The Denali Medical Research Project, 1982-85

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IN THE MONTHS OF MAY and June of 1982, 1983, and 1985 the Department of High Latitude Studies of the University of Alaska, Anchorage, with the consent of the National Park Service and the air support of the U.S. Army, operated a medical research facility on the 14,000-foot plateau of the West Buttress of Mount McKinley (Denali). Our purpose was to study altitude and cold problems of mountaineers. We also assisted with numerous rescues, provided emergency medical care to all climbers requesting such, offered screening tests to detect altitude problems, and provided advice on acclimatization, cold injury prevention and other medical and non-medical problems. There were no charges for our services. The positive impact of this project and some preliminary results have been discussed previously.[1-10] Various scientific papers have been published [11-13] or are soon to be published in medical journals, and abstracts have been presented at scientific meetings. The purpose of this report is to inform the climbing community of the results of some of the completed studies. It is particularly and gratefully directed to the hundreds of climbers who volunteered to be research subjects, and who gave us their enthusiastic support. Those wishing further information or reprints may write directly to Dr. Hackett; other work still in progress will be reported at a later date.

Studies of High Altitude Pulmonary Edema (HAPE)

1. Clinical observations. Between one in thirty and one in fifty Denali climbers developed life-threatening high altitude pulmonary edema (HAPE). Important risk factors included rapid ascent, the use of sleeping pills, and perhaps extreme cold. The criteria for early diagnosis were: rather sudden onset of fatigue and weakness, especially when trying to move uphill, a dry cough, increased breathlessness on exertion, an increased heart rate at rest and grayish or dark fingernails. Severe HAPE most often developed during the night. Since the illness responded so well to oxygen and descent, no victim of HAPE required helicopter evacuation. Diamox seemed to be beneficial when given

early in the course of the illness. No other medications were given. In 1982, we advised all climbers with HAPE to descend and not re-ascend. Of the last 20 HAPE cases, however, while all descended to 3000 meters (10,000 feet) for at least three days, more than half re-ascended, and many went on to the summit. No climber during re-ascent had a recurrence of HAPE.

2. *The protein, cellular, and biochemical characteristics of the edema fluid.* Pulmonary edema is the accumulation of fluid in the air sacs, or alveoli, of the lung. The reason it kills people is that alveoli full of fluid instead of air cannot exchange oxygen, and the blood oxygen level thus becomes extremely low. Exactly what causes the blood vessels of the lung to leak fluid into the alveoli is unknown. We thought that by collecting the edema fluid from the lungs of climbers with HAPE, and analyzing it for proteins, cells, and various chemicals, we could learn more about the cause of HAPE.

In 1983 and 1985, Drs. Schoene and Swenson performed bronchoscopy on a total of 14 climbers. Seven had HAPE, and of the seven controls, four had no symptoms at all, and three had acute mountain sickness. The procedure consisted of anesthetizing the throat and trachea, and passing a fiberoptic tube through the mouth into a segment of the right lung, then washing that segment with saline and suctioning out the fluid, which was then frozen. Dr. Tom Martin, in Seattle, led the team of scientists that analyzed the fluids. All climbers handled the procedure well; there were no complications.

The results were quite revealing. The protein level in the HAPE fluid was 60 times that in the fluid of the others. This means that there must be a "permeability leak" in the blood vessels of the lung. Further analysis found chemicals called leukotrienes and thromboxane. These are very potent hormone-like mediators, released by cells, that can cause increased pressure and leakiness of the blood vessels and also cause small blood clots. The presence of red blood cells in the fluid accounts for the pinkish color of the sputum in HAPE, and some other cells were present as well.

All pulmonary edemas are divided into two groups based on the protein content of the edema fluid. For years, researchers had wondered if HAPE was a low or high protein edema. This study is thus a significant breakthrough. Researchers trying to develop an animal model of HAPE, for example, now know to focus on producing a high protein type of edema. The fact that the chemical mediators we detected can be blocked by various drugs, such as aspirin and Motrin, opens the door to new research into treatment and prevention of HAPE. Exactly what triggers the leak in the pulmonary blood vessels is still not clear. The clinical observations and lung fluid analyses taken together, however, point to a rapidly reversible stretching or opening of the thin cellular walls of the blood vessels. This leak is likely to be triggered by high vascular pressures in the lung generated during periods of extreme hypoxia, such as occur during sleep.

3. A pressure mask for treatment of HAPE. Breathing against a resistance is a technique commonly used in treating various types of sea-level pulmonary edema in the intensive care unit. It tends to keep the air sacs open longer and thus improve transfer of oxygen. Dr. Schoene headed up a study of the effects of a lightweight plastic mask in which the resistance to exhalation could be easily adjusted. Thus, with this mask in place, a climber breathes regular air, not oxygen. He/she inhales normally, but has to work a little harder to exhale. The use of the mask is similar to exhaling against pursed lips and to grunt breathing, both of which are used by some persons with lung disease, and recommended by certain guide services to optimize performance at altitude. We studied both healthy climbers and those with HAPE. The mask definitely improved oxygen exchange in climbers with HAPE. Blood oxygen saturation went from 54% to 62%. Interestingly, it improved blood oxygen levels in the well climbers as well, simply by causing them to hyperventilate a bit. The mask was well tolerated, and although studied in only a small number of climbers (17), there were no adverse effects. The mask is called the "Downs Mask," weighs 4 ounces, and is available from Vital Signs, Inc. Expeditions might consider taking one along, and using it as a temporizing measure while arranging for oxygen and/or descent. This study also indicates that grunt breathing (or "pressure breathing") is not necessary for well persons, but may benefit those with HAPE. A well climber would do better to merely consciously increase breathing during exercise without grunt breathing, and thereby raise his blood oxygen level without increasing the work of breathing.

4. Control of breathing during and after HAPE. Dr. Hackett and Rob Roach headed this study, which examined the role of the hypoxic ventilatory response (HVR) in HAPE. The HVR is an apparently genetic characteristic that determines how much one increases the breathing in response to low levels of oxygen in the inspired air. We found that climbers with HAPE had very low HVR values, and that they were also low after recovering from HAPE, indicating that they were low to start with, and not the result of HAPE itself. In other words, persons who develop HAPE tend to not breathe enough on ascent to altitude. Inadequate ventilation leads to greater hypoxia and higher pulmonary artery pressure. However, a number of well climbers also had very low HVR values (including Peter Habeler). For this reason, we feel that a low HVR plays a permissive rather than a causative role. That is, HAPE will tend to develop unchecked in those with a low HVR, while those with a high HVR will increase their breathing in the face of hypoxia, which is somehow protective of the illness. During our studies, we also discovered episodes of extreme hypoxia during sleep, due to irregular breathing patterns, in persons with HAPE. Such episodes are more common in those with a low HVR, and may contribute to the development of HAPE. Since the HVR can be measured at sea level, high risk climbers can be identified prior to ascent, and can thus take extra precautions to avoid pulmonary edema. At present, however, this test is done only in research laboratories.

Studies of Acute Mountain Sickness (AMS)

5. Clinical observations. Some degree of AMS is a common problem on Denali, and generally occurs at 14,000 feet or higher. The data, collected by questionnaires, showed the following incidence of various symptoms amongst all climbers:

headache	47%
shortness of breath climbing	38%
periodic breathing at night	25%
difficulty sleeping	24%
poor appetite	22%
nausea	18%
dry cough	14%
lethargy	14%
shortness of breath at rest	13%
swelling of hands or face	11%
visual changes	7%
loss of coordination	7%

Overall, 30% of climbers met our criteria for a diagnosis of AMS. Risk factors were a fast rate of ascent and a previous history of AMS. Most cases were treated by descent and/or Diamox (acetazolamide). Diamox was also helpful for periodic breathing or headache alone.

6. Arterial oxygen saturation as a predictor of AMS. We are continuously looking for ways to detect altitude illness as early as possible. In addition to the obvious value in terms of prevention of serious illness, such studies also give us clues as to the cause of AMS, HAPE and high altitude cerebral edema (HACE). In 1982, Dr. Hackett led a study in which we examined, at 14,000 feet, 106 asymptomatic climbers on their way up the mountain. We measured the arterial oxygen saturation by means of a Hewlett-Packard ear oximeter. This device passes a spectrum of wavelengths of light through the outer part of the ear, and calculates the amount of oxygen in the blood by the absorption of different spectra. Essentially, the more red the blood, the higher the oxygen saturation. The measurement thus does not require drawing any blood, is painless, takes only one to two minutes, and is quite accurate. A normal saturation at sea level is 98%, while at 14,000 feet on Denali, the normal value is about 78 to 82%.

When the climbers came back through our camp a few days later, we interviewed them about symptoms of AMS. We found that those who developed AMS were the ones who had low oxygen saturation readings at 14,000 feet, before they went higher. The average value for the 45 who developed AMS had been 74.2%, while those who remained well averaged 81.5%, a highly statistically significant difference. Thus, a low oxygen saturation at 14,000 feet tended to predict who was going to develop AMS as they went higher. There are two reasons for a lower than normal oxygen level. One is an inadequate amount of breathing, the second is a mild degree of pulmonary edema.

This study was done in 1982. Since then, we have undertaken mass screening of the oxygen saturation of climbers coming through our camp, and advised those with low oxygen levels to acclimatize more before ascending, or to take Diamox. Because of this, serious AMS and pulmonary edema are becoming less common higher on the mountain. The ear oximeter has become an extremely useful tool in preventing, recognizing, and treating AMS and HAPE.

7. Lung abnormalities in acute mountain sickness. AMS is primarily a disorder of the brain. This is obvious to any climber who experiences headache, nausea, trouble sleeping, lethargy, and loss of coordination. Many with AMS, however, also have breathlessness and congestion in the chest, indicating low-grade pulmonary edema. We wondered if abnormalities of the lung are present in all persons with AMS. If so, the lung problem might play an important role in causing AMS.

To examine this question, we measured the difference in oxygen pressure between the "air side" and the "blood side" of the lung. The climber breathed into an oxygen analyzer to measure the "air side," and we took a specimen of arterial blood to measure the "blood side" oxygen level. Calculating the difference is a very sensitive way to measure the oxygen exchange function of the lung. The other test we did measured the stiffness of the lungs, and is called the peak expiratory flow rate. The climber merely blew into a tube as hard as he could, and the generated force was registered on a meter.

The results from 13 controls and 8 subjects with AMS were as follows. Sick persons had a lower blood oxygen (73% vs. 82%), but it was not because they were breathing less. The air to blood oxygen pressure difference was 7mmHg in the controls, but 17mmHg in those with AMS, a very substantial difference, and explains why the blood oxygen level was lower—oxygen was not diffusing well across the lung membrane. The peak flow rate in the ill was 20% less than in the well climbers, indicating that their lungs were stiffer. These results confirmed that there was indeed considerable lung dysfunction in persons with AMS, and it could be explained by the presence of extra fluid in the chest; i.e., low-grade pulmonary edema. Is it the lung or the brain changes that come first, or do they develop simultaneously?

We don't know for sure, but these findings of lung dysfunction may help explain AMS. The brain is sensitive to the blood oxygen and carbon dioxide levels, not to the altitude per se. For example, two climbers at the same altitude always breathe the same pressure of oxygen in the air, but if one has a lower *blood* oxygen because his lungs are not working as well, his brain is "physiologically" at a higher altitude. Therefore, a sick climber at 14,000 feet may have the same blood oxygen level as a well climber at 22,000 feet, but without the benefit of a period of acclimatization to get there. No wonder his brain does not do well!

8. The effect of Diamox on brain blood flow. Diamox is very effective in preventing AMS, and now is also being used for treatment. The exact mech-

PLATE 49

Photo by Peter Hackett

Dr. Robert Schoene holds the bronchoscope in place while a climber with high-altitude pulmonary edema looks into his own lung.

anism by which Diamox works is not clear. It makes the blood more acid, increases breathing, increases urination, eliminates periodic breathing during sleep and decreases the formation of cerebrospinal fluid. In large doses, it has been shown to increase brain blood flow. All of these actions are potentially beneficial. If we could learn which of these actions are essential, it would teach us more about the cause of AMS.

In order to answer this question, Dr. Hackett headed a study of the effect of 250mg intravenous Diamox on brain blood velocity, which is an index of brain blood flow. This measurement was made with a Teca Trans-cranial Doppler, which records the speed of blood in an artery in the brain by analyzing signals sent to the blood vessel from outside the head, and then reflected back, similar to a radar device. In ten well climbers and five with AMS, we found that only three persons increased blood flow at 30 minutes, and only one at 60 minutes, and that overall, there was no significant change with Diamox, in either the well or ill group. This indicates to us that a change in brain blood flow is not an important mechanism of action of Diamox, and that perhaps brain blood flow is not an important causative factor in AMS. More subjects need to be studied to confirm these findings.

Sleep Studies

9. Clinical observations during sleep. It is becoming more and more clear that events during sleep may have an important impact on well-being at high altitude. For example, we have noted extremely low oxygen levels of the blood during irregular breathing patterns in some persons with HAPE—much more severe abnormalities than the usual periodic breathing during sleep, which is "normal" at altitude and probably harmless. Whether these were the cause or the effect of illness is unknown. One point that *is* clear is that the use of sleeping pills can be very dangerous, especially in those who are ill. In 1983, for example, 7 of the 8 serious HAPE cases were associated with the use of a sleeping pill the night the illness developed.

10. A comparison of acetazolamide (Diamox) and almitrine for periodic breathing. This study, headed by Rob Roach, examined whether almitrine, a respiratory stimulant (as is Diamox), was a better drug to treat periodic breathing during sleep. Since the drugs act on different sites in the body to affect breathing a comparison of these two drugs would also provide more insight into the mechanism of action of Diamox for this disorder. Well climbers were studied during sleep on three nights; one night on a placebo, once on Diamox, and once on almitrine. The results showed that both drugs raised oxygen saturation during sleep, but that Diamox was superior in eliminating periodic breathing. In fact, almitrine increased periodic breathing. Significantly, there were no severe drops in oxygen saturation while on Diamox.

11. The effects of benzolamide on sleep periodic breathing. This study, headed by Dr. Swenson, looked at the effects of benzolamide, a cousin of

acetazolamide. Benzolamide, unlike acetazolamide, acts only on the kidney, forcing it to excrete bicarbonate, and thus making the blood more acid. Acetazolamide does this also, but it has many other effects as well. If benzolamide were as effective as acetazolamide in reducing periodic breathing, then we could conclude that it was due to its effect on the kidney, and also that this must be the mechanism by which acetazolamide works as well.

Well climbers were studied during sleep with and without benzolamide. Similar to acetazolamide, benzolamide reduced periodic breathing and eliminated periods of severe desaturation. Side effects, however, were more of a problem with benzolamide, and therefore Diamox still remains our choice for treating periodic breathing. We concluded that both of these drugs act by making the blood more acid; thus, they reverse the usual alkalinity of the blood caused by overbreathing.

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