Pulmonary arterial hypertension in man at altitude was first demonstrated by Rotta, Cánepa, Hurtado, Velásquez & Chávez (1956). One year before Vega (1955) had published the first comprehensive clinical account of high altitude pulmonary oedema. Since the mid-sixties, interest in both pulmonary hypertension and pulmonary oedema at altitude has continued to generate a great deal of clinical and experimental research.

**Pulmonary hypertension at altitude**

**Postnatal changes in pulmonary artery pressure**

Pulmonary arterial pressure in new-borns is similar at an altitude of 4540 m and at sea-level (Gamboa & Marticorena, 1971). In new-borns breathing ambient air the fall in pulmonary arterial pressure during the first 3 days of life is less marked at altitude than at sea-level (Reeves & Grover, 1975). Throughout childhood pulmonary arterial pressure is higher at altitude than at sea-level (Peñaloza, Arias-Stella, Sime, Recavarren & Marticorena, 1964). The heavily muscularized pulmonary arterioles of children at high altitude contrast with the sparsity of smooth muscle cells in distal pulmonary arteries of children at sea-level (Arias-Stella & Saldana, 1963; Penaloza et al., 1964). The above findings suggest that there is a delayed involution of the foetal characteristics of the pulmonary arterial tree and that this is related to the sustained pulmonary vasoconstriction caused by altitude hypoxia (Peñaloza et al., 1964; Reeves & Grover, 1975; Harris & Heath, 1977).

**From hypoxic pulmonary vasoconstriction to structural changes of pulmonary vessels**

The natural history of bovine pulmonary hypertension at altitude has been described by Jaenke & Alexander (1973). During the first 5 days physiological and anatomical observations at altitude were characteristic of isolated reversible vasoconstriction of muscular pulmonary arteries. During the following weeks a progressive increase in pulmonary arterial pressure and resistance was associated with the onset of ultrastructural changes in pulmonary arterial smooth muscle which were suggestive of enhanced protein synthesis. By week 5 severe pulmonary hypertension had developed and was associated with degenerative changes of both endothelial and smooth muscle cells and medial hypertrophy. Unlike steers, rats and llamas do not suffer from severe progressive pulmonary hypertension during chronic hypoxia. However, hypertrophy of smooth muscle cells of muscular pulmonary arteries and muscularization of pulmonary arterioles begin within 2 weeks of exposure to altitude in the rat (Smith & Heath, 1977) and are found after 10 weeks at altitude in llamas born at sea-level, by which time hyperoxia exerts no discernible vasodilator effect (Banchero, Grover & Will, 1971). That structural changes are secondary to vasoconstriction of pulmonary vessels has been confirmed by experiments in rats chronically exposed to hypobaric hypoxia; administration of drugs which interfere with hypoxic pulmonary vasoconstriction reduced the increase in weight of the right ventricle characteristic of sustained pulmonary hypertension and the medial hypertrophy of distal pulmonary arteries (Zakheim, Mattioli, Molteni, Mullis & Bartley, 1975; Kentera, Susić & Zdravković, 1979).

Observations in man at altitude suggest that the response of the human pulmonary circulation is similar to that of the rat and llama and differs from that of steers. The pulmonary arterial pressure of lowlanders rose within minutes of exposure to altitude and reached a plateau after 12–24 h. This early pulmonary hypertension was almost entirely reversible with oxygen
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(Kronenberg, Safar, Lee, Wright, Noble, Wahrenbrock, Hickey, Nemoto & Severinghaus, 1970). After 9 months in La Paz (3700 m) pulmonary arterial pressure at rest in a group of 11 acclimatized lowlanders was the same as that of native highlanders. However, acute hypoxia and hyperoxia elicited larger vasomotor changes in the acclimatized lowlanders than in natives (Coudert, 1976). Excessive muscularization of distal muscular arteries and arterioles is a prominent feature of the pulmonary vascular bed of native highlanders (Arias-Stella & Saldana, 1963). Since acute administration of oxygen caused little or no fall in pulmonary vascular resistance at rest, it is likely that sustained pulmonary vasoconstriction is not a major factor in the pulmonary hypertension of native highlanders. However, oxygen partially prevented the rise in pulmonary arterial pressure on exercise (Rotta et al., 1956; Sime, Peñaloza & Ruiz, 1971; Lockhart, Zelter, Mensch-Dechêne, Antezana, Paz-Zamora, Vargas & Coudert, 1976). Prolonged removal of the hypoxic stimulus by descent to sea-level results in the fall of pulmonary arterial pressure and pulmonary vascular resistance to normal values for lowlanders in both man (Grover, Vogel, Voigt & Blount, 1966; Sime et al., 1971) and the rat (Heath, 1975). Since a marked nocturnal drop of arterial oxygen saturation has been observed at altitude (Sutton, Houston, Mansell, McFadden, Hackett, Rigg & Powles, 1979) and even brief hypoxia caused by two tidal breaths of nitrogen causes a marked rise in pulmonary arterial pressure (Coudert, 1976), it can be postulated that bouts of pulmonary hypertension take place at night in acclimatized man. Such repeated episodes of pulmonary vasoconstriction might contribute to the production or maintenance of structural changes in the human pulmonary circulation, as has been shown to occur in rats (Widimský, Urbanová, Ressl, Ošťadál, Pelouch & Procházka, 1975).

Pulmonary arterial pressure in relation to altitude

Pulmonary arterial pressure increases with increasing altitude, whereas pulmonary wedge pressure and cardiac output remain normal. It has been stated that pulmonary arterial pressure of first or second generation residents of Leadville (3100 m) is higher than in South American highlanders, a finding which was interpreted as suggestive of elimination of natives with hyperreactive pulmonary vascular bed by natural selection over many generations (Blount & Vogel, 1967). However, this difference between Caucasian residents and South American highlanders may be more apparent than real (Fig. 1). Fig. 1 also suggests that pulmonary vascular resistance rises regularly with increasing altitude and does not support the theory that 3000 m represents a critical altitude so far as the pulmonary circulation is concerned (Micheli, Villacis, Guzy de la Mora & Alvarez, 1960; Blount & Vogel, 1967).

Individual susceptibility to pulmonary hypertension at altitude

Since cardiac output varies little with altitude, the scatter of measurements in Fig. 1 also confirms Reeves & Grover's (1975) observation that variations in pulmonary arterial pressure among individuals increase with increasing altitude.

Fig. 1. Pulmonary vascular resistance as a function of altitude (a) or alveolar partial pressure of oxygen (b). Data in normal highlanders were gathered in Peru by Hultgren, Kelly & Miller (1965) (△) and Banchero, Sime, Peñaloza, Cruz, Gamboa & Marticorena (1966) (●), in Bolivia by Spielvogel, Otero-Calderon, Calderon, Hartmann & Cudkowicz (1969) (▲), Moret, Covarrubias, Coudert & Duchosal (1972) (■) and Coudert (1976) (□) and in Mexico by Micheli et al. (1960) (▲). Data in Caucasians born or residing at altitude were obtained in Colorado by Vogel, Weaver, Rose, Blount & Grover (1962) (○).
altitude. This might be related to variations in the hypoxic stimulus to which pulmonary vessels are exposed, i.e., variable alveolar hypoxia among individuals living at the same altitude or variations in responsiveness of the pulmonary circulation to a given hypoxic stimulus. In fact, variations in alveolar or arterial partial pressure of oxygen (see Fig. 4 in Reeves & Grover, 1975), related to differences in ventilatory response to the hypoxic stimulus, appear to be the more important. The higher pulmonary arterial pressures are found in patients with chronic mountain sickness whose severe arterial hypoxaemia is attributable to a low hypoxic drive to breathe (Lefrançois, Gautier & Pasquis, 1968; Peñaloza & Sime, 1969). Cold is another environmental factor that may explain variations in pulmonary arterial pressure. Localized skin cooling in cattle (McMurtry, Reeves, Will & Grover, 1975) and environmental cold in shorn wethers and in cattle (Chauca & Bligh, 1976; Will, McMurtry, Reeves & Grover, 1978) enhance hypoxic pulmonary vasoconstriction. Pulmonary arterial pressure and pulmonary vascular resistance are slightly lower in normal highlanders in a neutral environment (25°C, 40% relative humidity) than at ambient temperature (19°C) and significantly increase on localized cooling of the skin (Coudert, Guieu, Antezana, Spielvogel, Zelter, Mensch-Dechene, Geyssant & Durand, 1977).

Notwithstanding the role of environmental factors, variations in responsiveness of the pulmonary circulation to hypoxia among individuals have been repeatedly confirmed. An excessive pulmonary vasoconstrictor response was first observed in certain steers exposed to acute normobaric hypoxia (Kuida, Brown, Thorne, Lange & Hecht, 1962) and prolonged altitude hypoxia (Alexander & Jensen, 1963). The severity of pulmonary hypertension on chronic exposure to altitude is directly correlated with the thickness of pre-existing medial smooth muscle of small muscular pulmonary arteries (Alexander & Jensen, 1963; Tucker, McMurtry, Reeves, Alexander, Will & Grover, 1975).

In-breeding studies in cattle have clearly demonstrated that the responsiveness of the pulmonary circulation to altitude hypoxia is genetically coded (Grover, Hill, Reeves, Weir, McMurtry & Alexander, 1975). A preliminary report suggests that the above finding also applies to the rat (McMurtry, Petrun, Tucker & Reeves, 1979).

Susceptibility to altitude hypertension is associated with hyper-reactivity of the pulmonary circulation to acute hypoxia as well as to serotonin and prostaglandin F_2α in cattle (Grover et al., 1975; Will, Hicks, Card, Reeves & Alexander, 1975; Weir, Will, Alexander, McMurtry, Looga, Reeves & Grover, 1979), and in highland compared with lowland dogs (Weir, Tucker, Reeves & Grover, 1977). Hyperreactivity of the pulmonary circulation also exists in man. Subjects with a past history of high altitude pulmonary oedema or severe pulmonary hypertension at altitude, and whose pulmonary pressure has been lowered to normal by a prolonged stay at sea-level, display a disproportionate pulmonary pressor response to exercise and acute normobaric hypoxia (Grover et al., 1966; Grover, Hartley, Miller & Hultgren, 1967; Viswanathan, Jain, Subramanian, Subramanian, Dua & Giri, 1969; Coudert, 1976).

High altitude pulmonary oedema

High altitude pulmonary oedema in context

There is now ample evidence that classic pulmonary oedema is one form of acute mountain sickness (Singh, Kapila, Khanna, Nanda & Rao, 1965; Singh, Khanna, Srivastavia, Lal, Roy & Subramanian, 1969; Hecht, 1971) and it has been suggested that altitude sickness and pulmonary oedema have a common pathophysiological basis (Sutton & Lassen, 1979).

Workers in the Andes (Vega, 1955; Hultgren, Spickard, Hellriegel & Houston, 1961; Marticorena, Tapia, Dyer, Severino, Banchero, Gamboa, Kruger & Peñaloza, 1964) and Colorado (Scogglin, Hyers, Reeves & Grover, 1977) have found that children experience high altitude pulmonary oedema more often than adults and that high altitude pulmonary oedema is confined almost exclusively to native highlanders re-ascending to altitude after a sojourn of variable duration at sea-level. However, others have shown conclusively that high altitude pulmonary oedema is by no means rare in lowlanders exposed for the first time to altitude (Houston, 1960; Fred, Schmidt, Bates & Hecht, 1962; Singh et al., 1965). Identified risk factors are: (i) the rapidity of ascent; (ii) the altitude above 3500 m, although high altitude pulmonary oedema may occur at lower altitudes (Fred et al., 1962; Frates, Harrison & Edwards, 1977); (iii) heavy physical exercise shortly after arrival at altitude; (iv) individual susceptibility as shown by the occurrence of familial cases in parents or siblings (Hultgren et al., 1961; Fred et al., 1962; Scogglin et al., 1977) and by recurrence of high altitude pulmonary oedema on successive re-entries to altitude (Vega, 1955; Hultgren et al., 1961; Fred et al., 1962; Hultgren, Lopez,

The presenting symptoms are acute shortness of breath and cough. In a matter of hours or days and without oxygen administration the clinical picture develops into full-fledged pulmonary oedema. Characteristically there are no signs of involvement of the heart (Vega, 1955; Hultgren et al., 1961; Marticorena et al., 1964; Singh et al., 1965; Blount & Vogel, 1967; Coudert, 1971). In most instances administration of oxygen, even without associated diuretics, causes a dramatic improvement within a few minutes (Hultgren et al., 1964; Scoggin et al., 1977) which eventually leads to complete clearing of lung fields within 1–5 days.

In the absence of, or even in spite of, prompt oxygen administration or removal from altitude, involvement of the central nervous system and respiratory distress may progress to unconsciousness and death may ensue. Pathologic findings include widespread intra-alveolar oedema and haemorrhage, occasional microthrombi and marked congestion of alveolar capillaries and pulmonary veins (Marticorena et al., 1964; Nayak, Roy & Narayanan, 1964). Intra-alveolar deposits of fibrinaceous material occasionally forming hyaline-like membranes are suggestive of a high concentration of protein in the oedema fluid and led Nayak et al. (1964) to postulate the existence of capillary damage. The contention that structural changes of pulmonary arteries characteristic of native highlanders are a prerequisite for high altitude pulmonary oedema to occur is no longer tenable since high altitude pulmonary oedema has been observed in lowlanders with structurally normal pulmonary arteries (Roy, 1966). Marked cerebral damage also occurs in autopsied cases with focal oedema, petechiae and focal degeneration apparently secondary to local haemorrhage (Singh et al., 1969; Houston & Dickinson, 1975).

Haemodynamics of high altitude pulmonary oedema

Catheterization studies (Fred et al., 1962; Hultgren et al., 1964; Peñalosa & Sime, 1969; Roy et al., 1969) have been performed in 13 cases of high altitude pulmonary oedema from a few hours to 4 days after the onset of respiratory symptoms. Patients were still quite ill, although most of them had been treated before the study and five had already been moved to a lower altitude. Pulmonary wedge pressure, left atrial pressure and pulmonary blood volume were normal or subnormal. Pulmonary arterial hypertension is more severe in native highlanders than in native lowlanders. Oxygen breathing causes a marked fall in pulmonary arterial pressure within minutes (Fred et al., 1962; Hultgren et al., 1964). Hyper-responsiveness of the pulmonary circulation has been proposed by Hultgren et al. (1964) to explain the marked rise in pulmonary arterial pressure in high altitude pulmonary oedema. However, the marked pulmonary hypertension may be precipitated by an unusually severe hypoxic stimulus related to exercise or sleep disturbances (Peñalosa & Sime, 1969) or to an abnormally low hypoxic drive (Kafer & Leigh, 1972; Lakshminarayan & Pierson, 1975).

Pathogenesis of high altitude pulmonary oedema

The mechanism(s) of high altitude pulmonary oedema is (are) still unknown. With high altitude pulmonary oedema as with most other forms of pulmonary oedema one has to consider two possible mechanisms (Staub, 1978): high pressure oedema and permeability oedema. The interpretation of a normal pulmonary wedge pressure is basic to any discussion of these alternatives.

Pulmonary wedge pressure is normal in the presence of obstructive lesions of small pulmonary veins (Harris & Heath, 1977; Heath & Williams, 1977). Thus structural changes and vasoconstriction of pulmonary veins whose outer diameter is 150 μm or less (Wagenvoort & Wagenvoort, 1976; Dingenmans & Wagenvoort, 1978) might be responsible for high pressure in the pulmonary microcirculation in chronic alveolar hypoxia that would not be detectable by conventional methods; however, the role of hypoxic pulmonary vasoconstriction as a causative factor of high altitude pulmonary oedema is as conjectural nowadays as it was in the early sixties (Hultgren et al., 1961; Fred et al., 1962; Nayak et al., 1964; Singh et al., 1965).

In 1961, Hultgren et al. suggested that acute left ventricular failure was the most likely immediate cause of high altitude pulmonary oedema. After later reports of normal pulmonary wedge (left atrial) pressure in high altitude pulmonary oedema this hypothesis was discarded. Whether the finding of a normal pulmonary wedge pressure suffices to rule out acute left ventricular failure needs re-evaluation. Reduced plasma volume (Hultgren et al., 1964; Peñalosa & Sime, 1969; Hultgren & Grover, 1968; Hansen & Evans, 1970) and prior treatment with diuretics and morphine (Roy et al., 1969) may oppose the rise in pulmonary wedge pressure.
pressure in high altitude pulmonary oedema as it does in cardiogenic oedema (Figueras & Weil, 1979). Indeed, Roy et al. (1969) have found in every instance a higher left atrial pressure after recovery than during the acute episode. Furthermore a single finding of normal pulmonary wedge pressure does not rule out high pressure oedema. Wray & Nicotra (1978) have shown that pulmonary wedge pressure can rise rapidly and fall within minutes in pulmonary oedema associated with stroke. In this respect, it is of interest to recall the close association of high altitude pulmonary oedema with cerebral oedema complicating acute mountain sickness (Roy, Guleria, Khanna, Talwar, Manchada, Pande, Kaushik, Subba & Wood, 1968; Singh et al., 1969; Hansen & Evans, 1970; Hecht, 1971; Wilson, 1973; Frayser, Gray & Houston, 1974; Houston & Dickinson, 1975; Maher, Cymerman, Reeves, Cruz, Denniston & Grover, 1975; Heath & Williams, 1977) which led to the hypothesis that high altitude pulmonary oedema is but one form of neurogenic pulmonary oedema (Singh et al., 1965; Wilson, 1973; Lakshminarayan & Pierson, 1975; Scoggins et al., 1977).

Ever since it was found that pulmonary wedge pressure is normal in high altitude pulmonary oedema, substantial research has been carried out to try to confirm that high altitude pulmonary oedema is a form of permeability oedema. The most direct evidence for permeability oedema in man is an oedema fluid/plasma protein ratio greater than 0.6 (Fein, Grossman, Jones, Overland, Pitts, Murray & Staub, 1979). Unfortunately, data on the protein content of oedema fluid in high altitude pulmonary oedema are not available. The post-mortem finding of abundant intra-alveolar fibrin-like material (Marticorena et al., 1964; Nayak et al., 1964) is suggestive of a protein-rich oedema fluid in human high altitude pulmonary oedema. The fact that ultrastructural changes are similar in rats exposed to chronic hypoxia and in pulmonary oedema caused by toxic substances (Heath, Moosavi & Smith, 1973; Vijeyaratnam & Corrin, 1974) also suggests that high altitude pulmonary oedema is a form of permeability oedema. Lastly, the rapid clearing of lung fields in high altitude pulmonary oedema does not rule out permeability oedema, since the latter does not always involve massive destruction of pulmonary endothelial cells and may be a reversible process (Brigham, Woolverton, Blake & Staub, 1974; Staub, 1978).

Three mechanisms of increased permeability in high altitude pulmonary oedema have been proposed: a direct effect of hypoxia, transarterial leakage and mechanical damage of the endothelium. Animal experiments designed to demonstrate that hypoxia causes permeability oedema have been unsuccessful in all (Hemingway, 1952; Courtice & Korner, 1952; Meyrick, Miller & Reid, 1972) or in a number of animals (Viswanathan, Jain, Subramanian & Puri, 1969; Heath et al., 1973). The role of transarterial leakage (Whayne & Severinghaus, 1968) is not borne out by the observation that pulmonary oedema is uncommon in other conditions associated with severe precapillary pulmonary hypertension and that high altitude pulmonary oedema is not always associated with exceedingly high pulmonary arterial pressure (Roy et al., 1969).

After the observation of disseminated microthrombi in the lung capillaries several authors have suggested that high altitude pulmonary oedema is due to the excessively high pressure prevailing in permeable vessels accommodating the diverted blood flow (Hultgren & Grover, 1968; Wilson, 1973; Staub, 1978; Sutton & Lassen, 1979). It is possible to reproduce overperfusion oedema by selective lobar artery obstruction in unanaesthetized sheep (Brigham et al., 1974; Okhuda, Nakahara, Weidner, Binder & Staub, 1978). A high lymph/plasma protein ratio resulted from the obstruction, i.e. the oedema was due to increased permeability of the pulmonary microcirculation. Staub (1978) postulated that the latter was caused by mechanical injury of endothelial cells caused by the high linear velocity of blood. An alternative possibility is a marked rise in pressure in pulmonary venous capillaries due to obstructive subendothelial blebs (Heath et al., 1973) or to the resistance to flow of small pulmonary veins (Hyman, 1969).

The pathogenesis of high altitude pulmonary oedema is still elusive. Measurements of the concentration of protein in the oedema fluid and prolonged monitoring of pulmonary arterial and wedge pressure may help in assessing the respective roles of high pressure and increased permeability.

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