

Meeting Report

25th Anniversary of Research in High Altitude Physiology and Medicine at the New Capanna Margherita, October 9–11, 2008, Varallo, Italy

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Marco Maggiorini, the new ISMM president crowned with the presidential kalpak.

TWENTY-FIVE YEARS AGO Oswald Oeltz (Zurich, Switzerland), Peter Bärtsch (Heidelberg, Germany), and colleagues climbed up to the Capanna Regina Margherita on Monte Rosa (4559 m) to carry out a program of altitude research. This inaugurated a series of projects that, over the next 25 years, saw scientists from many nations conduct research at the Capanna during most summers. To celebrate

this silver anniversary, Marco Maggiorini (Zurich, Switzerland) and Annalisa Cogo (Farrara, Italy) organized a conference at Varallo, the base town in the Val Sesia from which the easiest access to the Capanna is made.

Of course, altitude research was carried out at the Capanna long before 1983. The hut was built at the instigation of Angelo Mosso in 1894 expressly to carry out altitude physiological research. Fourteen years ago we celebrated the centenary of the building of the hut with a conference also at Varallo. However, in the middle years of the 20th century, hardly any research was done until Oeltz and Bärtsch rekindled interest in this facility.

The conference was endorsed by the International Society of Mountain Medicine (ISMM) and the Club Alpino Italiano. It was held in the very convenient Civic Theater in the center of town, within 3 minutes walk of the hotel where most participants stayed. About 65 delegates, mostly from Europe and the United States, attended. I should first apologize to the speakers if I misreport or shortchange their contributions. We did not have abstracts of the talks, so I have only my rather sketchy notes of the conference and some of the PowerPoint presentations. We enjoyed 35 presentations in 2 days, and it is impossible to keep 100% concentration on every one or, in a short report, to do justice to all of them.

Conference Sessions

In the opening session on Thursday, after a welcome from the organizers, Oswald Oeltz gave a delightful, self-deprecating talk on 25 years of modern research at the Capanna Regina Margherita, including describing its inauspicious start in 1983. Nowadays the route used by researchers and subjects to get to the hut is by the Alagna cable car, the Gnifetti Hut, and a 5-h glacier walk. But 25 years ago they elected to climb by the Monte Rosa Hut and glacier. Oswald, conqueror of Everest, companion of Messner, and a highly experienced Alpinist, led the way. The party included at least one inexperienced member dressed in T-shirt and jeans. The weather deteriorated, the party became lost, and they had to bivouac in a crevasse, arriving at the hut the next day!

After Oeltz, Paolo Cerretelli (Milan, Italy) talked about his research experience on a number of high altitude expeditions. Starting with a 1951 expedition to the Karakoram, he continued with expeditions to Greenland, then to Kenya, and in 1973 to Everest. More recently he worked in the "pyramid" laboratory (5050 m) in the Khumbu, Nepal. His earlier studies included classical work on exercise at altitude, the lactate paradox, and the performance of elite climbers. Recently, he has moved into muscle proteomics, including work on muscle biopsies from last year's Xtreme Everest Expedition.

We then had a session on the history of our subject. Jean-Paul Richalet (Paris, France) led us through the life and work of Paul Bert, scientist, politician, and administrator. Bert laid the scientific foundation of our subject by showing that the effects of altitude were due to the reduced partial pressure of oxygen (P_{O_2}) and were the same, whether produced by reducing the total atmospheric pressure or the percentage of oxygen at normal pressure. Bert was not a field physiologist, but he stimulated many others to study the effects of altitude in the field.

Giuseppe Miserocchi (Milan, Italy) reviewed the contribution of Angelo Mosso, who was a professor of physiology at Turin in the later half of the 19th century and was responsible for building the original Capanna Regina Margherita. Mosso is mainly remembered for his work on humans at high altitude and for a best-selling book in which he summarized many years of work in the Capanna.

Jim Milledge (London, UK) was asked to talk about John Scott Haldane, who was 14 years younger than Mosso and was active in the last few years of the 19th and the early 20th centuries. Haldane was based in Oxford in the department of physiology as lecturer, tutor, and reader, but never became professor. He did important work on the chemical control of breathing and on the carriage of oxygen and carbon dioxide in the blood. But Haldane is better known for his field studies in mines, on the causes of death after mine explosions and fires. In altitude studies he is remembered for his Pikes Peak expedition in 1911. During this 35-day stay at 4302 m, Haldane and his three colleagues reported on acute mountain sickness (AMS) in themselves and in visitors and studied many aspects of acclimatization. The most controversial results were in measurements of alveolar-arterial P_{O_2} gradients. They reported that the arterial P_{O_2} was higher than the alveolar and tended to increase with acclimatization. That is, the lungs seemed to secrete oxygen against the pressure gradient. Later, of course, this result was shown to be erroneous.

Finally, Robert Naeije (Brussels, Belgium) reviewed the contribution of Jack Reeves to the post-World War II era of altitude medicine, covering Reeves's early work on variations of the Fick equation; work with his great friend and colleague, Bob Grover, on brist disease in cows at altitude; work in Operation Everest II on left ventricular function at extreme (simulated) altitude; and work during a series of studies on Pikes Peak with colleagues from Denver on the causes of reduced VO_{2max} at altitude.

The first session on Friday was on adaptation to high altitude. Yvonne Nussbaumer (Zurich, Switzerland) reported on recent work with children on the Jungfrau Joch carried out by Susi Kriemler. It seems that on the first night children have less periodic breathing than adults and that they have

a greater rise in pulmonary artery pressures than their fathers. They also found evidence that the hypoxic pressor response was at least partly due to heredity.

Annalisa Cogo reviewed the evidence for the development of subclinical pulmonary edema on arrival at altitude being a common phenomenon. Endothelial cells in culture become more permeable when made hypoxic. Reduction in lung closing volume and reduction in FVC is found on arrival at altitude in about 75% of subjects. However, there was no correlation with pulmonary artery pressure or susceptibility to high altitude pulmonary edema (HAPE). She considered subclinical pulmonary edema to be an initial physiological response to altitude and that it does not preclude going higher and performing well.

Heimo Mairbaur (Heidelberg, Germany) followed with a paper on oxygen transport and delivery. He considered the various strategies for increasing oxygen delivery, such as hemoglobin with a left-shifted oxygen dissociation curve as exhibited by bar-headed geese when migrating over the Himalayas.

Gianfranco Parati (Milan, Italy) reviewed the role of endothelin and β -adrenergic receptors in the response to altitude hypoxia. Endothelin 1 rises on going to altitude, and this rise correlates with the rise in pulmonary artery pressure. He speculated that endothelin blockers might be of value in treating or preventing HAPE. Bosentan, an ET blocker, did reduce PA pressure at altitude, but also reduced diuresis of both sodium and free water.

Finally in this session, Niels Olsen (Copenhagen, Denmark) discussed renal adaptation and fluid homeostasis.

After coffee there was a session on exercise at altitude. Hanspeter Brunner (Basel, Switzerland) talked about cardiac function and exercise limitation. He concluded that there was no evidence that cardiac dysfunction limited exercise at altitude and that the reduced maximum cardiac output was a consequence of reduced VO_{2max} , not its cause.

Peter Wagner (San Diego, California, USA) reviewed the subject of oxygen uptake and exercise limitation. He agreed with the previous speaker that the cardiac function was not a limiting factor, but showed from data in the literature that lung (and possible tissue) diffusion of oxygen was. In Operation Everest II, the (A-a) O_2 gradient was found to be ~6 mmHg when exercising at the summit equivalent. Had it been zero, the saturation would have been raised from 51% to 62% and Everest would have been equivalent to Monte Rosa!

Andrea Aliverti (Milan, Italy) discussed lung volumes during exercise. She used a system of three video cameras and markers on the chest and abdomen to record chest and abdominal movement at rest and on exercise at low and high altitude (the Capanna). On increasing exercise work load, it was found that increased tidal volume was recruited from both inspiratory and expiratory reserve volumes. At altitude, ventilation increases more rapidly than at sea level, and extra volume came mainly from inspiratory reserve volume. The researchers also calculated the work of breathing and found that this was increased at altitude. They attributed this to the increased compressibility of gas at altitude and inertial effects.

Finally, Carsten Lundby (Copenhagen, Denmark) discussed the question as to why there was no increase in VO_{2max} with acclimatization to altitude. Actually, at moder-

ate altitude there is an increase in $\dot{V}O_{2max}$, but not above a threshold of 3500 to 4000 m. He considered this to be due to reduced blood flow to the legs at the higher altitude, possibly due to increased noradrenalin.

The next session was the first of two on high altitude illness. Peter Hackett (Telluride, Colorado, USA) reviewed the epidemiology of high altitude illness from his pioneering work at Pheriche in the 1970s to today. Then Walter Reinhardt (Chur, Switzerland) discussed changes in blood and its cells in high altitude illness. There seemed to be no change in red blood cells (RBCs) with AMS or HAPE, except possibly some tendency to greater aggregation of RBCs. Platelets also tended to aggregate more easily, and their number goes down in the first 18 to 24 h.

Finally, Chris Imray (Coventry, England) considered brain circulation in high altitude illness. On last year's Xtreme Everest expedition, he used ultrasound Doppler and near-infrared spectroscopy to measure changes in cerebral blood flow as high as the South Col! Middle cerebral artery velocity showed little change up to Base Camp. At higher altitudes there was some reduction in velocity. In AMS there was no significant change in cerebral blood flow, but possibly some reduction in autoregulation.

In the second high altitude illness session, we first heard from Damian Bailey (Glamorgan, Wales, UK) on whether AMS is a mild form of HAPE. He reviewed the evidence for and against this proposition. Small increases in brain volume are induced by hypoxia, but do not distinguish subjects with and without AMS. However, reduction in indexes of autoregulation of cerebral blood flow do correlate with severity of headache.

Ralf Bumgartner (Zurich, Switzerland) asked whether AMS is a neurologic disease. He noted, as had Bailey, that although there is some slight brain swelling with hypoxia it was only by ~ 35 mL in a brain volume of ~ 1400 mL, and the degree of swelling did not correlate with the AMS score nor was there good evidence of raised intracranial pressure in AMS. He concluded that high altitude headache and other AMS symptoms may result from a neurological disease, possibly a dysfunction of the trigeminovascular system.

Finally, in this session, Oswald Oelz gave us a clear lecture on how to prevent AMS (adequate acclimatization) and how to treat it.

After coffee we had a full session on HAPE. First Marco Maggiorini reviewed pulmonary circulation in HAPE, quoting especially his own work at the Capanna. There is intense vasoconstriction mainly in the arterioles, but also some in the veins. He discussed the various mechanisms that may be involved, including potassium and calcium channels in the endothelium, NO, endothelin, and prostaglandin. The net result is an increase in pulmonary capillary pressure and edema. He also mentioned that sympathetic activity was higher and expired NO lower in HAPE-susceptible subjects at altitude.

Next Claudio Sartori (Lausanne, Switzerland) told us the story of "labor and susceptibility to HAPE." A Canadian study found that mice exposed to a hypoxic insult as neonates had, as adults, a greatly increased hypoxic pulmonary vasoconstriction (HPV). By searching records in obstetric units, the study traced a group of people who had had hypoxic episodes as neonates. When tested, they too were found to have exaggerated HPV, which was reversed by NO. But they did not get HAPE on going to high altitude.

Continuing the topic of HAPE, Erik Swenson (Seattle, Washington, USA) discussed pulmonary capillary leak and coagulation. Pulmonary hypertension is essential in the mechanism of HAPE. HAPE-susceptible individuals have an exaggerated HPV, as well as rather low hypoxic respiratory response (HVR). There is evidence from Sue Hopkins's work of uneven pulmonary blood flow, supporting Hultren's original explanation for the production of high capillary pressures. Work by the speaker and others at the Capanna, when performing bronchoscopies in susceptible subjects at the start of HAPE, showed no rise in inflammatory cytokines. These are found later as the condition develops, and later still there may be coagulation problems.

Then Urs Scherrer (Lausanne, Switzerland) reviewed alveolar fluid clearance and HAPE susceptibility. He took up the story that Sartori had told us and wondered why these subjects, with brisk pressor responses and high pulmonary artery pressures, did not get HAPE. He asked if, together with a brisk response, one needed also a defect in fluid clearance from the alveolus to be HAPE susceptible? With colleagues, he studied ENaCl (a crucial channel for fluid clearance) knock-out mice and found that they died with pulmonary edema. They also had a low potential difference across their nasal epithelium. This is also found in HAPE-susceptible subjects. β_2 stimulation increases Na clearance, and salmeterol inhalation reduces HAPE incidence in HAPE-susceptible subjects by 50%.

Finally, Peter Bärtsch (Heidelberg, Germany) discussed the treatment and prevention of HAPE. In HAPE-susceptible subjects, HAPE can be largely prevented by a slow ascent and with drugs that lower pulmonary artery (PA) pressure, nifedipine being the most widely used drug. Dexamethasone should be held in reserve, but has also been shown to lower PA pressure and reduced HAPE incidence. Treatment was by descent and the same PA vasodilator drugs. If available, oxygen is beneficial, and the hyperbaric bag can be useful in the short term.

On Saturday we had two sessions. In the first, on how to prepare for altitude, Bärtsch reviewed the attempts to predict susceptibility to AMS or HAPE. Neither the hypoxic ventilatory response nor the SAO_2 response to breathing a hypoxic mixture has been found to predict susceptibility to AMS. Susceptibility to HAPE may possibly be predicted by measuring the PA pressure response to hypoxia by ultrasound. However, in an unselected population the numbers needing to be screened to pick up one susceptible subject would probably be too high to justify the test. At present, history is undoubtedly the best means of identifying susceptible subjects for both AMS and HAPE.

Christoph Dehert (Heidelberg, Germany) gave a talk on training and artificial hypoxia. There is increasing interest in using a widening range of devices to produce low-oxygen gas to provide artificial hypoxia. This allows a range of intermittent hypoxia programs, either to sleep in hypoxia or have sessions during the day with or without exercise. The object is to induce some altitude acclimatization before going to the mountains. Dehert reviewed a number of studies of this form of preacclimatization. For instance, some degree of respiratory acclimatization was achieved with 1 h/day for 10 days at an equivalent altitude of 4000 m. In his own study, he gave hypoxia at night for 8 h for 14 nights before going on a trek to 4500 m; a control group had normoxia. There was less AMS in the test group, although there was no difference in sleep

quality. In another study, hypoxia was used with exercise daily for 4 weeks before ascent to the Capanna. The test group had lower AMS scores, but the difference was not significant. Intermittent hypoxia does not increase red cell mass.

Next Susi Kriemler (Basel, Switzerland) discussed children at altitude. Infants may be at higher risk of sudden infant death syndrome (SIDS), though the evidence is meager. It has been shown that apneic spells may be pronounced and last up to 4 min! In preverbal children, the "fussiness" score is useful in scoring AMS. In school-age children and teenagers, the evidence is that their susceptibility to AMS is similar to that for adults. Children, because they have more muscularized pulmonary arteries, have greater pulmonary pressor response than adults. One might expect, therefore, that they are more at risk of HAPE. Children resident at high altitude are at risk of re-entry HAPE, but otherwise the evidence is that the risk of HAPE is about the same as for adults.

Finally in this session, Bengt Kayser (Geneva, Switzerland) considered whether we need drugs to better perform at high altitude. His short answer was yes, certainly for the treatment and prevention of AMS in its various forms. He then considered the use of drugs to enhance performance and the whole area of doping and its prevention.

The final session of the conference was on patients at altitude. Giorgio Mazzuero (Veruno, Italy) considered cardiac patients, drawing on literature and experience at the Capanna. There is no evidence that altitude is a risk factor for coronary occlusion. Electrocardiogram (ECG) abnormalities at altitude are common, but long-term follow-up showed no correlation with cardiac problems. Two subjects developed coronary artery disease during follow-up, but had had normal ECGs initially. Even patients with heart failure showed no change in ejection fraction at an altitude of 2874 m. Mazzuero found good correlation between sea-level and altitude performance in such patients.

Next Delfino Legnani (Milan, Italy) discussed the lung patient at altitude. With Annalisa Cogo, he studied asthma patients at altitude and, perhaps surprisingly, found that they usually did well at altitude. Their bronchial responsiveness is reduced, perhaps because of the absence of their usual allergens. They will also be producing more endogenous steroids. Chronic obstructive pulmonary disease patients, on the other hand, will have difficulty at altitude unless their condition is very mild. Patients with pulmonary hypertension should not go to altitude.

Finally, Andrea Ermolao (Padua, Italy) talked about the diabetic patient at altitude. Patients with type II diabetes are unlikely to run into trouble at altitude. In type I diabetic patients, experience on expeditions to Kilimanjaro, Cho Oyu, and Aconcagua showed that a number of problems could arise. Insulin requirements were reduced; there were frequent hypoglycemic attacks, and glucose levels tended to fluctuate considerably. Practical difficulties with glucose monitoring, storing of insulin, and the performance of glucose meters all have to be overcome by diabetic patients wishing to undertake such altitude trips. However, it was found that diabetics acclimatize at the same rate as nondiabetics and have no more AMS.

On Saturday afternoon, most delegates enjoyed an excursion up the Val Sesia and a walk to some chalets, from which we had a fine view of the southeast face of Monte Rosa. When the clouds cleared, we could just make out the Capanna on the summit of the Punta Gnifetti.

ISMM and Social Events

Earlier on Thursday, after a full day of conferencing, the ISMM executive met. After dealing with business items, outgoing president Jim Milledge handed over the office to the incoming president, Marco Maggiorini. When representing the ISMM in Kyrgyzstan I had been given a "kalpak," the traditional hat of that high altitude country. I passed this to Marco as a sign of the presidency (see photo).

Following our meeting, we enjoyed a splendid conference dinner at one of Varallo's grandest hotels. Altogether, a very good conference was enjoyed by its participants, and Marco, Annalisa, and their team are to be congratulated for putting on such a well-organized and wide-ranging event.

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