

Profiles in Pulmonary Hypertension

## Climbing With Dr John West in the Rarefied Air of Pulmonary Research: From Mount Everest to the University of California, San Diego



When you have been recruited as a clinical investigator to climb Mount Everest with Sir Edmund Hillary, have coauthored 427 articles and 21 books, one of which is still used as a classic medical text translated into 13 languages, what worlds are left to conquer? Quite a few, says John West, MD, Distinguished Professor of Medicine and Physiology, University of

John West, MD

California, San Diego.

It was 45 years ago when he heard about an upcoming physiological expedition to the Himalayas and, to his surprise, was picked to join Griffith Pugh, an eminent British physiologist. The Australian-born West and the team lived for several months in a laboratory at 19,000 feet and made field measurements of maximal exercise up to an altitude of 24,000 feet.

One of the critical questions to emerge from that expedition was whether humans would be able to reach the summit of Mount Everest without supplementary oxygen. Although two European climbers proved that it was possible, in 1981 Dr West led the American Medical Research Expedition to Everest, recording physiological measurements at unprecedented altitudes, including the summit. The results showed that humans made "almost incredible adaptations to this extremely hypoxic environment" with a calculated arterial PO<sub>2</sub> of about 30 torr, PCO<sub>2</sub> of 7 to 8 torr, and PH of over 7.7.

Closer to home and down to earth at the University of California, San Diego, Dr West has extended the direction of research he pursued at the pinnacle of Everest. "I'm still very interested in pulmonary hypertension from the standpoint of what happens at a high altitude," he says. "And I'm interested in the work being done on the fragility of pulmonary capillaries. We believe that when you raise pressure in pulmonary capillaries to either unphysiologically high levels or even to the highest level that you get under normal physiological conditions the wall of the capillaries is damaged in some way." Dr West and his colleagues found that in elite athletes who exercise at extremely high levels, changes apparently occur in the capillary wall as evidenced by results of bronchoalveolar lavage (BAL). After a period of heavy exercise, these athletes have increased red blood cells and higher protein concentrations in their BAL fluid than do controls.

The Pulmonary Thromboendarterectomy (PTE) program at UCSD is also a prime interest of Dr West. In patients who have undergone a PTE, research has shown that in areas where emboli have been removed, the capillaries have been damaged. "You see local acute lung injury with the high protein concentrations in the BAL fluid. I suspect that this has to do with remodeling of the capillaries that occurs when they are protected from the normal pressures because of the embolus. When the embolus is removed, damage may occur in the walls. However, that is very hypothetical."

## High Altitude and Pulmonary Hypertension

Considering his studies on high altitude, Dr West was asked what implications could be drawn for patients with pulmonary hypertension. "At high altitudes you get hypoxic pulmonary vasoconstriction, constriction of small pulmonary arteries as a result of low levels of oxygen in the lung. That's a reversible phenomenon. When you come down (from a higher altitude) the pulmonary artery pressure falls. It's a different situation that is found with primary pulmonary hypertension. People who remain at high altitudes can develop remodeling in the small arteries and then the pulmonary hypertension becomes to some extent nonreversible. This was shown, for example, in a study, Operation Everest 2, in 1985."

In this study, he said, subjects were kept in a low pressure chamber for a long period and they developed pulmonary hypertension because of the alveolar hypoxia. They found that after about 7 days when the subjects were administered 100% oxygen the pulmonary artery pressure did not return to the sea level value, indicating that there was some organic change, a structural change in the blood vessels that is now referred to as remodeling. "Remodeling is very rapid in the pulmonary circulation. Some people think the pulmonary circulation moves rather slowly in terms of histological changes but that is not true." He notes that an animal study by Tozzi, for example, of pulmonary arteries showed changes in messenger RNA and protein within 4 hours after rings from pulmonary arteries were stretched. "Things happen very quickly when you raise the pulmonary artery pressure."

## A Landmark Text and the Zones of West

The impact of Dr West's work is still much in evidence as a new generation of physicians prepares to enter (continued on page 11) 21. Trakada G, Nikolaou E, Pouli A, Tsiamita M, Spiropoulos K. Endothelin-1 levels in interstitial lung disease patients during sleep. *Sleep Breath.* 2003;7(3):111-8.

22. Takemura T, Matsui Y, Saiki S, Mikami R. Pulmonary vascular involvement in sarcoidosis: a report of 40 autopsy cases. *Hum Pathol*. 1992;23(11):1216-23.

23. Shorr AF, Davies DB, Nathan SD. Predicting mortality in patients with sarcoidosis awaiting lung transplantation. *Chest.* 2003;124(3): 922-8.

24. Fartoukh M, Humbert M, Capron F, Maitre S, Parent F, Le Gall C, et al. Severe pulmonary hypertension in histiocytosis X. *Am J Respir Crit Care Med.* 2000; 161(1):216-23.

25. Atwood CW Jr, McCrory D, Garcia JG, Abman SH, Ahearn GS. Pulmonary artery hypertension and sleep-disordered breathing: ACCP evidence-based clinical practice guidelines. *Chest.* 2004;126(1 Suppl):72S-7S.

26. Kessler R, Chaouat A, Schinkewitch P, Faller M, Casel S, Krieger

J, et al. The obesity-hypoventilation syndrome revisited: a prospective study of 34 consecutive cases. *Chest.* 2001;120(2):369-76.

27.Tan RT, Kuzo R, Goodman LR, Siegel R, Haasler GB, Presberg KW. Utility of CT scan evaluation for predicting pulmonary hypertension in patients with parenchymal lung disease. Medical College of Wisconsin Lung Transplant Group. *Chest.* 1998;113(5):1250-6.

28. Tramarin R, Torbicki A, Marchandise B, Laaban JP, Morpurgo M. Doppler echocardiographic evaluation of pulmonary artery pressure in chronic obstructive pulmonary disease. A European multicentre study. Working Group on Noninvasive Evaluation of Pulmonary Artery Pressure. European Office of the World Health Organization, Copenhagen. *Eur Heart J.* 1991;12(2):103-11.

29. Fletcher EC, Luckett RA, Miller T, Fletcher JG. Exercise hemodynamics and gas exchange in patients with chronic obstructive pulmonary disease, sleep desaturation, and a daytime PaO2 above 60 mm Hg. *Am Rev Respir Dis.* 1989;140(5):1237-45.

## **Profile** (continued from page 4)

practice. His landmark text, *Respiratory Physiology: the Essentials*, is used worldwide, including centers in Moscow and Beijing, and has been translated into 13 languages. The Zones of West—a three-zone model of blood flow in the lung—is part of a paradigm used throughout the world. It originated almost 50 years ago when Dr West and his colleagues encountered radioactive oxygen, which has a very short half life. "We were able to look at blood flow in the lung for the first time and we found a very uneven distribution from the top to the bottom of the lung. I spent several years figuring out the reason for that and that's where the three-zone model comes from."

Considering how his world has changed, Dr West reflects: "It is sad to see how junior faculty in the intensive care units sometimes founder when confronted with basic

questions about pulmonary gas exchange or mechanics. This is because the fashion in research over the last 20 years has very much been in molecular biology. I'm not saying that is a bad thing because it is terribly exciting. But, as a result, the interests of young physicians in pulmonary medicine have moved away from pulmonary gas exchange and pulmonary mechanisms. In fact, regrettably, many of the young people are not as well informed in those areas as they should be. And those areas are terribly important in the ICU, where the immediate problems are not molecular but have to do with maintaining adequate gas exchange and ventilating the lung in an appropriate way.

"It's a bit of an irony that we have a whole generation of young pulmonary physicians, but some of them tend to be rather weak in what I regard as the fundamentals of respiratory physiology."