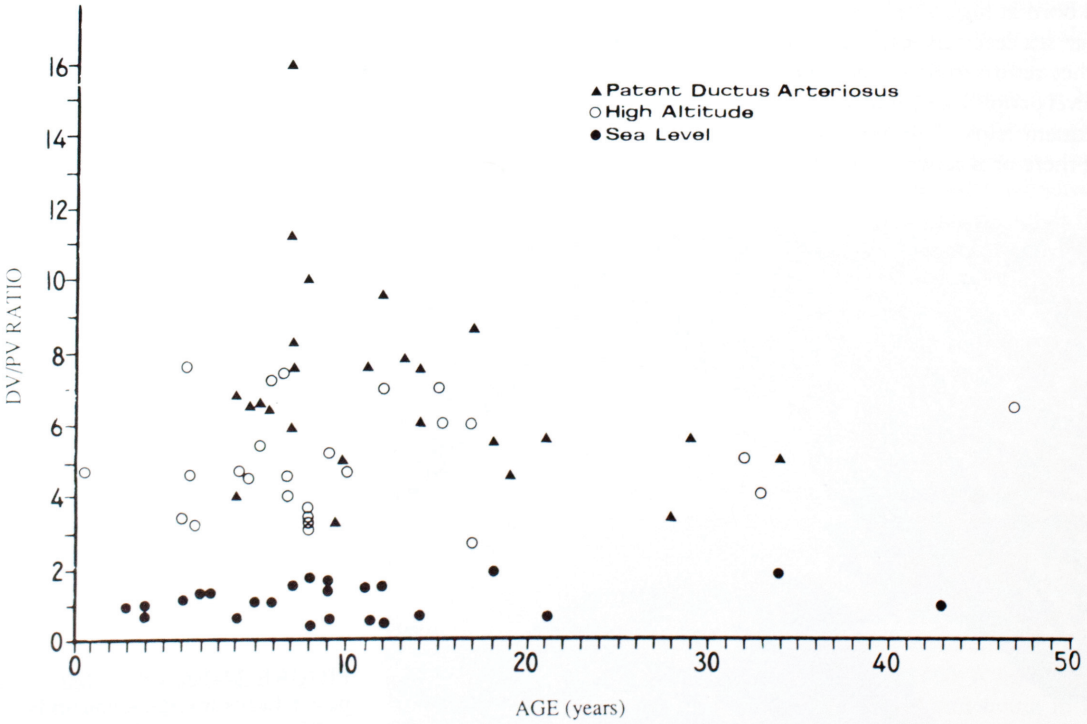

FIGURE 24-8. The ratio of distal pulmonary vessels with a distinct muscular wall (DV) to proximal vessels (*i.e.*, small pulmonary arteries; PV) is indicative of muscularization of the pulmonary arterioles in three different populations. (From Cassinelli-Ezeta MT. Alteraciones de la vasculatura pulmonar en nativos de altura con persistencia del conducto arterioso. Lima, Peru: Tesis de Grado. Universidad Peruana Cayetano Heredia, 1970.)

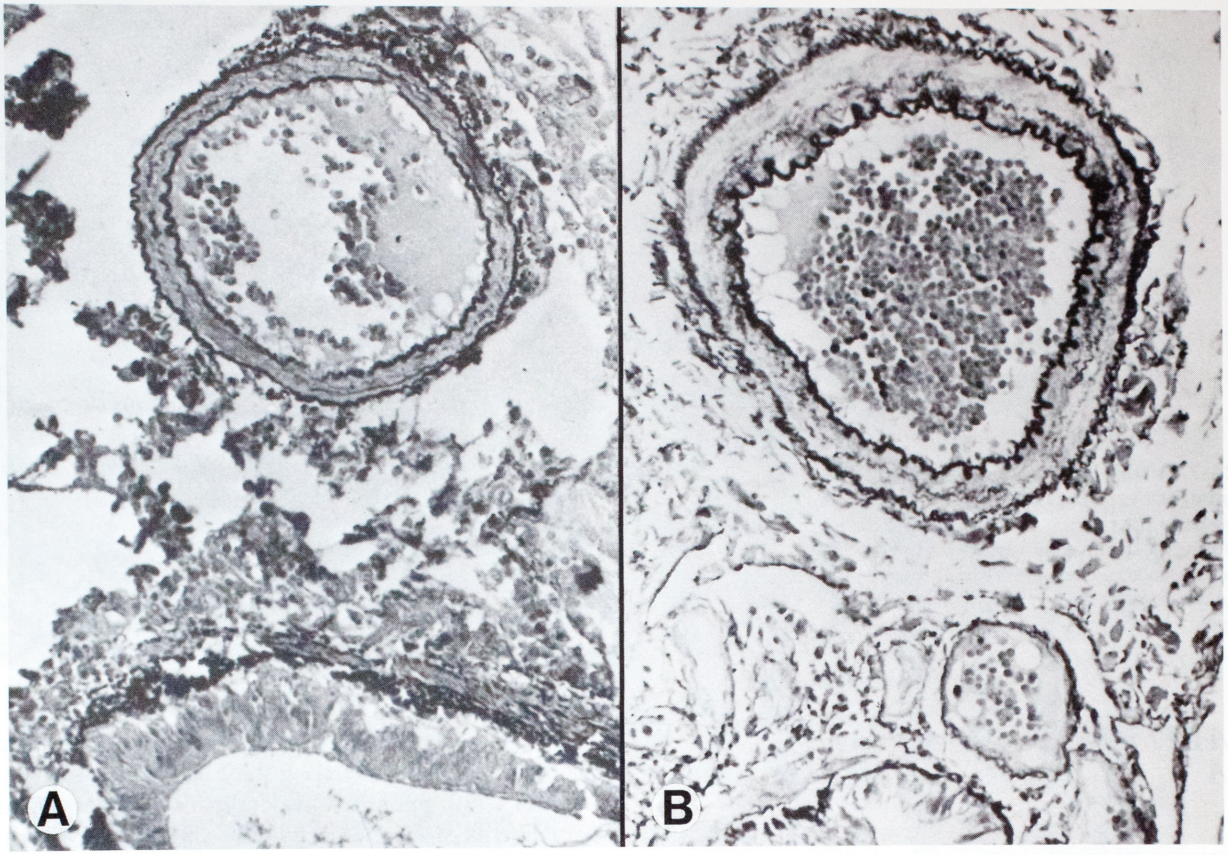

FIGURE 24-9. (**A**) Medial hypertrophy of a small pulmonary artery occurred in a normal, 6-year-old child born and living at an altitude of 4379 m (14,450 ft). (**B**) A comparable type of vessel is present in a 21-year-old high-altitude female with patent ductus arteriosus. The medial hypertrophy is severe in the latter, but no intimal changes are noted. The crenation of the internal elastic lamina suggests vasoconstriction. (Weigert elastic tissue stain; intermediate magnification.)

Individuals born at high altitudes who have stayed for a few days or weeks at sea level are especially prone to develop the disorder when they return to their place of origin. But the disease also affects sea-level people ascending to high altitudes on the first trip or in subsequent trips. Typically, the patient has been very active in getting there or is active upon arrival. There is a time lag between the arrival and the onset of symptoms that varies from a few hours to 36 hours. In addition to physical exercise, exposure to cold is an important contributory factor. The patient becomes short of breath and lethargic and may develop chest pain, tachycardia, tachypnea, and crackles at the lung bases and interscapular area. A dry cough develops, which later progresses to the produc-

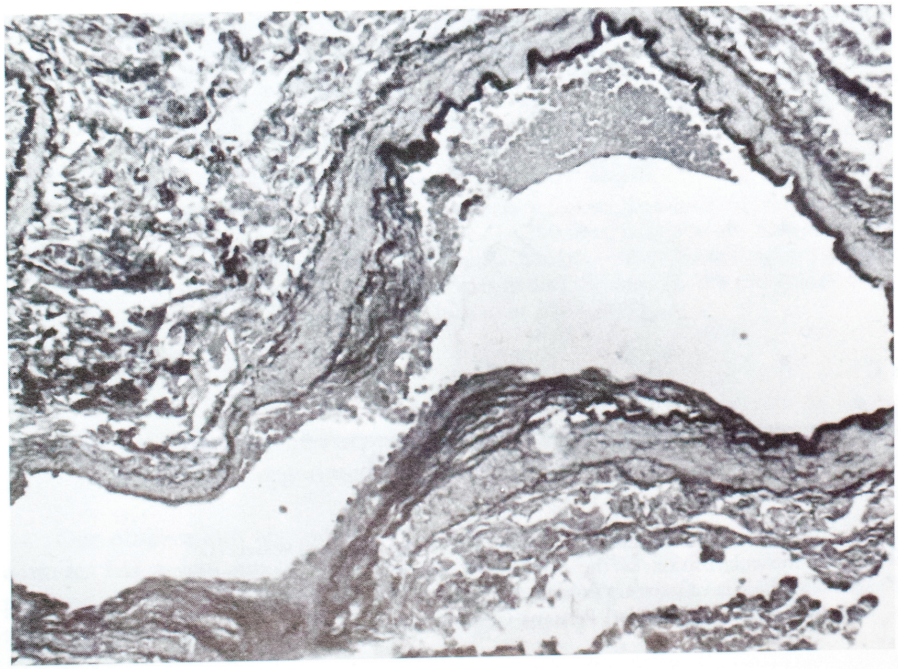

FIGURE 24-10. Of 27 high-altitude patients with patent ductus arteriosus, one patient had a fibroelastotic pad at a site of branching; this was the only intimal lesion found in the entire group. The media, however, show prominent medial hypertrophy, and the crenation of the internal elastic lamina suggests vasoconstriction. (Weigert elastic tissue stain; intermediate magnification.)

tion of frothy white sputum that eventually becomes blood-tinged. Over a few hours, the condition progresses, with increased respiratory distress, cyanosis, bubbling respirations, foam in the mouth, coma, and death.[32]

In all studies of HAPE, the pulmonary artery pressure is usually three to four times greater than that found in healthy subjects at the same altitude. The wedge pressure is normal, implying normal pulmonary venous and left atrial pressure, so the possibility of left ventricular failure is ruled out. The cardiac output is usually within the normal range, so pulmonary hypertension is the result of a markedly increased vascular resistance. In a group of five patients with HAPE studied by Antezana and colleagues, breathing 100% oxygen brought the pulmonary arterial pressures to normal levels within 3 minutes in two out of five cases, but in the other three cases it leveled out at 40 to 50 mm Hg of mean pulmonary artery pressure, which is still above the upper limits of normal for that altitude.[33]

There have been a number of postmortem studies in patients with HAPE.[34–38] Grossly, the lungs are heavy and solid and always weigh more than 1200 g together. The cut surface weeps blood-stained edema; however, a striking feature is the nonuniform distribution of the latter. Areas of clear edema alternate with others of hemorrhagic consolidation, and still other areas are virtually normal or overinflated. Thrombi within the pulmonary arteries are commonly found.

Microscopically, there is massive filling of alveoli by fluid containing erythrocytes, neutrophils, and macrophages. A striking finding is the presence of hyaline membranes lining alveoli, resembling hyaline membrane disease of the newborn. Pulmonary hemorrhage secondary to rupture of small pulmonary vessels is an outstanding feature in many cases. The alveolar capillaries are congested, and small pulmonary arteries and veins contain fibrin clots. The edema fluid is rich in high-molecular-weight proteins, erythrocytes, and macrophages, findings suggesting a large-pore leak type of edema.

HAPE is due to a powerful arteriolar constriction in response to hypoxia, and some degree of venular constriction has been suggested. The latter is probably uneven, which explains the patchy nature of the pulmonary edema. It has also been proposed that when the capillary pressure becomes high enough, pores open up, which explains the high-protein fluid.

The pathogenesis of HAPE appears multifactorial and includes mechanisms such as pulmonary hypertension, venular constriction with uneven pulmonary perfusion, arterial leakage, and multiple pulmonary emboli. The relative importance of these factors overall and in the individual patient remains yet to be ascertained.[32]

The most important step in treatment is to bring the patient down to lower levels as soon as possible. In the meantime, consideration should be given to other modalities, foremost oxygen, diuretics (*e.g.*, furosemide), and antibiotics to prevent pneumonia.

CHRONIC MOUNTAIN SICKNESS OR MONGE DISEASE

A sharp distinction should be made between AMS and chronic mountain sickness (CMS). The former was originally described by the Jesuit priest Joseph de Acosta in 1590 while traveling in the Andes.[39] His vivid description is worth quoting at length.

> There is in Peru a high mountaine which they call Pariacaca. . . . When I came to mount the degrees, as they call them, which is the top of this mountaine, I was suddenly surprised with so mortall and strange a pang, that I was ready to fall from the top to the ground and although we were many in company, yet everyone made haste (without any tarrying for his companion) to free himself speedily from this ill passage. . . . I was surprised with such pangs of straining and casting as I thought to cast up my heart too: for having cast up meate, fleugme and choller both yellow and greene, in the end I cast up blood with the straining of my stomach. To conclude, if this had continued I should undoubtedly have died.[39]

The most important factors in the production of AMS are the rapidity of ascent and the height reached, but there is also a great deal of personal variation. It seems clear that hypoxia produces some alteration of fluid or electrolyte homeostasis, with either water retention or a shift of water from the intracellular to the extracellular compartments.[39] This causes cerebral edema so severe in some cases to deserve the designation of malignant cerebral AMS. Acetazolamide (Diamox) is effective in reducing both the incidence and the severity of AMS. Aspirin is often ineffective.

CMS, on the other hand, was described in 1928 by Monge in a series of patients from Cerro de Pasco, Peru (altitude, 4376 m or 14,440 ft), with extreme cyanosis and erythrocyte counts significantly higher than those normally found at such altitude.[40] The condition is also known as Monge disease. Talbott and Dill in 1936 reported the first case of CMS in the English literature.[41] In 1942, Hurtado published detailed observations of CMS, including the effects of descent to sea level and return to altitude.[42]

CMS has also been recognized in Leadville, Colorado (altitude, 3073 m or 10,140 ft), by Wiel and colleagues[43] and Kryger and associates.[44,45] The latter authors have described 20 patients with this condition and mentioned that about 60 patients are known to physicians living in the area. A classic example of CMS in a 67-year-old woman living in California at an altitude of 2000 m (6600 ft) has been reported by Gronbeck.[46]

CMS appears to be extremely rare in the Himalayas. Residents from this area tend to have lower hemoglobin concentrations, periodically migrate to lower altitudes, and have greater mobility than their Andean counterparts, who live in considerable isolation. In a study from China, 21 individuals from Lhasa (altitude, 3568 m or 11,774 ft) had excessive polycythemia and normal (*i.e.*, A-a) O_2 gradient.[47] These people also live on a high-altitude plateau and cannot easily move to lower altitudes.

Neurologic and mental changes characterize CMS, and they include headache, dizziness, somnolence, difficulty in concentration, and loss of mental acuity. Easy fatigability and paresthesias of the extremities are also noted. Some patients are alternately irritable, depressed, or even hallucinatory. Characteristically, the manifestations disappear when the patient descends to sea level and reappear when he or she returns to altitude.

Physical findings are usually florid; as noted by Heath and Williams, "the combination of virtually black lips and wine-red mucosal surfaces against the olive-green pigmentation of the Indian give the patient with Monge's disease a striking appearance."[48] The conjunctiva are markedly congested, and clubbing of the fingers is common. In Caucasians living in Leadville, Colorado, the appearance of patients with CMS has been compared with that of patients with polycythemia secondary to hypoxic lung disease at sea level.[44,45]

Values of oxygen saturation as low as 70% or less, hematocrit of 80%, and 25 g of hemoglobin per 100 ml of blood are frequent

findings. The chest x-ray films show normal lung fields and global heart enlargement with prominence of the right chambers. The electrocardiogram demonstrates changes of right ventricular overloading. The pulmonary arterial pressure in CMS is twice as high as that found in the healthy dweller at high altitudes. The cardiac output may be increased, but the pulmonary wedge pressure is normal. An increased diastolic pressure in the right ventricle is sometimes observed; it is noteworthy, however, that clinical evidence of right ventricular failure is seldom observed.[4]

It is clear that many of the manifestations of CMS are due to increased blood viscosity. When individuals were taken to sea level, normal arterial oxygen saturation values and a considerable reduction in the hematocrit levels were noted in a period as brief as 2 months.[4] There is also considerable reduction in the pulmonary arterial pressure with return of the cardiac output to normal values. The fact that all of these changes take place after such a short stay at sea level suggests that functional factors are important in the genesis of pulmonary hypertension in CMS.[4]

In one of the few studies on the pathology of CMS, Arias-Stella and colleagues noted a greater degree of muscular thickening of the pulmonary arteries than in normal controls at high altitude.[49] The accentuation of the hypoxia probably favors a stronger pulmonary vasoconstriction and greater muscularization of the small pulmonary vessels. Other factors contributing to the pulmonary hypertension include increased cardiac output, hypervolemia, increased blood viscosity, elevated alveolar P_{CO_2}, and acidosis. Remarkably, no obliterative intimal changes or plexiform arteriopathy has been noted in CMS.

There seem to be three major types of patients who fall under the designation of CMS.[50] The first type of CMS occurs in people who move from sea level to high altitude but never adjust to the change (*i.e.*, lack of acclimatization). This type of CMS is relatively common among Caucasians who have only recently moved to high-altitude environments, such as Leadville, Colorado.[43–45]

The second type, presumably the most common form of CMS, is composed of native highlanders with pulmonary diseases that are capable of producing hypoxia and pulmonary hypertension, such as chronic obstructive pulmonary disease, fibrosis of the lung, kyphoscoliosis, and neuromuscular disorders. It should be noted that smoking is common among these people, and many work in dusty occupations and mining and develop pneumoconiosis. Infectious diseases, including tuberculosis, are rampant in some areas. My colleagues and I have described several patients of this type who also had associated tumors of the carotid body, bilateral in one case.[5]

A third group of patients is composed of natives well-adapted to their high-altitude environment who in the absence of cardiopulmonary disease and for unknown reasons lose their acclimatization to their high-altitude environment. This is true primary CMS, but the cause or the mechanisms of the condition are poorly understood.

As shown by Hurtado, hyperventilation in the normal high-altitude native helps to maintain the alveolar P_{CO_2} around 50 mm Hg and thus represents a main mechanism of acclimatization to the hypoxic environment.[51] But in cases of CMS, he noted that the hyperventilatory state was absent and that CO_2 stimulation of the respiratory center produces a weaker response than in the acclimatized individual.

Severinghaus and colleagues noted that patients with CMS had a markedly blunted hypoxic ventilatory response (HVR) compared with healthy controls of the same age.[52] They have suggested that maybe people at the low end of the spectrum of HVR in the high-altitude population are those destined to develop CMS if they remain for years at high altitude. It is pertinent to point out

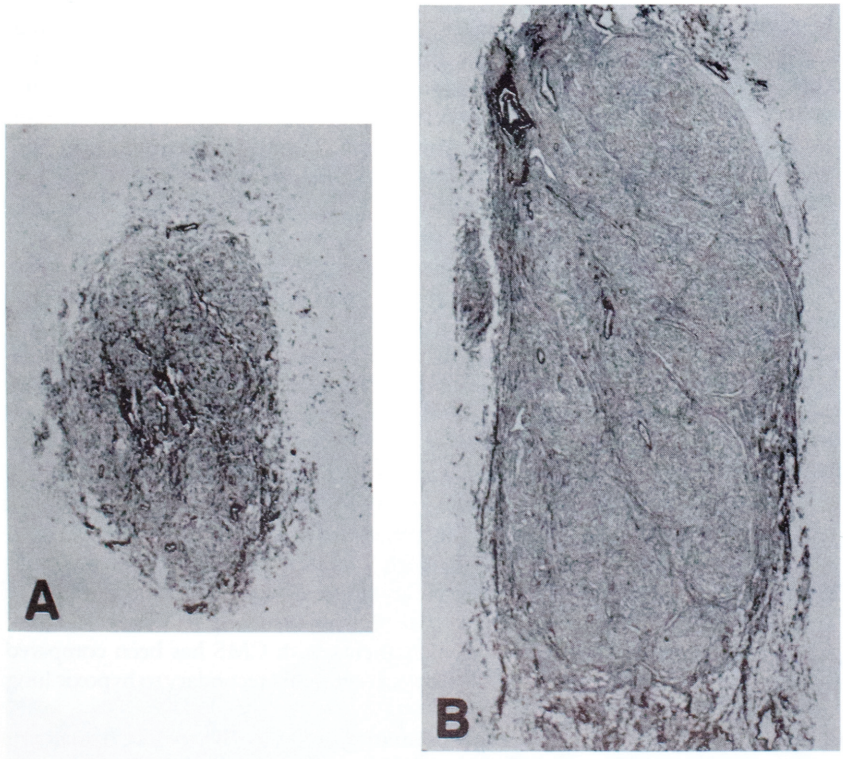

FIGURE 24-11. A normal carotid body (**A**) at sea level and (**B**) at high altitude. On average, the high-altitude carotid body is twice as heavy because of lobular hyperplasia. (Weigert elastic tissue stain; panoramic view; from Saldana MJ, Salem LE, Travezan R. High altitude hypoxia and chemodectomas. Hum Pathol 1973;4:251.)

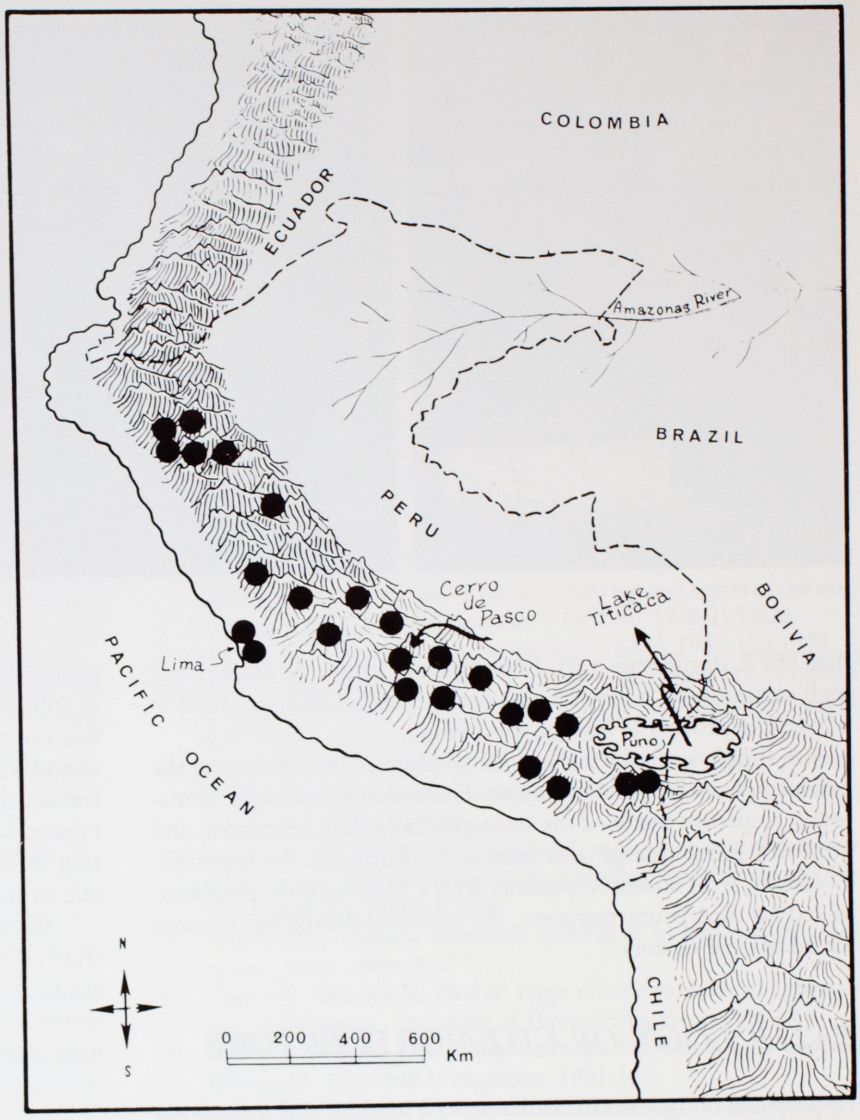

FIGURE 24-12. In the original study, 23 of 25 chemodectomas originated in the high-altitude Andean regions of Peru, and only 2 originated at sea level. The disparity becomes more striking if consideration is given to the fact that 75% to 80% of the Peruvian population lives in the coastal region at sea level.

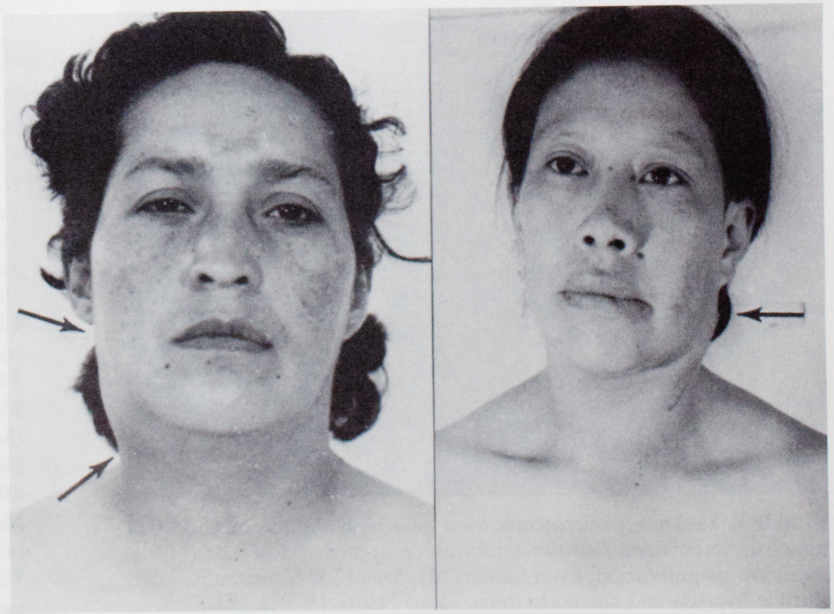

FIGURE 24-13. Two high-altitude Peruvian women of mixed Spanish and Indian ancestry show carotid body tumors. In this study, females predominated over males in a 6 : 1 proportion, and left-sided tumors predominated over right-sided tumors in a 3 : 1 ratio. (From Saldana MJ, Salem LE, Travezan R. High altitude hypoxia and chemodectomas. Hum Pathol 1973;4:251.)

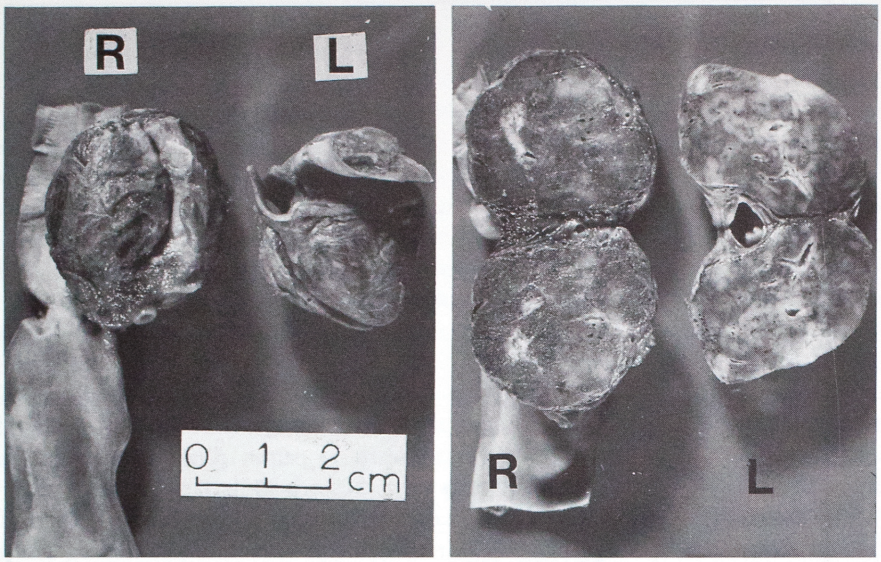

FIGURE 24-14. Bilateral carotid body tumor in a high-altitude man with extensive silicosis and secondary chronic mountain sickness. External surface (*left*) and cut-section of the tumors showed a rusty red, firm parenchyma with prominent hyalinized vessels. (From Saldana MJ, Salem LE, Travezan R. High altitude hypoxia and chemodectoma. Hum Pathol 1973;4:251.)

that HVR diminishes with both age and length of residence at high altitudes; so it may be that patients with CMS are those in whom the process is faster than average.

A simple and effective way of treating CMS is removing the patient to a sea-level environment. Phlebotomy lowers the hematocrit, improves many of the neuropsychological symptoms, and improves gas exchange and exercise performance. In Leadville, Colorado, with about 60 patients with CMS routinely phlebotomized for therapeutic purposes, the local blood bank has no need for additional donors.[44]

PATHOLOGY OF CHEMORECEPTORS

Hyperplasia of the carotid bodies in both humans and animals is a common finding at high altitudes (Fig. 24-11).[53,54] In 1973, my colleagues and I described a series of 25 high-altitude adults with chemodectomas of the head and neck.[5] Twenty-three of the 25 patients had been born and lived at altitudes between 2092 and 4324 m (6904–14,268 ft; Fig. 24-12). Estimates of prevalence indicate that carotid body tumors are about ten times more frequent at high altitudes than at sea level. There was a strong gender difference, with females predominating over males in a ratio of 6 to 1. Left-sided tumors were three times more common than right-sided tumors (Fig. 24-13). The tumor was bilateral in one case of secondary CMS due to silicosis (Fig. 24-14).

Carotid body tumors in highlanders represent hyperplasia of chief cells resulting in lobular hyperplasia and enlargement of the entire organ (Fig. 24-15). Vascular lesions and areas of sclerotic stoma are prominent in these tumors. All carotid body tumors in high-altitude natives were benign.

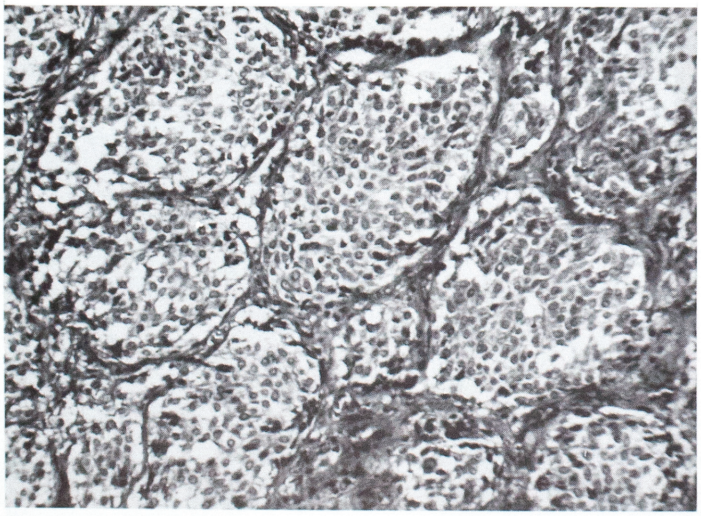

FIGURE 24-15. A microscopic view of a high-altitude carotid body tumor shows enlarged *Zellballen* uniformly composed of chief cells. (H & E stain; low magnification; from Saldana MJ, Salem LE, Travezan R. High altitude hypoxia and chemodectoma. Hum Pathol 1973;4:251.)

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