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Editorial

Missing link from Tibet

The pulmonary arteries of indigenous high altitude mammals are very thin walled. This has been reported in the llama and other camelids in the Andes[1] and in the mountain viscacha of Peru.[2] It is equally true of the yak in the Himalaya[3] and of the snow pig of the Tibetan plateau.[4] An explanation for this has been advanced by Harris,[5] who believes that during the course of evolution the lung has proved to be susceptible to airway obstruction. As a consequence a pressor response to hypoxia has developed in the pulmonary circulation. When an area of the lung becomes hypoxic, owing to local bronchial or bronchiolar obstruction, the small peripheral pulmonary arteries supplying it constrict so that the blood supply to the affected alveolar spaces is diminished and the effects of the local hypoxia are not transmitted to the systemic circulation. At high altitude the hypoxia is generalised throughout the lung as a result of the diminished barometric pressure. Should the hypoxic pulmonary pressor response operate widely in these circumstances it would carry with it serious risks of the development of pulmonary hypertension and high altitude pulmonary oedema. In fact, in indigenous mountain mammals the hypoxic pulmonary pressor response is greatly attenuated so that pulmonary arterial pressure and resistance are low, the pulmonary arteries remain thin walled, and there is no propensity for the development of right ventricular hypertrophy.[1]

In sharp contrast, the pulmonary arteries of cattle have very thick walled muscular pulmonary walls and they constrict vigorously in response to hypoxia. This is particularly so in some calves who fail to achieve initial acclimatisation to hypobaric hypoxia on their first ascent into mountains. This occurs in calves being taken up for spring grazing in the Wasatch mountains around Salt Lake City in Utah. They develop pulmonary vasconstriction, right ventricular hypertrophy, and congestive cardiac failure with oedema of the brisket, the region between the forelegs, and hence the condition is called brisket disease.[6]

Man has not adapted genetically to high altitude and retains a pressor response to hypoxia. In 1963 Arias-Stella and Saldaña[7] first reported that the Quechua Indians of the Peruvian altiplano, the direct descendants of the Incas, show muscularisation of their pulmonary arterioles and precapillaries so that vessels as small as 30 μm in diameter have a distinct coat of muscle. Our later studies in Bolivia[8] showed that the white and mestizo citizens of La Paz at 3600 m did not show the same tendency to arteriolar muscularisation as the Aymara and Quechua Indians.[7] Even today no data are available on the state of the pulmonary vasculature in the Sherpas and Ladakhis in the Himalaya and the Karakorams. Both adapted and acclimatised species can survive and live together very successfully at high altitude (fig 1).

Some native highlanders who have lived at altitudes usually exceeding 4000 m for several years lose their

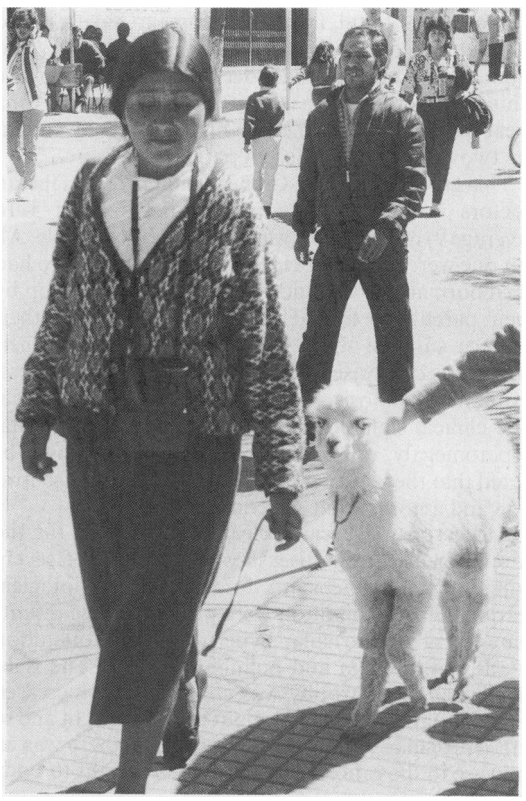

Fig 1 *La Paz, August 1989. As can be seen, the adapted llama and the acclimatised mestizo, with different histological structures to their respective pulmonary circulations, can both survive and live together successfully at high altitude.*

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natural acclimatisation to high altitude. There is progressive alveolar hypoventilation, leading to extreme arterial oxygen unsaturation and a rise of the haemoglobin concentration above 23 g/dl, which leads to a syndrome whose major features are produced by the polycythaemia. This is chronic mountain sickness, often called Monge's disease after the distinguished Peruvian physician who first described the condition in 1928.[9] It is becoming clear, however, that the condition is not confined to the Andes and it has now been reported from Tibet.[10]

Many workers have regarded Monge's disease as the human counterpart of brisket disease. It has never seemed appropriate, however, to equate failure to develop initial acclimatisation in young calves to loss of acclimatisation of many years' standing in middle aged men. There has clearly been a missing link.

On a visit to Tibet in 1987 Harris and Anand came across a new form of mountain sickness, which was familiar to their Chinese and Tibetan hosts but which was unknown to Western doctors.[11] This appeared to be the consequence of demographic changes in the community. As a result of the immigration of many Chinese, the capital, Lhasa, has come to have a mixed population of native Tibetan highlanders and immigrant Chinese lowlanders of Han origin. The Chinese government has unwittingly set the scene for a great biological experiment in high altitude by admixing two biologically different populations.

This group of British, Chinese, Indian, and Tibetan doctors was able to study 15 patients, aged 3–16 (average 9) months. Ten were male and five female. All but one were infants of Han origin and all but two had been born at low altitude. They had been taken up by their parents to live at Lhasa at 3600 m and their average survival there was only 2·1 months. Their symptoms comprised dyspnoea, cough, sleeplessness, irritability, cyanosis, oedema of the face, and oliguria. The clinical signs included tachypnoea, tachycardia, hepatomegaly, rales, and cardiomegaly. It should be noted that they had a normal haemoglobin concentration and a normal red cell count.

At necropsy it became clear that the basis for the development of this disease was the onset of severe pulmonary hypertension, for all the pathological features of this condition were present. These infants showed right ventricular hypertrophy and dilatation of the right atrium and pulmonary trunk. The right ventricular hypertrophy was confirmed by increased ratios of right ventricular weight to body weight and to left ventricular weight. At the same time there was an increase in the ratio of left ventricular weight to body weight.

The small pulmonary arteries of Tibetan infants who died free of cardiopulmonary disease and who served as controls in the study were thin walled. In striking contrast, the infants of Han origin who died on their first ascent to high altitude in Lhasa showed pronounced medial hypertrophy of pulmonary arteries and muscularisation of their pulmonary arterioles. Such vascular disease was surely the basis for the pulmonary hypertension and resulting right ventricular hypertrophy in these infants.

Clearly this disease of infants of Han origin in Tibet bears much closer similarities to bovine brisket disease than does Monge's disease. It occurs in infants and not in middle aged men and thus mirrors the onset of brisket disease in calves. Like the bovine disease, it is an expression of failure to achieve initial acclimatisation to hypobaric hypoxia rather than a loss of long established acclimatisation as in Monge's disease. As with brisket disease, it represents a cardiovascular syndrome secondary to hyperreactivity of a muscular pulmonary arterial tree rather than a respiratory syndome due to alveolar hypoventilation. There is only slight oxygen unsaturation of systemic arterial blood and a normal packed cell volume, as in the calves in Utah but not in Monge's disease, which shows severe oxygen unsaturation and a greatly increased packed cell volume. "Subacute infantile mountain sickness" in Chinese infants of Han origin ascending to live in Lhasa is the human counterpart of brisket disease in cattle and is the missing link from Tibet.

This disease of Chinese infants is of further interest for it highlights the fact that remodelling of the terminal portions of the pulmonary arterial tree in response to chronic alveolar hypoxia may assume one of two quite distinct forms. In chronic obstructive lung disease there is a formation of longitudinal smooth muscle in the intima of small pulmonary arteries with the development of a thin layer of circularly oriented smooth muscle internal to the fasciculi of longitudinal muscle, which then extends distally as muscle tubes through pulmonary arterioles to peter out on the walls of small pulmonary arterioles and precapillaries.[12] We originally thought that this form of remodelling was confined to cases of chronic obstructive lung disease, but we now have evidence that similar changes are to be found in native highlanders. This complex arrangement of longitudinal and circular smooth muscle is a far cry from the simple muscularisation of pulmonary arterioles previously envisaged.[7]

Subacute infantile mountain sickness presents a quite distinct form of remodelling, in which coats of mature smooth muscle cells are replaced by a migration of myocytes in the pulmonary arterioles into the intima[13] (fig 2). The same inward migration of myocytes is seen in the pulmonary veins, which become blocked and associated with pulmonary haemosiderosis.[13] Such migration of myocytes from the media through the inner elastic lamina into the

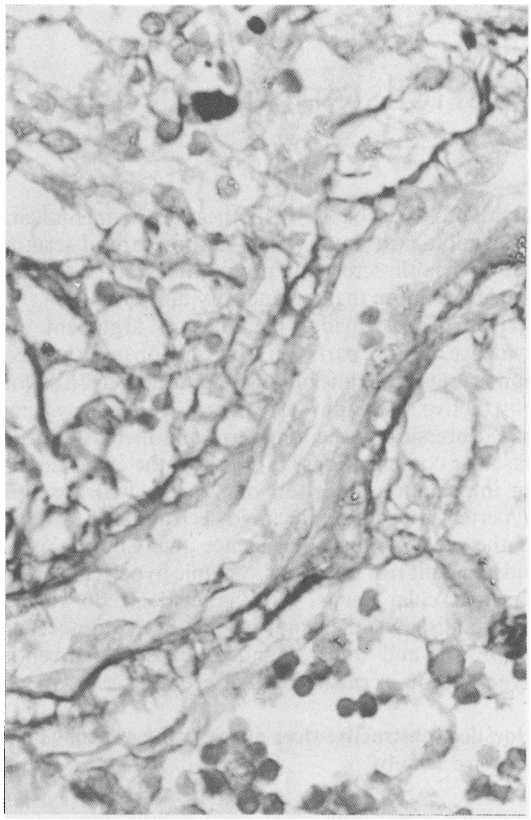

Fig 2 *Subacute infantile mountain sickness in a male infant of 16 months, of the Han race, who died in Lhasa (3600 m) after having been at that altitude for three months after ascent from his birthplace at a lower altitude in Tibet: a longitudinal section of muscularised pulmonary arteriole. Elongated smooth muscle cells have migrated into the intima and into the lumen of the vessel. (Elastic, Van Gieson.)*

intima and the subsequent proliferation of myofibroblasts in the lumen is reminiscent of what is found in plexogenic pulmonary arteriopathy, which forms the pathological basis for primary pulmonary hypertension.[14]

There is an interesting association between events in the terminal portions of the pulmonary arterial tree and the numbers of pulmonary endocrine cells in the terminal bronchioles containing prominent amounts of gastin releasing peptide (the human counterpart of bombesin in amphibian skin). The controlled remodelling of the terminal portions of the pulmonary arterial tree in chronic obstructive lung disease is not associated with any increase in pulmonary endocrine cells.[15] In contrast, the migration of myocytes into the intima in primary pulmonary hypertension, at its height in the stage of plexogenic pulmonary arteriopathy before the development of plexiform lesions, is associated with clusters of pulmonary endocrine cells containing gastrin releasing peptide.[15] Thus it is of interest that in subacute infantile mountain sickness the "uncontrolled" remodelling of the pulmonary arteries with the migration of myocytes is also associated with increased number of bombesin containing pulmonary endocrine cells.

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