The Newsletter of the International Society for Mountain Medicine

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Correspondence and Submissions for Publication in the Newsletter to:

Dr Andrew J POLLARD, Editor of the ISMM Newsletter,
BC Research Institute for Children's & Women's Health, Room 375
950, West 28th Ave, Vancouver, BC, V5Z 4H4, Canada
FAX: ++ 1 (604) 875 2226 Email: ajpollard@compuserve.com

Visit The ISMM Website at:

Http://www.medicine.mc.duke.edu/ismm/

International Society for Mountain Medicine

The International Society for Mountain Medicine, founded in 1985, has the following goals: to bring together physicians, scientists and allied professionals interested in mountain medicine; to encourage research on all aspects of mountains, mountain peoples and mountaineers; to organize and co-organize international scientific meetings and publish a newsletter to spread scientific and practical information about mountain medicine around the world.

FROM THE EDITOR

A little more than three years ago I took on the task of editing the ISMM Newsletter from Bengt Kayser and Rob Roach with some feelings of trepidation, for this was their baby, for which I was to take on parental responsibility. I was eager to ensure that the Newsletter maintained the style and energy that the previous editors had used and yet add something of my own. During the past 3 years, I hope that the increase in size of the Newsletter and the inclusion of some new features such as the case discussions and the regular presidential address have justified my position of Editor of our *Newsletter*. Now I find personal circumstances such that I no longer have time to indulge my 'hobby' as ISMM's Newsletter Editor and I will be stepping down from this position with the present edition, so that I might concentrate more fully on my career in paediatric infectious disease and provide more attention to my growing family.

During the past 3 years the ISMM has been led by Peter Bärtsch, who has supported the Newsletter throughout and worked hard to set up the ISMM's scientific prize and increase the membership of the Society.

The editorial board of the Newsletter has been of immense help during my period as Editor, providing referees reports of some articles and writing many of the reviews that we have included in these pages and contributing to the case discussions.

My co-editor David Murdoch has been an invaluable part of the editorial team, providing incisive reviews of each edition before it goes to press and keeping the reference list current. I would like to thank him for his help with both the Newsletter and the website.

Jean-Paul Richalet continues to be responsible for the thankless task of printing and mailing of the ISMM Newsletter from Paris and I would like to take this opportunity to express my gratitude to him for this service to our Society. Bruno Durrer has provided an enormous service to the Society with responsibility for the mailing list and, of course, the money.

I took on the role of Editor with the intention of making the Newsletter an attractive glossy colour production, the appearance of which would justify the efforts of the authors and the editorial board. Unfortunately we were never sufficiently resourced to achieve this, and I regret that this was never accomplished.

The debate about the future of the Newsletter, and a new Editor, and possible ties for our Society with other organisations around the world is currently ongoing. I will certainly offer the new Editor and the new President any support that I can with the next edition of the Newsletter. By the time most of you receive this October copy of the Newsletter, the Society will be headed by a new President (Peter Hackett) who will have the task of moving the Society forward into the new millenium. Like all of you, I would like to take this opportunity to offer him, and the new editor of the Newsletter, great success on the behalf of our Society.

Andrew J Pollard

Editor 1997-2000

FROM THE PRESIDENT

Times of Transition again

Reading the lines from our editor your regret is probably as big as mine. Although we can understand the reasons for Andy Pollard's resigning very well, it is difficult to cope with because he was very successful in making the newsletter attractive for all of us. Taking advantage of the rapid communication through the internet, Andy has added the new feature of "case discussions" which make the newsletter especially valuable for those working in practical medicine. There is no evidence-based medicine for most practical questions related to high altitude exposure, yet the patient or mountaineer wants an answer. Thus to see how different "experts" approach or try to solve the problems may be very helpful for those exposed to similar situations. The spontaneity of many answers reflects the situation in daily practice and adds life to the newsletter. Andy was also very successful in acquiring review articles on important topics and reports on ongoing work around the world. I would like to express our sincere thanks to Andy for his excellent work.

In the last 3 years Andy and myself tried to enlarge the membership of ISMM. We did this because the contents of the newsletter are invaluable and should be available to all who are interested in mountain medicine. They also deserve to be distributed in a more professional look. Furthermore Mountain Medicine would profit if all who are interested in this field could combine their efforts. All we have achieved so far is a stable number of about 400 members paying their annual fees regularly and an ongoing discussion with

the national societies of mountain medicine and the Wilderness Medical Society (WMS) about possible co-operation. This discussion may hopefully (and soon) lead to the desired changes and make the position of editor of the newsletter very attractive.

At the General Assembly of ISMM held on the occasion of the 4th World Congress of Mountain Medicine and High Altitude Physiology in Arica, Chile, from October 1-6, 2000, it is also the time for me to pass the presidency of ISMM to the President elect, Peter Hackett. I am very confident that he will be joined by another excellent editor and I hope that his team will arrive at the envisaged goals.

Peter Bärtsch

OXIDATIVELY STRESSED OUT AT HIGH-ALTITUDE!

Free radical damage at high-altitude; isolating the source and implications for the pathophysiology of acute mountain sickness

DM Bailey[1], B Davies[1], GW Davison[1] and IS Young[2]
[1]Hypoxia Research Unit, Health and Exercise Sciences Research Laboratory, School of Applied Sciences, University of Glamorgan, Pontypridd, Mid-Glamorgan, South Wales, UK CF37 1DL and [2]Department of Clinical Biochemistry, Queens University, Belfast, Northern Ireland BT12 6BJ.

Introduction

What causes acute mountain sickness (AMS) and how can it be prevented? These questions are consistently asked by even the most up-to-date expedition doctor yet despite almost a century of investigation we are still far from understanding a syndrome that continues to command fear and respect amongst the climbing population. The anorexia, nausea, vomiting, headache, dizziness and insomnia associated with AMS can interfere with a mountaineer's ascent to high-altitude and in more serious cases can develop into the life-threatening condition of high-altitude cerebral oedema (HACE).

The most recent evidence suggests that AMS and HACE share a common pathophysiology characterised by a predominantly vasogenic oedema which incriminates a shift of fluid from intracellular to extracellular compartments due to blood-brain barrier leakage (4). But what affects the integrity of the blood-brain barrier at high-altitude? This paper presents preliminary evidence obtained from three separate studies that systematically addresses the potential contributory role for free radicals in the pathophysiology of altitude-illness.

What are free radicals?

Justice to the definition of the related terms and concepts involved in free radical biochemistry is beyond the scope of the present paper and the reader is directed to an elegant review by Halliwell (6). In short, electrons positioned around the nucleus of an atom are usually found in pairs occupying a defined space referred to as an atomic or molecular orbital. A *free* radical is defined as any species capable of independent existence that contains one or more unpaired electrons and is characterised in chemical terms by a superscript dot as illustrated in Table 1.

Table 1. Types of free radicals

Free radical	Chemical formula
Superoxide	$O_2^{\bullet -}$
Hydroxyl	$OH^{\bullet}$
Peroxyl	$\mathbf{RO_2^{\bullet}}$
Alkoxyl	$\mathbf{RO^{\bullet}}$
Hydroperoxyl	$\mathbf{HO_2^{\bullet}}$
Nitric oxide	$\mathbf{NO^{\bullet}}$

An unavoidable consequence of cellular metabolism using molecular O_2, these highly energised free radicals are capable of abstracting hydrogen from a polyunsaturated fatty acid side-chain in membranes, a process referred to as lipid peroxidation. Propagation of this process sets up a "chain reaction" that ultimately causes membrane destabilisation and cell damage. The degree of oxidative damage is controlled by the body's

sophisticated antioxidant defense system which is armed with a plethora of chemical compounds and enzymes capable of stabilising or terminating the radical species. However, there is accumulating evidence to suggest that these defense mechanisms are to some extent overpowered during ascent to high-altitude; a consequence of the pro-oxidant effects of physical exercise, UV-$_{A/B}$ radiation, ambient temperature shifts, dehydration and anorexia (14).

Whilst the mechanisms of free radical generation during physical exercise are numerous and the subject of continued interest, emerging evidence also defines a contributory role for hypoxia. Associated mechanisms implicate the release of oxygen radicals from erythrocytes (11) and also increased electron "leakage" from the mitochondrial respiratory chain. A build up of reducing equivalents that cannot be transferred to O_2 at cytochrome oxidase has been incriminated in the latter observation; a phenomenon termed "reductive stress" (8).

Why is the brain susceptible to oxidative damage?

The anatomical and metabolic characteristics of the human brain renders this organ particularly susceptible to oxidative stress. Its antioxidant defenses are modest compared with other tissues and neuronal membrane lipids are particularly rich in highly polyunsaturated fatty-acid side-chains that for reasons previously discussed are sensitive to oxidation reactions (2). The high rate of O_2 consumption per unit mass of tissue, dynamic calcium flux across neuronal membranes and autoxidation of neurotransmitters all represent potentially potent sources of free radical generation. Thus it would appear that the blood-brain barrier, so crucial for the maintenance of normal physiological function, is subjected to constant free radical attack!

Indications that damage to the blood-brain barrier at high-altitude is linked to free radicals can be seen in studies demonstrating the relative success of dexamethasone in the prevention and treatment of AMS and HACE (7). The protective action of this potent glucorticoid has not been fully elucidated but it seems to act as a non-enzymatic antioxidant by suppressing lipid peroxidation and preventing the normal increase in permeability of cultured endothelial cell monolayers exposed to hypoxia (9). But before we consider the relative merits of antioxidant supplementation, what evidence is there that free radical generation actually increases at high-altitude and what are the potential sources? Studies 1 and 2 outlined below were designed with precisely these questions in mind.

Study 1: Is there any evidence of free radical damage at high-altitude?

Overview and aims:

A field-based study was designed to investigate changes in free radical "footprints" and to assess subsequent implications for muscle damage and muscle soreness during the 1998 British Mt Kanchenjunga Medical Expedition. A secondary aim was to determine whether these parameters were different in subjects who developed AMS compared to those who remained apparently healthy.

Methodology:

Design: Nineteen experienced male mountaineers aged 38 ± 12 years old were examined at rest and after a standardised cycling test to volitional exhaustion on three separate occassions at sea-level before (SL_1) and after (SL_2) an expedition and within 14-19 h of arrival at Mt Kanchenjunga basecamp (BC) located at 5100m. The trek to BC lasted 20 ± 5 days with subjects engaging in 250 ± 44 min of trekking at 68 ± 5% of their predicted sea-level maximal heart rate. All subjects were instructed to refrain from taking any vitamin/mineral supplements specifically antioxidant therapies, analgesics/anti-inflammatories or prophylactic medication against AMS (eg acetazolamide, spironolactone and dexamethasone) for at least 2 months prior to the start and for the duration of the study.

Blood samples: Overnight fasted venous blood samples were collected at rest and immediately following the exercise test and evidence for lipid peroxidation was assessed by measuring plasma malondialdehyde (MDA) and serum lipid hydroperoxides (LH) according to established methods. Muscle damage assays included the serum activity of total creatine phosphokinase (CPK) determined using a standard diagnostic kit and the serum concentration of myoglobin and cardiac troponin I (cTnI) measured using an automated-chemiluminescence radioimmunoassay. All exercise blood samples were corrected for plasma volume shifts. Specific care was taken to minimise and standardise tourniquet constriction due to the potential increase in oxidative stress introduced by an ischemia-reperfusion manoeuvre. This was achieved by tightening the tourniquet so that its circumference was 8 cm less than the relaxed girth measured at the belly of the biceps brachi.

Quantification of perceived muscle soreness

Resting muscle soreness; pain threshold. The muscle belly and distal region of the vastus lateralis and gastrocnemius were located via palpation and marked with a permanent pen. A pressure algometer (Force Dial™ FDK2, Wagner Instruments, USA), which consisted of a round-ended metal probe with a 10mm diameter rubber tip was randomly applied to each site of both legs with the subject prone. The investigator gradually increased the force up to a maximum of 30 kg. Following ten practice trials on alternative sites, the subject was instructed to verbally indicate when the stimulus became "uncomfortable". The force was subsequently recorded. If no indication of discomfort was reported up to 30 kg, soreness was not considered to be present at that specific site. The pain threshold

was quantified as the summed forces divided by the number of sites with soreness (maximum of 8 sites).

Exercise muscle soreness. Each subject was asked to perceive the intensity of lower limb soreness using a modified Borg CR-10 scale during the last 10s of each 3 min stage of an incremental cycling test to volitional exhaustion. Subjects were familiarised with this procedure prior to the experiment and pointed to a digit or verbal descriptor rating muscle soreness from 0 (no soreness) to 10 (very very sore).

AMS symptoms. Symptoms of AMS were quantified using the Lake Louise Consensus scoring system (3) that was administered between 16:00-18:00h at least three hours after the subjects had eaten and/or performed any physical exercise. The cumulative AMS score was calculated for each day from a maximum of 28 points. Mean baseline AMS scores were calculated over a 7d period during sea-level tests and on a daily basis at BC. Subjects were retrospectively divided into those with AMS (≥3 points at BC).

Results and discussion

Free radical footprints: Figure 1 demonstrates that exposure to high-altitude resulted in a selective increase in serum LH both at rest and after exercise. The increase in LH in the present study is one of the initial major reactants of lipid peroxidation and provides indirect evidence for increased molecular oxidative damage at high altitude.

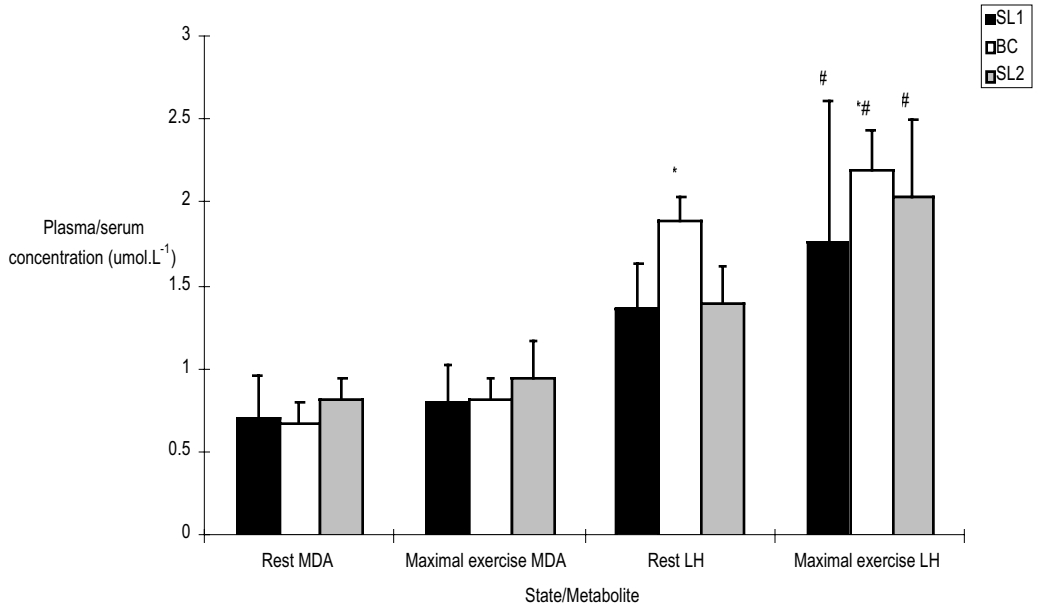

Figure 1. Lipid peroxidation at rest and after maximal exercise at sea-level and high altitude. Values are means ± SD; SL_1, sea-level before ascent to high altitude; BC, basecamp located at 5100m; SL_2, after return to sea-level. A main effect for state (rest *v* exercise) was established for MDA ($P < 0.05$, exercise > rest). A main effect for time (SL_1 *v* BC *v* SL_2), state and time *x* state interaction ($P < 0.05$) was established for LH. BC > SL_1/SL_2 and exercise > rest. * Significantly different from SL_1 and SL_2 value ($P < 0.05$) as a function of state. # Significantly different from rest ($P < 0.05$) as a function of time.

A significant correlation was observed between the cumulative AMS score (days 1 + 2 after arrival at BC) and the exercise LH response ($r = 0.69$, $P < 0.05$) which may implicate exercise-induced oxidative stress as a constitutional risk factor for the pathogenesis of AMS. This may provide an alternative reason to explain why physical exercise has long been recognised as an important risk factor for altitude illness. Another intriguing correlation was observed between the increase in resting LH at BC and the increase in plasma cholecystokinin (CCK), a short-term satiety neuropeptide which was also shown to increase markedly at BC and was associated with a marked caloric deficit (1). Subjects with AMS also presented with a greater increase in CCK at BC relative to their healthy counterparts, perhaps suggestive of a common mechanism. These data may also suggest at least a contributory role for free radicals in the hypophagia and cachexia typically experienced at high-altitude by altering the hypothalamic control of appetite.

Muscle damage and soreness: Figure 2 illustrates the marked elevation of selected serum myofibre proteins suggestive of an increase in sarcolemmal membrane permeability at high altitude. These changes appeared to be more pronounced in those subjects diagnosed with AMS compared to those who remained apparently healthy (Figure 3).

The specificity and stability of cTnI would tend to discount the possibility of myocardial injury which when combined with the marked lower limb soreness

(Figures 4 and 5) would support the contention that the major site of global tissue damage at altitude was confined to skeletal muscle.

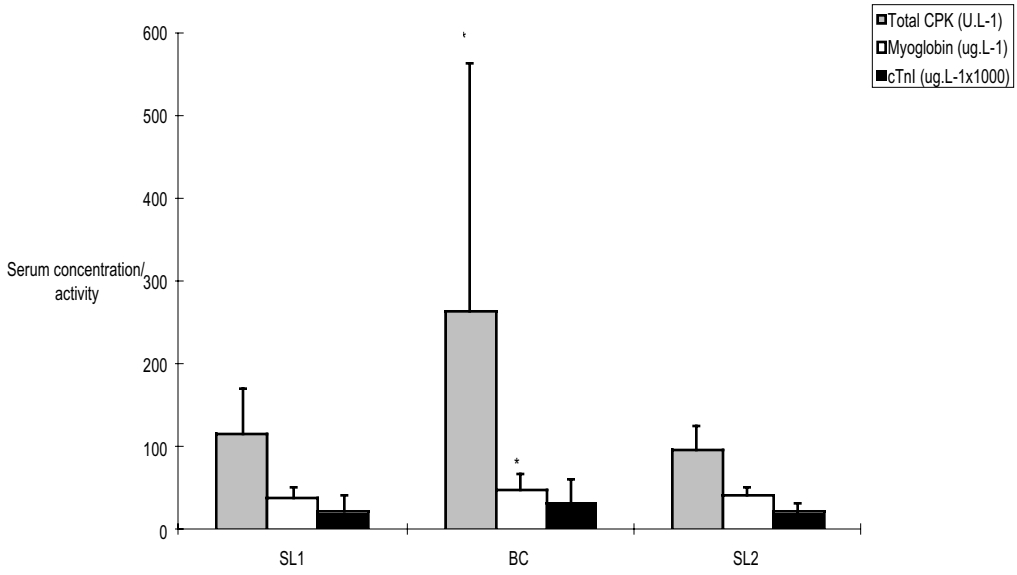

Figure 2. Resting serum concentration/activity of selected myofibre proteins at sea-level and high altitude. CPK, total creatine phosphokinase; cTnI, cardiac troponin I. * Significantly different from SL_1 and SL_2 ($P < 0.05$).

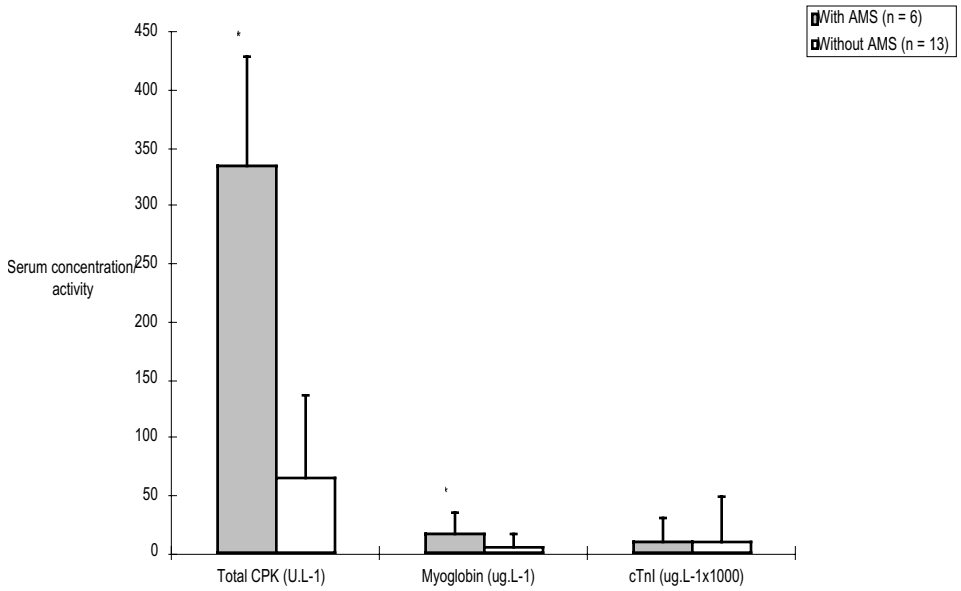

Figure. 3. Changes (BC minus SL_1) in selected myofibre proteins in subjects with and without AMS. AMS was defined as a Lake Louise score of ≥ 3 points on day 2 at BC. * Significantly different from group without AMS ($P < 0.05$).

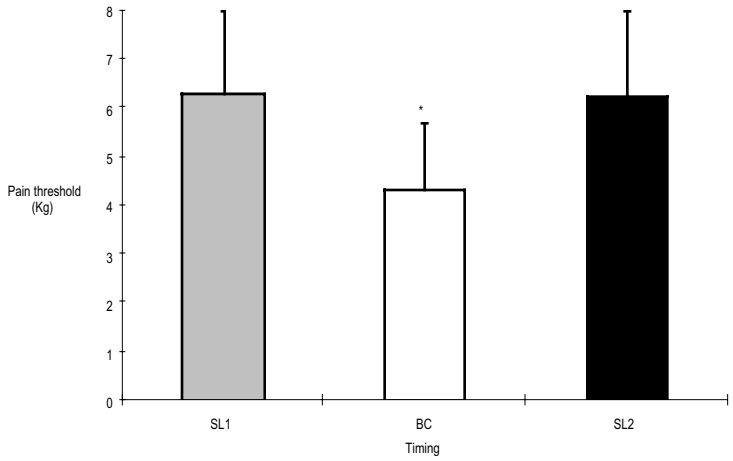

Figure 4. Resting pain threshold at sea-level and high altitude. A decrease in the pain threshold indicates that subjects were more sensitive to the controlled application of an external force. * Significantly different from SL_1 and SL_2 ($P < 0.05$).

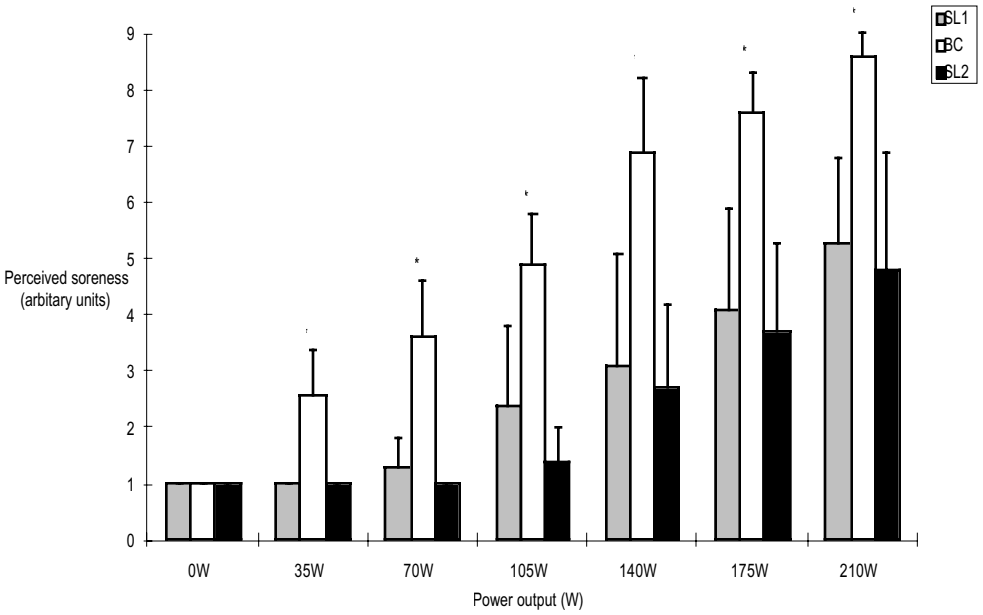

Figure 5. Rating of perceived lower limb muscle soreness during an incremental exercise test at sea-level and high altitude
A main effect for both timing ($P < 0.05$) and power output was established ($P < 0.05$) as well as a timing *x* power output interaction ($P < 0.05$). BC > SL_1/SL_2.

- Significantly different from SL_1/SL_2 ($P < 0.05$) as a function of power output.

A correlation was observed between the cumulative AMS score (day 1 + day 2 at BC) and Δ (BC minus SL_1) mean exercise muscle soreness score ($r = 0.84$, $P < 0.05$). While there was no apparent association between the metabolic markers of oxidative stress and muscle damage, an association was observed between Δ (BC minus SL_1) mean perceived lower limb soreness during exercise and Δ exercise LH ($r = 0.96$, $P < 0.05$); a phenomenon which, like the acute phase response, may implicate PGE_2 which has been shown to sensitize type III/IV pain afferents leading to the sensation of soreness (12).

Whilst we did not demonstrate whether oxidative stress was a direct cause or merely a consequence of myocellular enzyme release initiated by other chemical, hypoxic or mechanical events, considerable evidence suggests that damaged tissue peroxidises more rapidly than healthy tissue which can significantly impede recovery (5). Tissue damage and muscle soreness was more apparent in subjects with AMS despite the fact that these sensations are not featured in the present scoring system employed to quantify AMS symptomatology. Whilst purely speculative, individual susceptibility to AMS may be partially attributable to a deficiency in antioxidant defenses. The chronic tissue damage of AMS may over time contribute to enhanced membrane peroxidation and increase susceptibility to the more malignant condition of HACE.

Closing remarks

The physical demands of an ascent to high-altitude are usually quite exceptional and it is possible that the oxidative stress observed in the present study was merely a consequence of vigorous physical exercise. There appears to be no studies in the literature which have attempted to isolate the potentially pro-oxidant effects of acute hypoxia and physical exercise *in vivo*; this was the focus of the second study.

Study 2: Are acute hypoxia and physical exercise independent sources of oxidative stress?

Overview and aims:

A randomised double-blind placebo-controlled study was designed to independently quantify the effects of acute hypoxia and physical exercise for free radical generation and to address subsequent implications for peripheral vascular function. Some preliminary evidence isolating *the species* of free radical using the technique of spin-trapping and electron paramagnetic resonance (EPR) spectroscopy will also be briefly presented (direct versus indirect methods of assessing free radical damage).

Methodology:

Design: Eighteen University undergraduate students aged 22 ± 3 years old were randomly assigned double-blind to perform a test in normobaric normoxia ($F_IO_2 = 0.21$) and moderate normobaric hypoxia ($F_IO_2 = 0.16$) following two months of abstention from any vitamin supplemements. Each test was separated by a 48 h recovery period and consisted of 30 mins of seated exposure (rest) followed by a standardised incremental cycling test to volitional exhaustion (exercise).

Blood samples: Overnight fasted venous samples were obtained at the end of the rest and exercise periods for the measurement of LH, MDA and the plasma concentration of a variety of lipid soluble antioxidant vitamins (LSA) which included retinol (vitamin A), α-tocopherol (vitamin E) and the carotenoids, lycopene and α/β-carotene. Arterial distensibility was derived from pulse-wave velocity (PWV) which is inversely related to the square root of distensibility. The conduction velocities of arterial pressure waveforms between the right brachial and radial arteries were determined at the end of the passive and active phases using a technique described by Ramsey *et al.* (10).

Results and discussion

Free radical footprints: Figure 6 demonstrates that both acute hypoxia and physical exercise were *independent* sources of free radical-mediated lipid peroxidation. Lipid peroxidation during the hypoxic insult was clearly evident despite a selective mobilisation of α-tocopherol (Figure 7), a chain-breaking antioxidant which inhibits lipid peroxidation by scavenging peroxyl and hydroxyl radicals (Table 1). Whilst not providing complete protection, mobilisation of α-tocopherol from adipose tissue and the liver may serve to limit the degree of oxidative damage inflicted by free radicals.

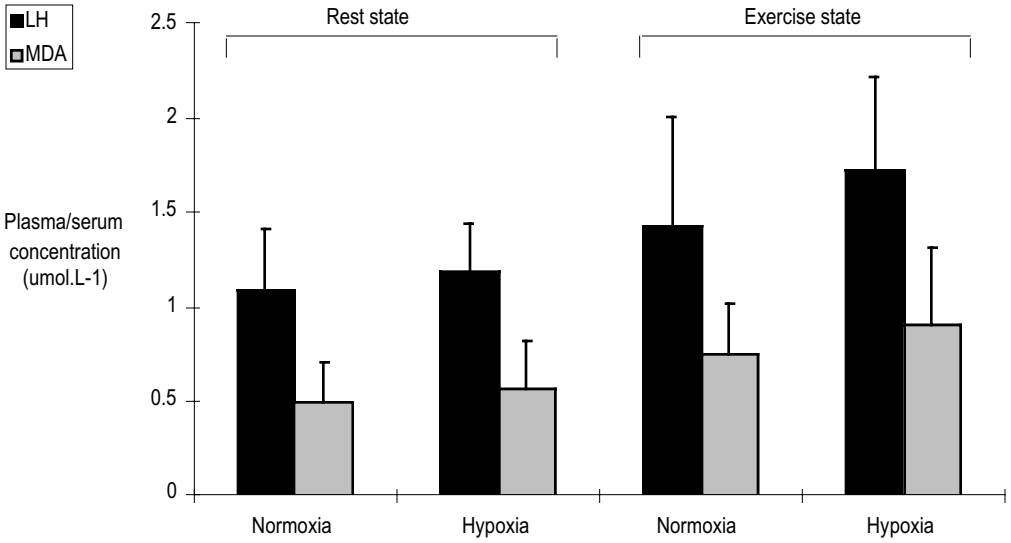

Figure 6. Lipid peroxidation after 30 minutes of rest and immediately after maximal exercise in normobaric normoxic and hypoxic conditions. Main effects for condition (normoxia *v* hypoxia) and state (rest *v* exercise) were established for both dependent variables ($P < 0.05$).

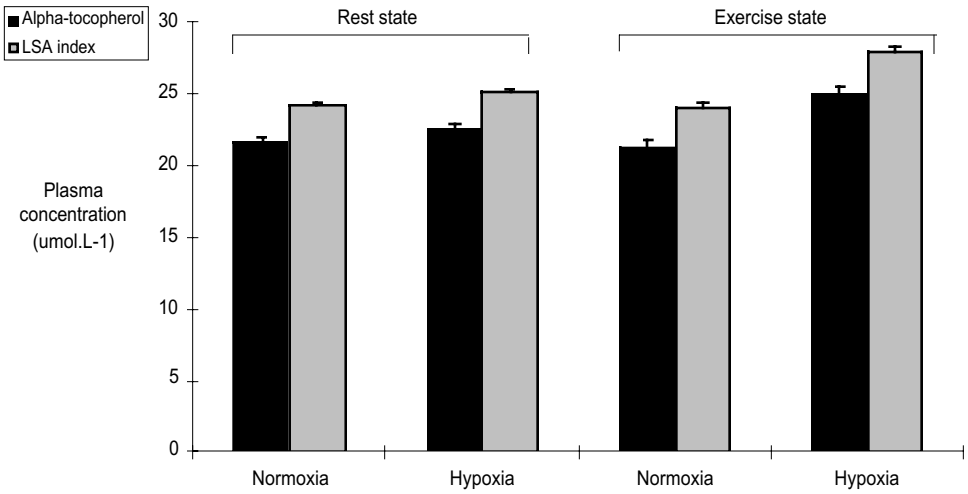

Figure **7.** Changes in α-tocopherol and cumulative lipid soluble antioxidants (LSA index) after 30 minutes of rest and immediately after maximal exercise in normobaric normoxic and hypoxic conditions. A main effect for condition (normoxia *v* hypoxia) was identified for both dependent variables ($P < 0.05$).

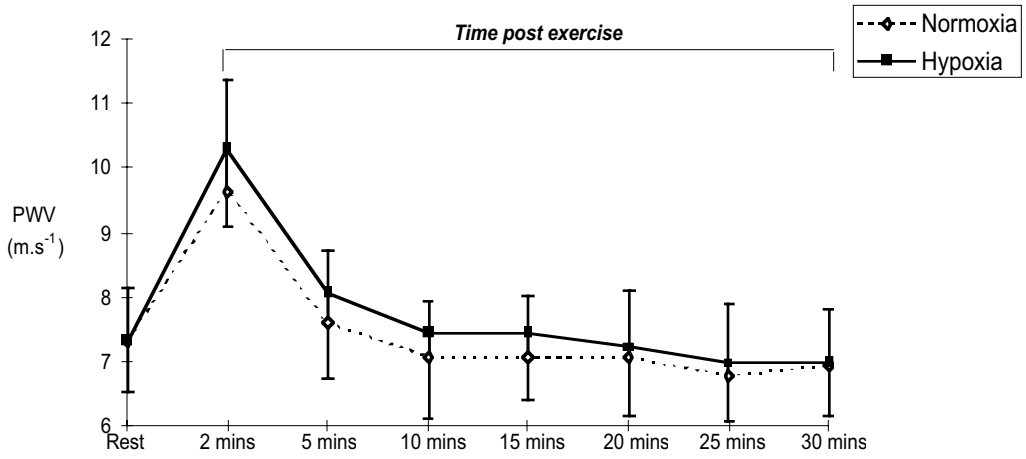

Figure **8.** Conduction velocities of arterial pressure waveforms between the right brachial and radial arteries at rest and following recovery from hypoxic exercise. Main effects for time and condition ($P < 0.05$)

Inverse correlations were observed between the increase in LH/α-tocopherol (hypoxic minus normoxic maximal values) and the decrease (hypoxic minus normoxic maximal values) in arterial oxygen saturation [($Sa\overline{O}_2$), $\Delta LH \propto \Delta Sa\overline{O}_2$, $r = -0.75$, $P < 0.05$ and Δ α-tocopherol $\propto \Delta Sa\overline{O}_2$, $r = -0.71$, $P < 0.05$]. These intriguing findings, whilst clearly not establishing cause and effect may suggest that free radical generation and antioxidant mobilisation are to some extent regulated by changes in tissue $\overline{PO}_2$. It would therefore be of interest to examine if a dose-response relationship exists between ambient $\overline{PO}_2$ and free radical generation *in vivo,* particularly at lower $\overline{PO}_2$'s than that encountered in the present study.

Physical exercise and hypoxia both decreased arterial distensibility as indicated by the pulse wave velocity data (Figure 8). Whether free radicals were implicated in these subtle alterations of peripheral vascular function remains speculative but nonetheless a possibility. The acute downregulation of endothelial function may have been caused by nitric oxide depletion following its reaction with superoxide radicals (Table 1) to form the reactive nitrogen oxide species, peroxynitrite ($ONOO^-$) which in itself is a potent oxidant that possesses "$OH^{\bullet}$-like activity". This mechanism has recently been established as the major cause for enhanced leucocyte-endothelial adhesive interactions during acute hypoxia ($F_I\overline{O}_2$~0.10) in the mesenteric circulation of the rat (15). Whether impaired endothelial function is a cause or consequence of AMS is an important question that is currently the focus of our research.

Direct detection of the free radical species in hypoxia

Direct detection of the free radical species during hypoxic exercise is currently under investigation in our laboratory using the spectroscopic technique of EPR combined with spin trapping. The latter incorporates a specific trap molecule such as α-phenyl-*tert*-butylnitrone (PBN) which on reaction with a free radical forms a stable product which can subsequently be measured. EPR assesses the physical properties of radicals as they spin and measures the strength of the signal emitted; the greater the resonance signal peak, the greater the radical production and close inspection of the morphological characteristics of the EPR spectra (nuclear hyperfine strucure) facilitates the quantification of the *species*. Figure 9 illustrates typical EPR spectra obtained at rest in hypoxia (F_IO_2~0.16) and following 2 hours of hypoxic exercise at a 60% of an individual's normoxic maximal oxygen uptake ($\dot{V}$ O_{2MAX}). Note the increase in peak height; subsequent measurement of the hyperfine coupling constants would suggest that the species detected are secondary oxygen-centred alkoxyl radicals ($RO^{\bullet}$) most likely derived from membrane phospholipids. Direct detection coupled with the *footprinting* method provides convincing evidence that the damage inflicted during hypoxic exercise is in fact free radical-mediated.

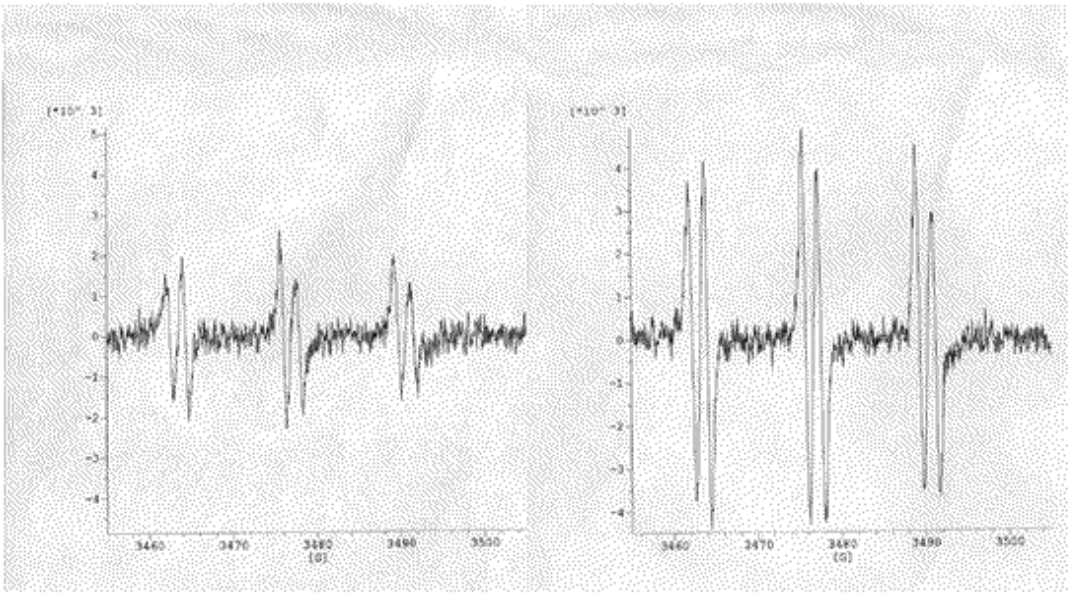

Figure 9. Examples of EPR spectra at rest (left-hand panel) and immediately after 2 hours of cycling exercise (right-hand panel) in normobaric hypoxia (F_IO_2~0.15) at an intensity equivalent to 60% normoxic $\dot{V}$ O_{2MAX}. *n* = 1. Ordinate = free radical concentration in arbitrary units; Abscissa = magnetic field in Gauss.

Closing remarks

Studies 1 and 2 have demonstrated indirect evidence for free radical damage at high-altitude; a consequence in part of the environmental hypoxia and vigorous physical exercise that mountaineers typically indulge in. Antioxidant supplementation at high-altitude would appear the next "logical" step and if found to be of any prophylactic benefit would further add support to the contributions made by free radicals in the pathophysiology of altitude illness. This constitutes the third and final study.

Study 3. Are there any prophylactic benefits of antioxidant supplementation at high-altitude?

Overview and aims:

A randomised double-blind placebo-controlled study was designed to determine the prophylactic benefits of an antioxidant "cocktail" during an ascent to Mt Everest basecamp.

Methodology:

Physiological testing: Eighteen mountaineers (16 males, 2 females) aged 35 ± 10 years participated in a

battery of physiological tests at sea-level and within 15 h of arrival to Mt Everest basecamp (~5180 m). Lake Louise AMS score and resting SaO_2 were measured on a daily basis immediately on waking and prior to retiring. Hunger (how strong is your desire to eat?) and satiety (how full do you feel?) were quantified before and after a standardised meal using a visual analogue scale that ranged from 0 to 100mm. A microvascular fragility test was conducted according to the methods described by Stirrups *et al*. (13). Briefly, a 1cm diameter barrel of a 2ml syringe was applied to two adjacent sites of the buccal mucous membrane of the lower lip and a subatmospheric pressure of 200 mmHg subsequently generated. The petechiae at each respective site were counted and summed.

Supplementation: Subjects were matched for age and physical activity levels and were randomly assigned double-blind to either an antioxidant (n = 9) or placebo group (n = 9). The antioxidant group ingested 4 vegetable-based capsules per day *each* containing 250 mg of L-ascorbic acid, 100 IU of dl-α-tocopherol acetate and 150 mg of α-lipoic acid. The placebo group ingested 4 capsules of identical external appearance that each contained an equal quantity of plant cellulose (Cultech Ltd, UK). Supplementation was enforced for 3 weeks at sea-level prior to departure to Kathmandhu and during an 11 day ascent to Everest basecamp (5180 m). Subjects were instructed to refrain from any prophylactic medication against AMS as described in Study 1.

Results and discussion:

Figures 10 and 11 clearly indicate the physiological protection conferred by antioxidant supplementation at high-altitude. The antioxidant cocktail attenuated the normal increase in AMS at altitude (Figure 10) and resulted in a higher mean resting SaO_2 during the altitude sojourn (antioxidant group = 89 ± 5% *v* placebo group = 85 ± 5%, $P < 0.05$). These responses did not appear to be due to changes in *localised* microvascular fragility as no differences in the petechiae count were observed between the antioxidant and placebo groups. Supplementation appeared to exert a positive effect on appetite control. Subjects in the antioxidant group appeared to be hungrier and less satiated after a standardised meal (data not shown) which ultimately translated into a higher caloric intake relative to the placebo group (Figure 11).

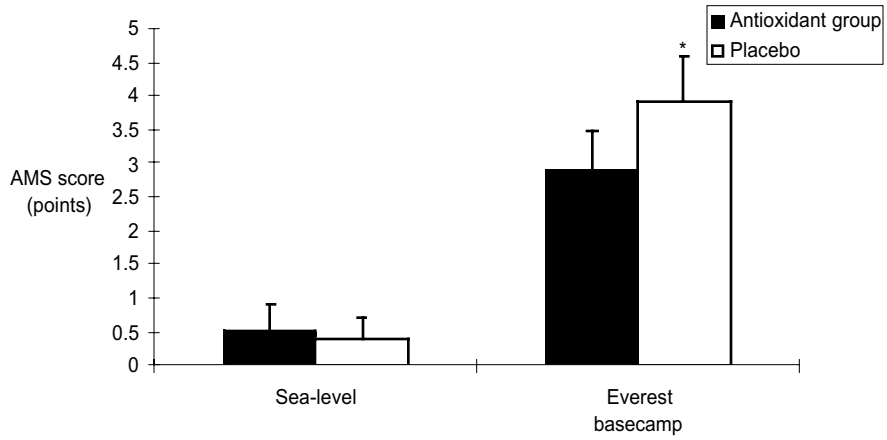

Figure 10. Implications of antioxidant supplementation for acute mountain sickness (AMS) at high-altitude. Sea-level/altitude data represent mean scores obtained over a 7 day and 11 day period respectively. Main effects observed for time (sea-level *v* 5180 m), group (antioxidant *v* placebo) and time *x* group interaction. * Significantly different between groups as a function of time ($P < 0.05$)

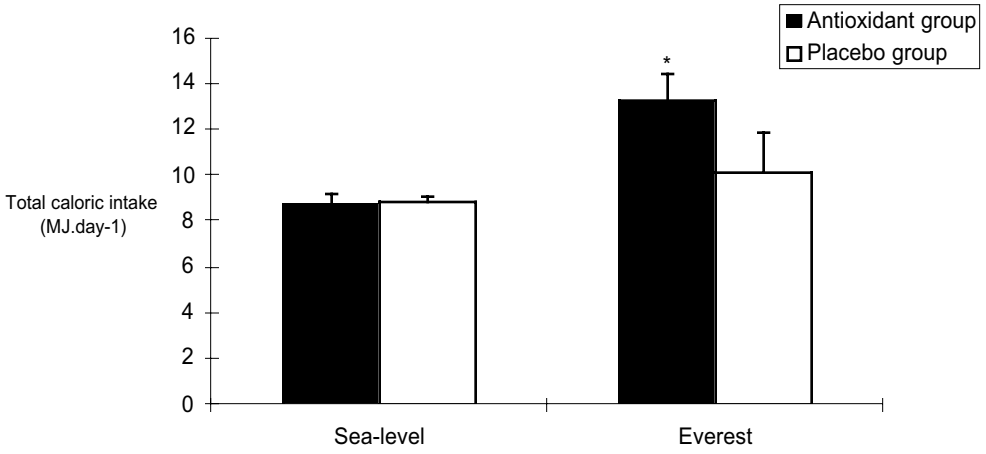

Figure 11. Hyperphagic effects of antioxidant supplementation at altitude. Altitude data obtained during the last 7 days of ascent to Everest basecamp. Main effects observed for time, group and time *x* group interaction. * Significantly different between groups as a function of time ($P < 0.05$).

Conclusions:

These data have systematically defined a potential role for free radicals in the pathophysiology of AMS and other potentially adverse metabolic reactions at high-altitude. The sources of oxidative damage are most likely multifactorial with physical exercise and environmental hypoxia known contributors. The hypophagia and subsequent weight loss during prolonged sojourns appears to be linked to alterations in the hypothalamic release of anorexigenic molecules which may also have a free radical basis. Exogenous antioxidant supplementation would appear to be a safe and effective strategy to confer *some* degree of physiological protection against the ravages of high-altitude.

Acknowledgements:

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HIGH ALTITUDE MEDICINE - ILLUSION AND REALITY

Summary
A short history of mountain medicine reveals the development and growth by mountaineering doctors and amateurs. Carefully controlled scientific experiments were with a few exceptions only performed in the last thirty years. Hopefully, the partly playful character of this new discipline remains alive among the more serious protagonists of this enterprise.

The medical development of the last twenty years is characterized by an irresistible desire for specialisation. The big mother "internal medicine" has fallen apart into disciplines like geriatric medicine, hypertension medicine or cardiology and this discipline once again into echocardiology, rhythmology, interventional cardiology and so on. This centrifugal development is caused by the gigantic development of medical sciences which makes it impossible to overlook the entire mother but also by the fight for chunks of the market which is more successful if one is specialist.

The interdisciplinary hybrid mountain medicine has played around in this scenario for 10 to 15 years.

In earlier days a limited number of physiologists were interested in the consequences of hypoxia. These scientists performed heroic experiments using themselves and their unfortunate technicians and students as guinea pigs and studied the effects of thin air on pulse rate, ventilation, basal metabolic rate and excretions. They themselves and their victims frequently suffered from headache and shortness of breath which were stoically registered and assumed to be a necessary tribute to science. The real doctors, the physicians and surgeons were busy taking care for patients with tuberculosis and syphilis and had - also since their number was still limited - enough business in the low lands preventing them from ascending to cold huts and windy tents to perform medical experiments at high altitude. Therefore, it was enthusiastic amateurs who described serious high altitude illnesses for the first time: Ravenhill's almost forgotten classical paper described in 1913 gave a visionary description of the various forms of high altitude diseases and in fact described acute mountain sickness and high altitude pulmonary edema. He was a mining doctor in Chile. High altitude pulmonary edema was described by a cardiologist with a particular love for mountain climbing, that was Herb Hultgren and independently by the expedition doctor and general practitioner Charlie Houston. Peter Hackett was a doctor of Sherpas and hippies in the early seventies when he described the symptoms and signs of AMS in trekkers in Nepal and produced the first scoring system for this condition. Expedition doctors were surgeons such as Michael Ward, general practitioners as Charlie Houston and eventually also internists. If medical students or medical doctors were not available students of geography like Sepp Jöchler at Herbert Tichy's Cho Oyu expedition, 1954 or students of world trade like Kurt Diemberger on Hermann Buhl's expedition to Broad Peak 1957 were engaged as doctors. The Swiss Everest Lhotse expedition 1956 had to rely on the medical student Edi Leuthold who wanted to do his doctoral thesis on Mount Everest. His notes of measurements of pulse blood pressure, respiratory rate and urine volumes of his friends became victims to the needs of a friend who suffered from severe diarrhoea at the south col and ran out of toilet paper. One expedition member suffered from acute appendicitis and was treated with antibiotics only. This chap subsequently made the first ascent of Lhotse. It was easy going in those days, one went mountain climbing or participated in an expedition, health problems were managed when they ocurred.

This shall be changed now and there has to be some order. National and international societies for mountain medicine are founded even in countries where the highest mountain rises 300 m above sea level. Guidelines, working papers, certificates and so on should educate the high altitude doctor on rational behaviour and courses for mountain medicine which may even bring some fortune to the teachers and organizers are offered to make future high altitude and expedition doctors fit for their enterprises. There are no academic controls yet and the papers of mountain medicine that are published in first class peer review journals are still rare. The practise of mountain medicine reminds us in many ways of the barefoot colleagues somewhere in Africa. However, the claim for academic status has been made. The ideal high altitude doctors should cloned from the excellent and aggressive surgeon, Raimund Margreiter, who, in 1978, on our Everest expedition, even operated an open skull fracture with great success. An internist with a X-ray eye who is able to make the right diagnosis without X-ray, CT-scan and laboratory values an ultrafast mountaineer like Erhard Loretan who reaches his patients even at 8'500 m within a few hours. In addition this man should also be like Dr Karl Maria Herrligkofer who stays in base camp all the time since many patients concentrate there and since larger expeditions these days have a hospital tent in base camp. Nevertheless this multitalented doctor will be mainly busy with blisters and diarrhoea during the approach march since emergency situations at extreme altitude usually occur when a doctor is not around. The expedition doctor will always be more or less a telephone doctor like those colleagues of the Dutch expedition who in 1982 were asked by their friends on the south col whether a dead man could still move. "No, a dead man does not move" the doctor said

from base camp "therefore this man is obviously still alive." Nevertheless his friends left the dying sherpa outside 15 m from their tent. On the other hand there can be good value from telephone medicine as practised by Dr Donner in 1996 on Everest when he recommended a colleague with severe dyspnea at 7'400 m the right exercises for relief of his dyspnoea and the necessary support for survival. Walkie-talkie or telephone medicine thus is still better than nothing.

There is a growing claim that every larger trekking group and every so called expedition has to include an experienced trekking or expedition doctor. However, this is absurd. After all these are entirely healthy people who take some walking exercise in their vacation or climb mountains and therefore should not get sick. The fact that many of them nevertheless get sick is a consequence of self-overestimation, stupidity, lack of moderation and the hectic lifestyle of our time. Furthermore the trekking and expedition doctor is a drug against insurance claims and liability demands. This gap in the medical supply system shall now be closed by education and certificates.

High altitude medical research is a variety of research projects covering the whole spectrum of quality and is thus a general reflection of scientific research. Until now most of the amateur mountain medicine scientists wanted to climb some mountains in some remote part of the world and in addition do something meaningful by measuring haematocrits or such like. Many of these scientists never asked why they should measure something, they measure to see how the number comes out. This lack of a real question characterises also most field studies that are presented in beautiful poster presentations at high altitude medicine meetings which attract more by the beautiful photographs of the mountains surrounding the data. The spectrum of these meetings which once started as a get together of seasoned mountain veterans and young cracks, ranges from the national meetings of a Swiss or Dutch society to "world congresses" of mountain medicine. The same is true of the scientific program which ranges from recommendations for the building of a toilet to the scientific reviews of poorly understood physiological changes, to papers on molecular biology about subcellular aspects of hypoxia. The cosy meetings have developed to large and sometimes very expensive congresses. Nevertheless, it is heartening to experience this mixture of very basic mountain medicine with scientific presentations where even the title is not understandable.

The development of mountain medicine into something more or less a science, at least in some parts, is welcome. This will help us to understand the bad consequences of our strange doing and eventually also to limit them to some extent. However, let's always keep in mind that our hobby is on the edge of modern medicine and just deals with the side effect of our most favourite play.

Oswald Oelz, Switzerland

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MEDICAL TOURISM CAN DO HARM

The following article has been reprinted with permission from a recent issue of the British Medical Journal (BMJ 2000;320:1017 (8 April)). Clearly, this topic not only applies to Nepal. I hope it will provoke some discussion – David Murdoch.

We are expatriate doctors living at 3900 metres in the Mount Everest region of Nepal and running a health care system serving a population of 10 000. The area is remote, mountainous, and roadless, with the villages scattered along high valleys. Over the past 32 years a health system of one hospital and eight health clinics has been established so that most residents are within an hour's walk of a health clinic or hospital.

The area is popular with tourists. Last year 19 000 visitors came into the Sagarmartha National Park where Mount Everest, the hospital, and five of the eight health clinics are located. Inevitably, there are many doctors and other healthcare professionals among them. Although the presence of the hospital is well publicised, many doctors touring the area hold ad hoc clinics along the trail. They often conduct these clinics just a 100 yards from the local village health clinic. At a time when we are developing the skills of the local resident health workers and increasing the confidence that the local people have in them such misdirected good will undermine progress in the existing health system.

It is inappropriate arrogance to assume that anything that a Western doctor has to offer his less developed neighbour is progress. These tourists are often working outside their trained specialty or have little concept of how that specialty applies to Nepal. They frequently don't understand local illness presentation, culture, or language. They often offer inappropriate treatment because they think they "must give something." The consultations are often one off, with little possibility for follow up and the local health providers are left to pick up the pieces with no record of the consultation. If an unregistered Nepali doctor on holiday in the United

Kingdom offered general medical consultations in a shopping centre there would be a public and professional outcry. The problem is extended when applied to nurses, paramedical staff, and medical students.

Furthermore, legally these doctors are on difficult ground. The Nepal Medical Council is striving to develop and maintain a professional body and requires all doctors who practise in Nepal to register with the council. For certain services, such as family planning, practitioners are required to have Nepali training certificates. This is setting a standard of medical professionalism that is required and respected in the West so it should be respected in Nepal.

We are seeing the development of medical tourism - exotic travel to a developing region with a brief opportunity to practise medicine on local residents. This seems to occur on two levels. Firstly, doctors travel independently to areas that seem to have no system of health care and while there perform good acts. We see this regularly with trekking doctors who give residents short courses of antibiotics, which is fine until you consider tuberculosis control and resistance. Recently, a chest physician gave one of our long term psychiatric patients an injection, but we don't know what it was. On the other hand, the acts performed in a life or limb threatening emergency are justified, but there should still be follow up with the nearest local provider.

The second level, which is more alarming, is the development of adventure holidays sold to groups of doctors specifically for the purposes of research or providing health care. The most recent example was an American group of two subspecialists and a selection of house officers and medical students who actively sought out patients along the trail without making any prior contact with the hospital and health posts along the way. They brought an ultrasound machine and a microscope. Can you realistically treat chronic disease after a single consultation? But working with the senior doctors we might have used the equipment and instruction with lasting benefit.

Medical work overseas can be constructive. It takes little effort to find out what health care exists in an area and for doctors to work with or refer to the local system. For more long term work there are numerous agencies in the United Kingdom and in other countries which recruit doctors to work in developing countries.

A fundamental principle of medical training is "first do no harm." If as a doctor you cannot resist the lure of medical tourism and insist on the casual or opportunistic treating of local residents, consider whether you are treating the patient for your own good or for theirs, and whether your actions may actually do more harm than good.

Rachel A Bishop and James A Litch, Codirectors and Physicians, Kunde Hospital, Solukhumbu District, Nepal

OCTOBER CASE DISCUSSION

There are plans to put a very large radiotelescope at Chajnantor in north Chile, altitude 5000 m. There is a reasonably good road down to San Pedro de Atacama, altitude 2440 m, and the trip can be done in an hour or so. If an astronomer develops HAPE or HACE at the telescope site, would it be sufficient to take him down to San Pedro? If not, to what altitude should he be sent? Does anyone think that it is necessary to have an emergency plan to fly people to Antofagasta at sea level? (Case supplied by John West)

Jean-Paul Richalet, France

An emergency plan is mandatory since the hospital facilities in San Pedro de Atacama are not sufficient to treat severe cases or emergency cardiac problems. However, in most cases of HAPE or HACE, a rapid descent to 2440m, helped by inhaled oxygen during the trip, will be sufficient. All will depend on the medical facilities in San Pedro.

Ken Zafren, USA

Every effort should be made to avoid having an astronomer develop HAPE or HACE by using graded ascent and by following the usual rules for altitude illness. The astronomers would do well to sleep lower than the observatory, either physically or by using oxygen enrichment in their sleeping quarters. In the event that an astronomer was to develop HAPE or HACE, oxygen treatment should be begun at once along with nifedipine and/or dexamethasone as indicated. Availability of a portable hyperbaric chamber might also be advisable for cases in which evacuation was delayed due to vehicle problems. For most cases immediate descent as you describe to San Pedro de Atacama would then be sufficient.

There should be an emergency plan to fly people to Antofagasta at sea level, not only for altitude problems, but for other medical emergencies such as suspected myocardial infarctions or other conditions which would require a higher level of care than that available at San Pedro.

Buddha Basnyat, Nepal

From our experience in the Himalays dropping down from 5000m to 2440 m is " plenty " good!! Just a 300m drop may make all the difference. Forget the flight just drive carefully.

Franz Berghold, Austria
Flying down a suspicious HAPE-patient to Antofagasta would be the best, of course. But the patient would have to wait for the aircraft, and this could be a critical delay. If there is always a car available at the observatory the descent would be quicker on the road. However, additional oxygen should be given. A quick evacuation from 5000 to 2440 m should be completely sufficient if it is only HAPE. If there is no immediate and complete recovery at 2440 m it might be not (or not only) HAPE. If there is an airfield in San Pedro, the patient evacuated by car to San Pedro could be taken over there by an emergency-physican brought in by the aircraft. This could be the "emergency plan".

James Milledge, UK
A descent from 5000m to 2440m in one hour by road should be adequate treatment for HAPE or HACE assuming some reasonable ascent profile had been undertaken to get to 5000m i.e. the subject should have been acclimatized to 2440m before going on up to 5000m. It should not be necessary to fly him down to sea level for HAPE or HACE. For other medical or surgical emergencies, of course, it depends upon the facilities at San Pedro.

Robert Schoene, USA
I've been in that area and know the logistics. Based on all that is known about HACE/HAPE and their improvement with descent, I think getting them down to San Pedro (a wonderful place) would be adequate, particularly if there is some oxygen there if perchance they don't perk up quickly, but even then I don't think necessary.

David Hillebrandt, UK
No plane. A jeep with petrol and driver. Nifedipine, Dexamethasone, Oxygen to buy time for descent. Good education to all staff on how to recognise problems, need for descent and a protocol for use of treatment as one descends. A policy that means that anybody descending is not penalised financially or in any other way.

Michael Yaron, USA
Considering the rapid improvement likely to occur with vehicle descent, flying out is probably not needed. it would be wise to stock a hyperbaric chamber to buy time in the event that weather conditions make road (or air travel) impossible.

Stephen Bezruchka, USA
I think Peter Hackett and Brownie Schoene have been to such places, and apparently the keepers at such altitudes are a selected set of people who do well there. For astronomers, it would depend on their acclimatization profile, what altitudes and times they spent en route, as their risk. I would not see problems in descending to San Pedro, as long as there was a road going lower, that did not need to cross a higher pass, for example, or if oxygen etc. were reliably available there.
Given the costs associated with the telescope, it would not be unreasonable to have emergency plan to fly people to Antofagasta at sea level

Simon Gibbs, UK
Descent to 2440 m is likely to be adequate provided medical treatments (oxygen, nifedipine, dexamethasone) are available. The main issue is that somebody at the telescope site can make the correct diagnosis and make a prompt decision to order descent to lower altitude.

John West, USA
In almost every instance rapid descent to 2440 m should be adequate. However, there should be an emergency plan to fly the patient to Antofagasta if necessary.

Peter Bärtsch, Germany
Usually a descent of about 2500m is sufficient for recovery from HAPE in cases with early diagnosis. A plane stationed at San Pedro is not necessary for this type of emergencies. If descent by itself is not sufficient or if one wants to be on the absolutely safe side, one can
start with nifedipine treatment while descending and continue the medication for 2 or 3 days at San Pedro. Furthermore, oxygen bottles should be kept in reserve at this location. With these measures, almost any case of HAPE should be manageable at 2420 m, particularly when attention is paid to early diagnosis and descent. In the unlikely case of an insufficient response with these measures further descent by road is the next option.

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FORTHCOMING MEETING

12th International Hypoxia Symposium, March 10-14, 2001.

Jasper Park Lodge, Jasper, Alberta, Canada. Contact info@hypoxia.net for more information, or visit www.hypoxia.net. Preliminary program will be available online in January 2000.

Wilderness medicine Society Annual Meeting, August 8-12th, 2000

The meeting will be held in Park City, Utah. Information from www.wms.org

ANNOUNCEMENTS

Hypoxia Symposia:

The complete proceedings of the ten Hypoxia Symposia (1981-1997) are available on one CD. Email: studd@fhs.mcmaster.ca Sharron Studd, Division of Continuing education, McMaster University, 1200 Main St West, Hamilton, Ontario L8N 3Z5, Canada.

Bibliography of High Altitude Medicine and Physiology

The Bibliography of High Altitude Medicine and Physiology (BHAMP) is online at a new web site, with a faster search engine. The site is still sponsored by the National Radioastronomy Laboratory. You can find the BHAMP online at: http://annie.cv.nrao.edu/habibqbe.htm. As before, you can search to your heart's content, but you cannot download references. For full functionality you must purchase the BHAMP ($75 US + shipping and handling). It comes in formats compatible with all word processors, but for database functionality you must purchase separately one of the popular bibliography management packages (EndNote, Reference Manager, Procite can all import the BHAMP). BHAMP is provided on one CD in several formats. The CD version now includes bonus libraries with all citations from Index Medicus containing the keysords altitude, hypoxia and mountain. On special request, CDs can be provided for Macintosh computer systems. Orders to: BHAMP, PO Box 343, Montezuma, NM 87731 USA. Enquiries to rroach@hypoxia.net.

Mountain Medicine Website

Mountain Medicine Website: www.mountainmedicine.org
This site was installed 1999 by ICAR-MEDCOM. It is a meeting point for mountaineering physicians and rescuers and offers a wide range of mountain medicine information. The homepage is linked to the most important mountain medicine organisations of ICAR, UIAA and ISMM and many others. So you can choose from a lot of different sources in this field. It will be our aim to collect all scientific and practical data about mountaineering medicine and its medical emergency aspects.
Furthermore you will find also on this site the homepage of ICAR-MEDCOM, the Commission for Mountain Emergency Medicine. Try it!
Hermann Brugger, Bruneck
brugger.med@pass.dnet.it

Austrian Society For Mountain And Altitude Medicine, German Society For Mountain And Expedition Medicine
International Courses For Mountain Medicine

Programme 2001

Special winter course 1
21. Bis 27. April 2001 franz-senn-hütte (stubaier alpen)
Winter course 2
5. Bis 11. Mai 2001 franz-senn-hütte (stubaier alpen)
Basic course 1
9. Bis 15. Juni 2001 adamekhütte (dachsteingebiet)
Basic course 2
23. Bis 29. Juni 2001 adamekhütte (dachsteingebiet)
Special sommer course
7. Bis 13. Juli 2001 franz-senn-hütte (stubaier alpen)
Refresher course
6. - 9. September 2001 oberst klinke hütte (gesäuse)
Please contact: Austrian society for mountain and altitude medicine
Univ.Doz.Dr.Franz Berghold, A-5710 Kaprun 130, Austria
Tel + 43 6547 8227, Fax + 43 6547 7772, Email bergi@eunet.at

INTERNATIONAL SOCIETY FOR MOUNTAIN MEDICINE
APPLICATION FOR MEMBERSHIP and MEMBERSHIP RENEWAL FORM

There are several ways by which you can pay your membership fees: **1.** By credit card: please use the form below or **2.** Send a ***Euro***check (in Swiss Francs) in favour of the ISMM directly to the Membership Secretary **3.** Give your bank the order to transfer the appropriate equivalent amount to our account: nr.CO-257.980.0, United Bank of Switzerland (UBS), CH-1211 Geneva 4, Switzerland. **4.** *Swiss* members can pay by postal check to PC 12-172-9 and mention the ISMM account number CO-257.980.0 at UBS. Renewal of membership is due on the 1st January each year. If fees are not received on time, membership will cease, after a single reminder.

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