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HYPOXIA AND EXERCISE 2007
Roach, R., Wagner, P.D., Hackett, P. (Eds.),

HYPOXIA AND EXERCISE

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The 14th International Hypoxia Symposium was dedicated to the memory of Dr. John T. "Jack" Reeves.

As most of you know, Dr. John T. "Jack" Reeves passed away in September, 2004 following a motor vehicle-bicycle accident. Jack was a former Professor of Medicine, Pediatrics and Surgery and Professor Emeritus at the University of Colorado Health Sciences Center, having joined the faculty in 1972. He made exceptional contributions in teaching/mentoring, research, administration and leadership. He was a scientist of international stature. He made major advances at the molecular, cellular, animal and human level with regard to the pulmonary circulation and adaptation to high altitude. For many years Jack was a senior member of the Cardiovascular Pulmonary Laboratory of the School of Medicine within the Department of Medicine and most recently played a significant role in the establishment of the Colorado Center for Altitude Medicine and Physiology (CCAMP). He was a key, active and memorably vocal member of the Hypoxia family. No one who ever met Jack at Hypoxia will forget him; his spirit lives on within the Hypoxia community.

In honor of Jack, we established The Reeves Prize for Presentation Excellence. This prize will be awarded at the biennial International Hypoxia Symposium to the speaker judged to present the most outstanding scientific talk, with special emphasis on clarity of presentation skills that were cherished, taught and practiced by Jack. The recipient will be named at the closing banquet by the organizers of the International Hypoxia Symposia with funds coming from the John Sutton Fund, McMaster University, the Colorado Center for Altitude Medicine and Physiology, University of Colorado at Denver and Health Sciences Center, and the International Hypoxia Symposia. The winner for 2005 was Dr. Randy Sprague. See his written contribution starting on page 207.

PREFACE AND ACKNOWLEDGEMENTS

The International Hypoxia Symposia convenes every other year to bring together international experts from many fields to explore the state of the art in normal and pathophysiological responses to hypoxia. Representatives from 18 countries joined together in February 2005 for four days of intense scientific discourse in the dramatic mountain setting of Lake Louise, Canada.

The 14th International Hypoxia Symposium was a rewarding experience due to the outstanding faculty and the lively participation of our largest-ever group of participants. At this, our fourth meeting as the organizers, we were especially pleased that the experience known as the Hypoxia Meetings can continue to prosper. We remain always thankful for the kind and wise guidance of Charlie Houston, the originator of the Hypoxia meetings.

As editors of the Proceedings of the International Hypoxia Symposia, we strive to maintain a 28 year tradition of presenting a stimulating blend of clinical and basic science papers focused on hypoxia. Topics covered in 2005 included a history of high altitude physiology, arterial hypoxemia in exercise, sleep and hypoxia, genetic components of adaptation to hypoxia, erythropoietin, cell stress pathways and hypoxia, the role of red blood cells, ATP release and hemoglobin in the control of vasoreactivity, exercise and altitude training, the eye at high altitude and pulmonary hypertension in high altitude residents. An update on methods to measure the hypoxic ventilatory response was also featured.

The abstracts from the 2005 meeting were published in High Altitude Medicine & Biology Dec 2004, Vol. 5, No. 4: 471-509. Late abstracts are presented staring on page 311, this volume.

We hope that this collection of papers especially prepared for this volume allows us to share with a broader audience some of the intellectual excitement that embodies the spirit of the Hypoxia meetings.

In 2005 we had the generous support of a number of organizations and individuals, including the U.S. Army Research and Development Command, The White Mountain Research Station, our International Advisory Committee. At the meeting we were greatly helped by Barbara Lommen, Paige Sheen, Mollie Pritcher, Gene and Rosann McCullough and Andy Subudhi who each made a tremendous effort to make every delegate feel at home, and to make the meeting go very smoothly.

Please join us by the light of the full moon in February 2007 at the Chateau Lake Louise, Lake Louise, Alberta, Canada for the 15th International Hypoxia Symposium.

Robert C. Roach, Peter D. Wagner, Peter H. Hackett, Editors, Fall 2005
(www.hypoxia.net)

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Chapter 1

A TRIBUTE TO JOHN BURNARD WEST

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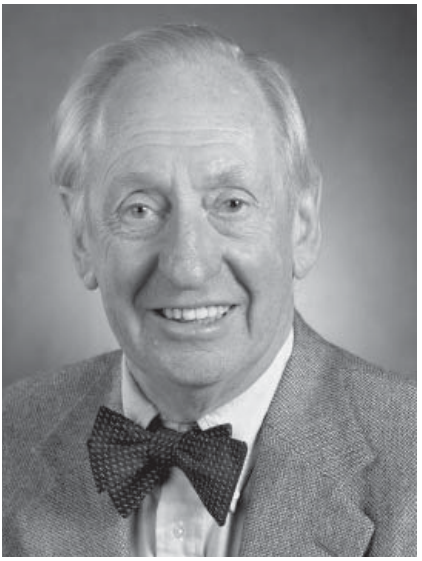

Abstract: John West is well known to the "Hypoxia" community for his many contributions to the physiology and Pathophysiology of high altitude and for his leadership of the 1981 American Medical Research Expedition to Everest. He is known to the wider medical world for his researches into respiratory physiology especially gas exchange in the lung and perhaps even more for his numerous books on these topics. His publication list numbers over 400 original papers. His research career started in the UK but since 1969 he has been Professor of Medicine at UCSD, leading a very productive team at La Jolla. He has been honoured by numerous prizes and named lectureships, the latest honour being to be elected to the Institute of Medicine, National Academies (USA).

Hypoxia and Exercise, edited by R.C. Roach *et al.*
Springer, New York, 2006.

Key Words: biography, gas exchange, altitude physiology, altitude pathology, cardio-respiratory physiology, space medicine

INTRODUCTION

It is entirely fitting that this year when he has recently been honoured by being elected a Member of the Institute of Medicine, National Academies, the Symposium organisers should select John West to be the scientist who we are honouring. I am pleased to be asked to compose this tribute but if it is not as fulsome and laudatory in tone as some previous ones, I ask John's indulgence and plead the twin handicaps of the British love of understatement and an old friend's licence to tell it as he sees it!

I have known John West as a friend, expedition companion and scientific colleague for about 45 years. We first met in 1960 when preparing for the 1960-61 Himalayan Scientific and Mountaineering Expedition, popularly known as the Silver Hut Expedition. I was, even then, aware of his reputation as a bright young medical researcher at the Postgraduate Medical School, Hammersmith Hospital where he had done work on lung gas transfer, exploiting the unique opportunity afforded by the MRC cyclotron sited there.

Since then our paths have crossed and re-crossed. He invited me on his American Medical Research Expedition to Everest (AMREE) in 1981, and we were together on a trek in Sikkim in 2000. From 1985 to the present we have worked as joint authors, with Michael Ward, on the textbook "High Altitude Medicine and Physiology" as well as frequent meetings at conferences and social occasions.

John is a man of many parts, researcher, teacher, author, editor, and organiser/administrator. His interests also include music, ham radio, radio-controlled gliders, tennis, skiing, mountaineering and of course he is a family man.

In this short tribute I can only give the reader a flavour of the man and a few personal reminiscences. No doubt there will, in time, be a full biography of John B. West!

The Researcher

John West is probably best known to the Hypoxia community for his research work in the field of high altitude medicine and physiology. His interest in the effects of altitude hypoxia followed naturally from his early work on pulmonary gas exchange which started when he was a junior doctor at the Postgraduate Medical School. The MRC cyclotron could produce short-lived radio-isotopes of oxygen. The oxygen-15 could be inhaled or infused either as O_2 or CO_2 and the activity counted over the chest wall. This resulted in a number of important papers in 1960. The one I remember reading at the time I first met John was in the *BMJ*. There was also one in *J. Appl. Physiol.* in the same year. This was the time when I was working with Dr Griffith Pugh (honoured at Hypoxia 1993) preparing for the Silver Hut Expedition of which he was the Scientific Leader. John had also been invited to be a member and we met doing base line exercise experiments at Griff's MRC lab in Hampstead and again in Oxford for control of breathing studies, my particular responsibility (Figure 2).

The work John did on the Silver Hut was again on gas exchange. He measured the diffusing capacity of the lung for carbon monoxide and showed there to be no change with acclimatization, apart from the small effect of increased haemoglobin concentration. He

was also involved, as we all were, in the exercise studies and with Mike Ward measured $\dot{V}O_2$ max on the Makalu Col (7440m), still, 44 years later, the highest altitude at which it has been measured! (Figure 3) The reduction in $\dot{V}O_2$ max with altitude, he showed, was largely due to diffusion limitation, again a matter of gas exchange.

Figure 2. John West as subject of a control of breathing experiment inside the Silver Hut, 1961.

Figure 3. John West and Michael Ward setting up the bicycle ergometer on the Makalu Col, (7440m) to measure $\dot{V}O_2$max on themselves.

After the Silver Hut, he did a post-doc fellowship with Herman Rhan (an Honouree at Hypoxia 1991) in Buffalo and then became leader of a MRC Respiratory Physiology Group at the Hammersmith studying pulmonary gas exchange. He had a sabbatical year 1967-8 with NASA at the Ames Research Center. Here he has the opportunity to work on computer models of gas exchange. He put in his first research proposal to NASA on lung function in astronauts at the end of this year and since then has had a continuing connection with space research on the effect of micro-gravity on gas exchange.

In 1969 John joined the faculty of University of California, San Diego where he is still working as Professor of Medicine. On arrival, his NASA project was approved and a check for $100,000 started his career in La Jolla on the right foot! Work on computer modelling of gas exchange led, in collaboration with Peter Wagner, to the multiple inert gas method for measuring V/Q ratio inequalities in health and disease. His more recent research includes work on stress failure of the alveolar-capillary wall as part of the mechanism of high altitude pulmonary edema and the use of oxygen enrichment of room air in high altitude living quarters.

Publications

John's bibliography is impressive and can be found on the web at: http://medicine.ucsd.edu/faculty/west/.

He has published 424 papers, in 290 of which he is the first author (68.4%). The great majority of these have been in prestigious peer reviewed journals. By today's standards he was a late starter. His first paper, on ventilation-perfusion ratio inequality in the lung by single breath analysis, was in *Clinical Science* in 1957 when he was 28 and had been qualified for 6 years. However once John got started, he was soon churning out significant papers in respectable numbers as shown in Fig 4.

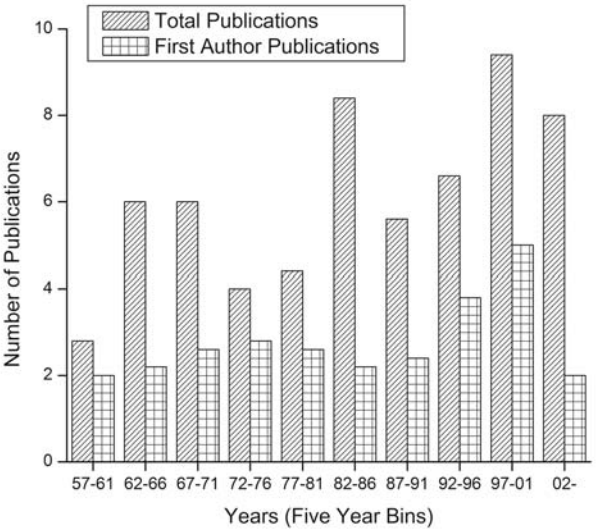

Figure 4. Papers published by John West, average number per year in 5 year bins, showing 1st author and totals.

As impressive as the numbers and quality of his papers, is the fact that with the passing years his output, far from diminishing, has actually increased! There is a significant linear increase in numbers of paper with each quinquennium of his career ($p=0.015$). If the trend continues, I can confidently predict, that on reaching his centenary, he will be publishing at the rate of 16.5 papers per year!

The Teacher

I cannot report on John's ability as a teacher in medical school though I am sure his courses are very well appreciated. As a lecturer I have heard him on numerous occasions and can vouch for his ability to give a clear and exciting account of even the most difficult of subjects such as *V/Q ratio inequalities*. His lecture on AMREE and Peter Hackett's solo summit climb is exciting in both scientific and mountaineering content and style. Evidence of the widespread appreciation of his abilities as a lecturer is the number of prestigious named lecturers he has been asked to give: 57 at the last count, mostly in the USA but also in UK, Canada, Australia and Russia.

However, I think that his most important role as a teacher is as author of numerous textbooks and monographs. These have made him well known to the wider medical world. John has 21 books on his publications list; in some, he is the editor of multi-author books or conference proceedings but in the majority he is sole author. The titles range from *Ventilation/Blood flow and Gas Exchange,* his first monograph, through *The Use of Radioactive Materials in the Study of Lung Function; Translations in Respiratory Physiology*, his first assay into the history of our subject, to *Gravity and the Lung: Lessons from Microgravity,* his latest book. For the Hypoxia community, John's excellent history of our subject, *High Life,* and our joint book *High Altitude Medicine and Physiology* are, no doubt the best known. However, John's most influential book is probably *Respiratory Physiology - The Essentials* followed by *Pulmonary Pathophysiology - The Essentials*. The former was originally written for Medical Students and both are required reading for many postgraduate courses. Both books have been translated into many languages and have gone into 7 and 6 editions in English, respectively. Mention John West's name to any young anaesthetic trainee and (s)he is likely to respond, "Not *The* John West of *Respiratory Physiology*!"

Also important in the wider teaching role of promoting scientific communication, is John's work in the thankless task of editorship. He showed early promise of this by starting a journal whilst still a school boy at Prince Alfred College in Adelaide. The PAC Science Journal is still being published 60 years later! John is on the editorial board of 17 learned journals and of course is the Editor-in-chief and founder of our own, very successful journal, *High Altitude Medicine and Biology.* We all hope his latest journal proves to be as long lived as his first!

The Man

He chose to head up quite a small division of physiology at La Jolla rather than build up a big empire but his organisational abilities are considerable. Anyone who can put together an Everest Expedition, especially one that carries through both scientific and mountaineering objectives as he did with AMREE has to have such skills in spades! He has received numerous honours including being elected President of the American Physiological Society and the International Society of Mountain Medicine. His most recent honour, last year, is to have been elected to the Institute of Medicine of the National Academy of Sciences (USA)!

I personally owe John a lot, in that he was one of three or four men who influenced me in becoming interested in academic medicine and specifically respiratory physiology. We had many long discussions whilst trekking on the Silver Hut Expedition or sharing a tent in the Western Cwm on AMREE. One of the earliest of these I remember was his unfolding to me the beauties of the Rhan/Otis O_2/CO_2 diagram! Happy days!

John never claimed to be a climber but he has a love of mountains and enjoys trekking and skiing. The pinnacle of his mountaineering was probably, at the end of the Silver Hut Expedition. He made a solo ascent to the Makalu Col and organised the rescue of the near dead climber, Pete Mulgrew, from the Col when other members of the team were exhausted and devoid of drive.

John has been fortunate in having a wonderfully supportive wife in Penny and two children to be proud of in Joanna and Robert.

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Chapter 2

ADVENTURES IN HIGH-ALTITUDE PHYSIOLOGY

John B. West
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Abstract: I have probably had more fun doing high-altitude physiology than most people. Some 45 years ago I applied to be a member of Sir Edmund Hillary's Silver Hut expedition and was accepted in spite of having no previous climbing experience. On this project a group of physiologists wintered at an altitude of 5800 m just south of Everest and carried out an extensive research program. Subsequently measurements were extended up to an altitude of 7440 m on Makalu. In fact the altitude of these field measurements of $\dot{V}O_{2max}$ has never been exceeded. This led to a long interest in high-altitude medicine and physiology which culminated in the 1981 American Medical Research Expedition to Everest during which 5 people reached the summit and the first physiological measurements on the summit were made. Among the extraordinary findings were an extremely low alveolar PCO_2 of 7-8 mmHg, an arterial pH (from the measured PCO_2 and blood base excess) of over 7.7, and a $\dot{V}O_{2max}$ of just over one liter/min. More recently a major interest has been the pathogenesis of high altitude pulmonary edema which we believe is caused by damage to pulmonary capillaries when the pressure inside some of them increases as a result of uneven hypoxic pulmonary vasoconstriction ("stress failure"). Another interest is improving the conditions of people who need to work at high altitude by oxygen enrichment of room air. This enhances well-being and productivity, and is now being used or planned for several high-altitude telescopes up to altitudes of 5600 m. Other recent high-altitude projects include establishing an international archive on high-altitude medicine and physiology at UCSD, several books in the area including the historical study *High Life*, and editing the journal *High Altitude Medicine & Biology*.

Key Words: Everest, stress failure, oxygen enrichment, gas exchange, history

INTRODUCTION

Naturally it is a great pleasure and honor to be recognized in this way by the 14th Hypoxia Symposium. I have attended essentially all of the symposia since the first at Banff

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Springs Hotel in 1979 and on every occasion there has been a very special mixture of science and camaraderie. Long may the tradition continue.

I want to take the opportunity to relate some of the high points in a career in high-altitude physiology. This talk is directed at the young people in the audience who are starting their careers. The gray hairs in the front row know most of this but I hope will indulge me.

SILVER HUT EXPEDITION

There can be few introductions to a new area of science as dramatic as being invited to join Sir Edmund Hillary's 1960-1961 Himalayan Scientific and Mountaineering Expedition now universally known as "Silver Hut". In 1959 I had had several years of training in respiratory physiology, first at the Medical Research Council Pneumoconiosis Research Unit in South Wales, U.K. and then at the Postgraduate Medical School, Hammersmith Hospital, London. But I knew almost nothing about high-altitude physiology and, apart from some skiing, had never been on a mountain. It happened that I was sitting next to someone at a meeting of the (British) Physiological Society when she happened to remark that Griff Pugh was arranging a medical research expedition to the Himalayas. I knew something of Griff because he had been the physiologist on the first successful ascent of Everest some six years before. On a whim I decided to approach him and to my astonishment he invited me to join the expedition of which he was scientific leader. Of course Ed Hillary also wanted to interview everybody before taking them on. The story I tell is that I met him in London and he asked me to climb a flight of stairs whereupon he said "Please join us." This may be apocryphal. However the whole process was a remarkable piece of serendipity for a 30 year old.

The expedition was in three parts (1, 4). In September of 1960 a large group walked in to the Everest region carrying pieces of the Silver Hut which was then erected on a glacier at an altitude of 5800 m (19,000 ft) about 10 miles south of Everest (Figure 1). A group of about 7 physiologists then lived in the Silver Hut during the winter studying the effects of acclimatization at this very considerable altitude over several months. Happily two of these are here today including Jim Milledge and Sukamay Lahiri (Figure 2). In the spring the third phase of the expedition took place when we were rejoined by the climbers and the group moved across to Makalu, the fifth-highest mountain in the world at 8481 m. The plan was to try and climb this without supplementary oxygen but a severe illness in one of the climbers near the summit prevented this.

Interestingly some new information on the planning of the expedition has recently come to light. Pugh's daughter, Harriet Tuckey, is writing a biography of her father and she has been mining the Pugh archive at UCSD (see below). She came across some correspondence in 1958 between Pugh and Philip Hugh-Jones about a possible physiological expedition to Kamet (7756 m) in the Garhwal Himalayas about 300 km northeast of New Delhi. Kamet was one of the peaks that attracted the remarkable early British mountaineer/physiologist Alexander Kellas (1868-1921) and he carried out physiological studies on Kamet in 1920 (5, 7). However funding for a major physiological expedition would have been very difficult to come by at that time, and in the event Pugh found himself with Hillary on an expedition in Antarctica in 1959 where apparently the plan of the hybrid scientific and mountaineering expedition was hatched. Remarkably Hillary was successful in obtaining

almost all of the funding for the expedition from the American publishers of *World Book Encyclopedia* (1).

There is no space here to do justice to the science of the Silver Hut expedition which has been the subject of at least two communications in previous Hypoxia Symposia (3, 8). In the Silver Hut itself there were extensive studies of exercise, pulmonary gas exchange including arterial oxygen saturation and the diffusing capacity of the lung, control of ventilation, blood studies, electrocardiogram, basal metabolism, weight loss, intestinal and psychomotor function. When the party moved to Makalu the physiological studies were extended up to Camp 5 on the Makalu Col at 7440 m where maximal exercise and electrocardiograms were studied, and alveolar gas samples were obtained as high as 7830 m. The Silver Hut expedition was the most ambitious and successful high-altitude field expedition of its time and a number of its conclusions are still cited.

Figure 1. Silver Hut at an altitude of 5800 m.

Figure 2. Four of the physiologists on the Silver Hut expedition. Left-to-right: Sukhamay Lahiri, West, Griffith Pugh, Jim Milledge. The photograph was taken in 1977.

1981 AMERICAN MEDICAL RESEARCH EXPEDITION TO EVEREST

Of all the projects in my academic career, none has given more satisfaction than the privilege of leading this expedition which obtained the first physiological measurements at the highest point in the world. Following the success of the Silver Hut expedition I often wondered whether it might be possible to make measurements high on Mt. Everest. The data point for maximal oxygen consumption that Mike Ward and I obtained on the Makalu Col (7440 m) (Figure 3) renewed the intriguing question originally posed by Kellas in 1921: can a human being reach the Everest summit without supplementary oxygen? The answer came in 1978 in dramatic fashion when Messner and Habeler made their memorable ascent, a feat that has now been repeated many times.

In many respects AMREE owed a lot to Silver Hut. For example the design of the Base Camp laboratory at 5400 m was a smaller version of the Silver Hut structure. However whereas the principal scientific question of the Silver Hut expedition was what physiological changes take place in lowlanders when they are exposed to an altitude of 5800 m for several months, the question we hoped to answer on AMREE was what physiological adaptations allow humans to reach the summit of Mt. Everest.

Again it is impossible to do justice to the science here. However the general plan of the expedition was to place laboratories at the Base Camp (5400 m), Camp 2 (6300 m) and if possible carry out some measurements at the highest Camp 5 (8050 m). Each of these sites had its own experimental projects. However in a sense they were all focused on the central aim of getting measurements at the highest possible altitude, hopefully the summit. In this the expedition was extremely lucky and a number of measurements were indeed made at an altitude of 8050 m and above, including the summit (Figure 4). Some of the most dramatic results are shown in Table 1 where it can be seen that on the summit the extreme hyperventilation reduced the alveolar PCO_2 to 7-8 mmHg with an extraordinary respiratory alkalosis and pH (based on the alveolar PCO_2 and measured base excess) of over 7.7 (11). The maximal oxygen consumption measured on extremely well-acclimatized climbers with an inspired PO_2 of 43 mmHg corresponding to the Everest summit was just over 1 liter.min^{-1} (10). It is a lucky person who can be involved an experiment like this once in a lifetime.

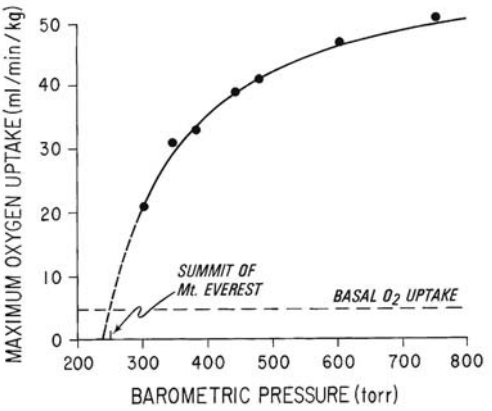

Figure 3. Maximal oxygen consumption plotted against barometric pressure at different altitudes. The lowest point was obtained on the Makalu Col (7440 m). Extrapolation of the line suggests that all the oxygen available on the Everest summit will be required for basal metabolism. These were the data available prior to AMREE.

Figure 4. Chris Pizzo, M.D. sitting on the summit of Mt. Everest collecting samples of alveolar gas.

Table 1. Alveolar gas and estimated arterial blood values on the summit of Mt. Everest.

	BAROMETRIC	INSPIRED	ALVEOLAR	---ARTERIAL VALUES---		
ALTITUDE	PRESSURE	PO2	PO2	PO2	PO2	pH
m	mmHg	mmHg	mmHg	mmHg	mmHg	
8848 (summit)	253	43	35	28	7.5	>7.7
Sea level	760	149	100	95	40	7.40

PATHOGENESIS OF HIGH-ALTITUDE PULMONARY EDEMA

Of course the opportunities for field experiments such as Silver Hut and AMREE are rare and most of us spend most of our time in the more humdrum environment of the laboratory. But in some way this next project has given me as much satisfaction as any, particularly as it started with a seemingly simple question but has progressed to an intriguing biological problem.

In the late 1980s the pathogenesis of high-altitude pulmonary edema (HAPE) was a puzzle. There was a wealth of evidence that pulmonary hypertension played a vital role. For example catheterization studies showed high pulmonary artery pressures in patients with HAPE, susceptible individuals tended to have an unusually strong hypoxic pulmonary vasoconstriction response, pulmonary vasodilator drugs were useful both for treatment and prevention, and a restricted pulmonary vascular bed was a risk factor as was exercise. Then in 1986 Brownie Schoene and Peter Hackett boldly performed bronchoalveolar lavage on climbers with HAPE high on Denali and made the critical observation that the edema fluid was of the high-permeability type (6). This immediately suggested that the capillary wall was damaged and raised the question of whether the pulmonary hypertension could be the mechanism.

Nobody had previously exposed pulmonary capillaries to graded increases in hydrostatic pressure and examined them by electron microscopy for ultrastructural changes. When Odile Mathieu-Costello and I did this we were astonished to see obvious disruptions of the capillary endothelium and alveolar epithelium at pressures that we believed could occur in HAPE (Figure 5). Incidentally, it is perhaps surprising that no one has bothered to repeat these ultrastructural studies that were first published 14 years ago. We then recognized a

feature of pulmonary capillaries that had apparently previously been overlooked, namely because of the excruciatingly thin blood-gas barrier required for gas exchange, the wall stresses become enormous at high capillary pressures. We therefore coined the term "stress failure" which was borrowed from engineering, and we stated in 1991 that this could explain the pathogenesis of HAPE (12). This explanation has stood the test of time.

But the project did not stop there. One day while we were doing experiments someone walked into the lab and asked us whether we knew that racehorses bled into their lungs. I had never heard of this before but indeed it transpires that every Thoroughbred in training breaks its pulmonary capillaries as evidenced by hemosiderin-laden macrophages in tracheal washings (13). The reasons for this extraordinary situation is that these animals have been inbred for hundreds of years for great speed and this requires an enormous cardiac output. The horses therefore have very high left ventricular filling pressures leading to high pulmonary venous and capillary pressures. Interestingly elite human athletes also apparently develop changes in the integrity of their blood-gas barrier during maximal exercise (2). A further example of edema caused by stress failure is high states of lung inflation caused for example by PEEP in the intensive care unit.

What ultimately turned out to be of greater biological interest were questions like what is responsible for the strength of this highly vulnerable blood-gas barrier. The answer apparently is the type IV collagen in the basement membranes. Another question was how special is the makeup of the mammalian blood-gas barrier, the answer being not special at all in that the three-ply design (alveolar epithelium, extracellular matrix, capillary endothelium) has been highly conserved since animals first ventured on to land, such as the ancestors of the present-day lungfishes some 400 million years ago. Finally how is it that the blood-gas barrier is able to remain so excruciatingly thin but just strong enough to withstand the maximal physiological stresses to which it is exposed. The answer presumably is that it is being continually regulated in response to the wall stress, a lively area of research at the present time. Thus this project has been exceptionally stimulating because what appeared to be a relatively simple question on pathogenesis of HAPE has led us into much more fundamental questions of lung biology.

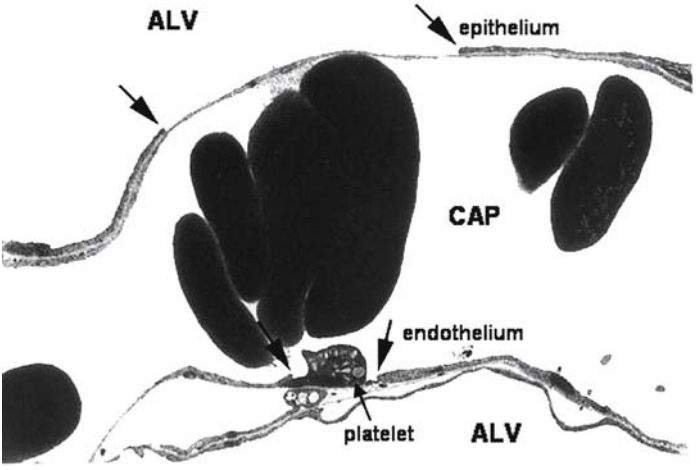

Figure 5. Ultrastructural changes in the wall of a pulmonary capillary when the capillary hydrostatic pressure was raised. The arrows at the top show a disruption in the alveolar epithelial layer; the arrows at the bottom show a break in the capillary endothelial layer with a platelet adhering to the exposed basement membrane. ALV, alveolus; CAP, capillary lumen. Modified from (12).

OXYGEN ENRICHMENT OF ROOM AIR AT HIGH ALTITUDE

In contrast to the last project, this subject has no broad biological significance. Indeed it might be argued initially that it is trivial from a scientific point of view. Yet it also has proved to be enormously satisfying because it is changing the way that people work at high altitude and, for example, makes it possible for astronomers to operate at altitudes that would be impossible without this advance.

The general principle could hardly be simpler. The detrimental effects of high altitude are caused by the low PO_2 in the air and so the obvious way to circumvent these is by raising the PO_2. Of course this can be done using portable oxygen equipment but this is cumbersome and awkward to use 24 hours a day. The solution is to add oxygen to the ventilation of the room thus raising its concentration (9). At a typical facility at an altitude of 5000 m, the oxygen concentration is raised from 21 to 27%, and this reduces the equivalent altitude (based on the inspired PO_2) to about 3200 m. Since most people working at these altitudes already have some acclimatization, an altitude of 3200 m is easily tolerated.

This procedure has some interesting technical problems. First it has only become economically feasible since the introduction of oxygen concentrators that produce oxygen from air. These are now used by the thousands in homes of people with chronic lung disease. The concentrators work by pumping air at high pressure through a tube of synthetic zeolite with the result that the nitrogen is preferentially adsorbed and the effluent gas has a high oxygen concentration. These concentrators are robust, self-contained and typically only require about 350 watts of electrical power to produce 5 $l \cdot min^{-1}$ of 90-95% oxygen. This is then fed into the ventilation duct of the room. A typical room containing 2 people at an altitude of 5000 m requires 4 concentrators. It is also possible to provide the oxygen from liquid oxygen tanks but the running costs are about ten times higher in a typical facility.

The amount of ventilation with fresh air is an important factor. Clearly the higher the ventilation, the more oxygen that has to be generated. We use the ASHRAE (American Society of Heating, Refrigeration, and Air Conditioning Engineers) 1975 standard which is 8.5 $m^3 \cdot h^{-1}$ per person. The CO_2 concentration in the room is monitored and kept at or below 0.3%. Much higher concentrations can be present without causing a health hazard or the occupants being aware of them, but the CO_2 level is a useful index of the adequacy of ventilation. Of course the oxygen concentration is also monitored.

Another important issue is the possible fire hazard. This has been carefully studied by the National Fire Protection Association and it is possible to choose a room oxygen concentration that provides substantial benefit to the occupants at high altitude but that is below the fire hazard level. It should be remembered that although the PO_2 of the air in the room at high altitude is raised by the addition of oxygen, the resulting PO_2 is always far below the sea level value.

The principal use of oxygen enrichment of room air to date has been in high-altitude telescope facilities. The longest experience has been in a radiotelescope operated by the California Institute of Technology at an altitude of 5050 m in north Chile (Figure 6). This has been in continuous operation for 5 years and the astronomers are adamant that the project could not have gone ahead without room oxygen enrichment. A number of other high-altitude telescopes are installing or planning oxygen enrichment of room air. The principle has also been used in the sleeping quarters of the Collahuasi mine which is situ-

ated at an altitude of about 4500 m though the dormitories are lower at 3800 m. Sleep is often impaired at high altitude and oxygen enrichment of room air has proved to be very valuable to some of the miners.

Rarely in my experience does a project progress from an idea to implementation in a few years. However in this case the Cal Tech astronomers were using it in their telescope less than 5 years after the initial description (9) and this certainly resulted in a warm fuzzy feeling.

Figure 6. Oxygen-enriched room at the Cal Tech radio-telescope (5050 m). The oxygen concentration in the room is 27% giving an inspired PO_2 equivalent to that of an altitude of 3200 m. Courtesy of the California Institute of Technology.

HISTORY OF HIGH-ALTITUDE PHYSIOLOGY AND A JOURNAL

The last adventure is something of a hodgepodge but no less satisfying for that. We are fortunate at UCSD to have an excellent archival library known as the Mandeville Special Collections Library. Some years ago I was talking to the librarian about depositing some material there and she suggested that we start an archive in high-altitude medicine and physiology. This was done and as far as we know is the only such archival collection in the world.

The primary purpose of an archival collection of this kind is to gather correspondence, documents, experimental protocols, laboratory notebooks, field journals and the like. Published material is of less interest because it is available elsewhere. The archive now contains a very extensive collection from Griffith Pugh which was referred to earlier. Another large collection is from Ulrich Luft, and there are various amounts of material from other workers in the field including Bruno Balke, Elsworth Buskirk, Erik Christensen, David Bruce Dill, Thomas Hornbein, Steven M. Horvath, Herbert Hultgren, Alberto Hurtado, James S. Milledge, Nello Pace, Edward J. Van Liere, Michael P. Ward, Oscar A.M. Wyss and myself. An archive like this increases in value as time passes and more material is added. The archive can be accessed on the web at <roger.ucsd.edu> and searching for the title High Altitude Medicine and Physiology Collection. Potential donors should contact

the librarian in charge, Lynda Claassen <Lynda@library.ucsd.edu>.

Another historical interest has been researching some prominent figures in high-altitude medicine and physiology including: Robert Boyle, George Finch, Stephen Hales, Alexander Kellas, and Thomas Ravenhill. This interest has been stimulated by the enlightened policy of the editors of the *Journal of Applied Physiology* who have welcomed occasional historical articles. The most ambitious product of this research has been the book *High Life: A History of High-Altitude Physiology and Medicine* which I am glad I took the trouble to write because it is so useful for reference.

A final adventure in this list has been the journal *High Altitude Medicine & Biology*. Initially I was reluctant to take this on because I thought there were enough journals and I told the publisher so. However Mary Ann Liebert was very persuasive and she convinced me that there was a niche and indeed I now think she was right. There are a number of articles in the area that are important but do not fit easily into existing clinical, physiological or other biological journals. It was gratifying to see the Journal adopted by the International Society for Mountain Medicine, and its trajectory is definitely upward as befits its topic.

Hopefully other adventures in high-altitude physiology and medicine will come my way but even if they do not I have had more than my share and am grateful for this.

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Chapter 3

EXERCISE INDUCED ARTERIAL HYPOXEMIA: THE ROLE OF VENTILATION-PERFUSION INEQUALITY AND PULMONARY DIFFUSION LIMITATION

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Abstract: Many apparently healthy individuals experience pulmonary gas exchange limitations during exercise, and the term "exercise induced arterial hypoxemia" (EIAH) has been used to describe the increase in alveolar-arterial difference for oxygen ($AaDO_2$), which combined with a minimal alveolar hyperventilatory response, results in a reduction in arterial PO_2. Despite more than two decades of research, the mechanisms of pulmonary gas exchange limitations during exercise are still debated. Using data in 166 healthy normal subjects collated from several previously published studies it can be shown that ~20% of the variation in PaO_2 between individuals can be explained on the basis of variations in alveolar ventilation, whereas variations in $AaDO_2$ explain ~80%. Using multiple inert gas data the relative contributions of ventilation-perfusion ("$\dot{V}_A/\dot{Q}$") inequality and diffusion limitation to the $AaDO_2$ can be assessed. During maximal exercise, both in individuals with minimal ($AaDO_2$ < 20 Torr, x = 13±5, means ± SD, n = 35) and moderate to severe ($AaDO_2$= 25-40 Torr, x = 33±6, n = 20) gas exchange limitations, $\dot{V}_A/\dot{Q}$ inequality is an important contributor to the $AaDO_2$. However, in subjects with minimal gas exchange impairment, $\dot{V}_A/\dot{Q}$ inequality accounts for virtually all of the $AaDO_2$ (12±6 Torr), whereas in subjects with moderate to severe gas exchange impairment it accounts for less than 50% of the $AaDO_2$ (15±6 Torr). Using this framework, the difficulties associated with unraveling the mechanisms of pulmonary gas exchange limitations during exercise are explored, and current data discussed.

Key Words: multiple inert gas elimination technique, pulmonary gas exchange, perfusion heterogeneity

Hypoxia and Exercise, edited by R.C. Roach *et al.*
Springer, New York, 2006.

INTRODUCTION

For many years researchers have been fascinated by the apparent paradox that some highly aerobically trained humans and animals experience pulmonary limitations to maximal exercise performance. These are of sufficient magnitude to cause a reduction in arterial partial pressure of oxygen (PaO_2) and saturation (5, 17, 42, 52). This condition, termed exercise induced arterial hypoxemia (EIAH), poses a potential limitation to maximal exercise performance. Evidence suggests that a consequence of EIAH is that even small amounts of EIAH have a significant detrimental effect on limiting O_2 transport and utilization during maximal exercise (16, 40). The reader is referred to an excellent review of the topic (8), which reviews the potential causes of EIAH in detail and provides the framework for classification of the severity of hypoxemia which is utilized here.

Definitions of EIAH

In the past EIAH was defined in terms of a decrement in PaO_2 from resting levels, but this definition does not allow hypoxemia related to inadequate ventilation, to be distinguished from that due to from inefficient gas exchange. For example, a subject could have a increased alveolar-arterial difference for oxygen ($AaDO_2$) to 40 Torr, but if they were able to reduce markedly hyperventilate, and reduce the partial pressure of carbon dioxide to 25 Torr, PaO_2 would be maintained near resting levels. Thus, the effect of inefficient gas exchange would be obscured by a brisk hyperventilatory response. The most appropriate classification of the severity of EIAH therefore, depends on the type of research question is being asked. Where one is concerned with issues related to systemic oxygen transport and delivery, then arterial oxygen saturation (SaO_2) is the best indicator of the consequences of EIAH. If the main research question is concerned with efficiency of gas exchange, then a classification based on the extent of the increase of the $AaDO_2$ with exercise is more appropriate. An $AaDO_2$ greater than 25 Torr is consistent with a mild gas exchange impairment, whereas $AaDO_2$ greater than 35-40 Torr consistent with a severe gas exchange impairment (7). Similarly, when the hyperventilatory response to exercise is considered, a $PaCO_2$ at maximal exercise in the 35-38 Torr range represents a borderline hyperventilatory response and $PaCO_2$ greater than 38 Torr, an absent hyperventilatory response (7). The use of these different criteria allow the identification of key components of EIAH, which individually may not result in a decrement in PaO_2 or SaO_2. It should be noted that EIAH is not confined to humans and is especially notable in the horse which develops a large $AaDO_2$ during maximal exercise, associated with a considerable decline in PaO_2 (to ~70 Torr) and SaO_2 (~88%) (8, 52).

Why don't we know more about EIAH?

Despite considerable research effort, the causes of EIAH are still debated. Once issue is that the amount of data collected in healthy normal exercising subjects is rather small compared to the clinical data collected in patients with disease. In research studies, because of the technical difficulties associated with data collection, many studies are conducted using 8-12 subjects and generalizations to populations are therefore limited. Also, many of the desirable measurements can only be made indirectly, such as the quantification of pulmonary diffusion limitation using the multiple inert gas elimination technique (49). Many