Chapter 2

ADVENTURES IN HIGH-ALTITUDE PHYSIOLOGY

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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.

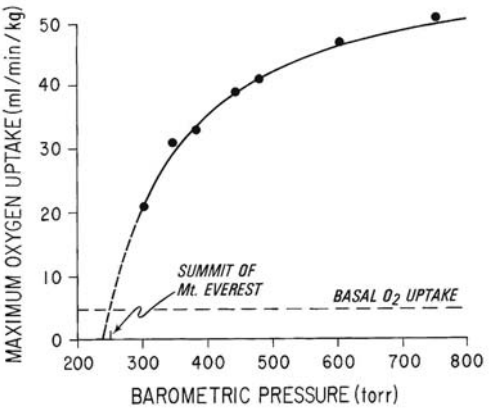

Figure 3. Maximal oxygen consumption plotted against barometric pressure at different altitudes. The lowest point was obtained on the Makalu Col (7440 m). Extrapolation of the line suggests that all the oxygen available on the Everest summit will be required for basal metabolism. These were the data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

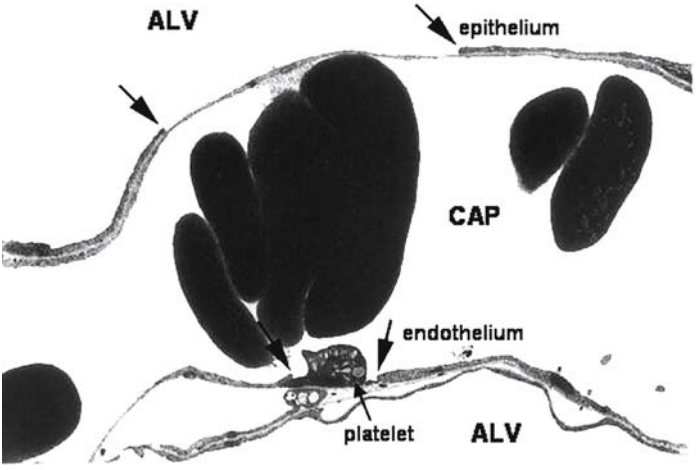

Figure 5. Ultrastructural changes in the wall of a pulmonary capillary when the capillary hydrostatic pressure was raised. The arrows at the top show a disruption in the alveolar epithelial layer; the arrows at the bottom show a break in the capillary endothelial layer with a platelet adhering to the 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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