Caudwell Xtreme Everest:
understanding hypoxia in the critically ill

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On 23 and 24 May this year five anaesthetists, two GPs and a vascular surgeon stood on the summit of Mount Everest along with two cameramen and 15 Sherpas. This is the story of why they were there and of the Caudwell Xtreme Everest expedition of which they were a part.

Caudwell Extreme Everest (CXE) climbers on the Hillary Step

The 2007 Caudwell Xtreme Everest expedition is the largest ever high altitude research expedition. In April and May, more than 200 volunteers trekked to Everest Base Camp as subjects of an investigational team of more than 60 doctors and scientists. Individuals aged 18–73 voluntarily gave up three weeks of their holidays to climb on foot to 5,300 m in order to provide unique and extraordinary scientific data.

The expedition set out to answer two questions. First, which adaptive changes explain alterations in performance after prolonged exposure to hypoxia? Functional capacity is severely limited at altitude in the face of normal oxygen content. Sea-level aerobic capacity does not predict performance at altitude; indeed, elite high altitude climbers have a remarkably normal capacity for oxygen delivery and consumption (VO_2max). Yet the classical explanation of adaptation to prolonged hypoxia (acclimatisation) is built entirely around factors relating to the flux of oxygen from the atmosphere to the tissues. We sought to understand if alternative mechanisms at a microcirculatory or cellular level had a key role. Second, we sought to understand how differences in the ability of individuals to adapt to hypoxia relate to genetic variations. Most members of the research team have a background in critical care and the reason we asked these questions was to explore how humans adapt to hypoxia during critical illness. Heterogeneity of premorbid state, presenting injury, evolving critical illness, and complex interventions are typical of any group of critically ill patients. This makes isolating and studying the effect of a single variable, such as hypoxia, extraordinarily difficult – never mind the added complexities of obtaining consent or assent for studies in a very vulnerable group of patients. The alternative approach that we chose was to study healthy

individuals undergoing a homogeneous environmental hypoxic challenge. Our ultimate hope: to develop novel therapies for critically ill patients so that individuals who adapt poorly to hypoxia can mirror the responses of those who adapt well.

CXE climbers descending towards the Hillary Step

Origins

The expedition is the flagship project of the Centre for Altitude, Space and Extreme Environment Medicine (CASE) at University College London (**www.case-medicine.ucl.ac.uk**). Set up in 2000, CASE was the brainchild of a small group of young doctors fascinated in equal part by human physiology and adventure in extreme environments. The centre grew in the supportive environment of the successful group of anaesthesia and critical care researchers at University College London (UCL). The idea of an Everest related project was long in gestation. An obvious opportunity to investigate responses to hypoxia from the early days of CASE, the expedition plan grew from discussions in the pub in the late 1990s, into a project framework pulled together in Parisian street cafés by a group attending the 13th World Congress of Anaesthesia in April 2004.

CXE follows in a long tradition of Anglophone high altitude research on and around Everest. In 1960–1961 six doctors and scientists over-wintered at 5,800 m on a glacier only a few miles from Everest Base Camp. The investigators lived in the eponymous Silver Hut. The Silver Hut team, living much lower than the highest altitude reached by the CXE team, was much more pioneering; it was unknown in 1960 if anyone could survive for so long at this altitude. The result was a vast amount of unique data that rewrote the textbooks of high altitude physiology. Twenty years later in 1981 the American Medical Research Expedition to Everest (AMREE) went higher still and conducted detailed studies on a small group of subjects at Everest Base Camp (5,300 m) and in the Western Cwm (6,300 m). Subsequently some of the team ascended to the summit (8,850 m) and made unique measurements including an extraordinary alveolar gas sample. From these data comes the closest estimate until now of the limits of hypoxia tolerance in humans. Several facts support the idea that the top of the world's highest mountain is also very close to the limit of human hypoxia tolerance. When Hillary and Tenzing first climbed Everest in 1953, both used supplemental oxygen. A further 25 years passed before the first climbers reached the summit without using supplemental oxygen. Since then only about 100 of the several thousand climbers who have climbed Everest have done so breathing only air. More recently, the UK based Medex research group have taken larger numbers of subjects to the base-camps of several Himalayan peaks conducting several small parallel studies.

The study

The CXE strategy built on elements of all these expeditions and incorporated two distinct research approaches. First, and most importantly, we wanted to study a large population in order to achieve our goal of exploring difference between individuals and pinpointing the genetic correlates of phenotypic responses. Second, we hoped to make unique measurements high on the mountain in order to define better the limits of human tolerance to hypoxia. The primary hypothesis we tested was that differences in performance in hypoxia (at altitude) are due, in part, to factors unrelated to changes in global oxygen delivery. We therefore set out to identify changes in the microcirculation, in tissue oxygenation and in cellular (mitochondrial) 'metabolic efficiency' that might explain these observed variations in performance and organ function. The study design involved two complementary groups of subjects. The most valuable data derived from a 200-strong group of trekkers. These subjects allowed us to explore variation in response to hypoxia and test specific hypotheses. Alongside this group of subjects, a smaller sample of 24 climbers and investigators, 'The Xtreme Team',

studied themselves. They conducted more invasive and comprehensive studies, higher on the mountain and over a longer period. The aim of this group was to provide the novel 'edge of the envelope' physiological data relating to tolerance of profound hypoxia and to redefine the limits of what is measurable at extreme altitude. Meanwhile, at more alpine heights, the Smiths Medical Young Everest Study took the opportunity to acquire unique data on a small group of children aged six to 13 who were already visiting members of the team at the lower laboratories (up to 3,900 m).

A commonly asked question is whether we could have met our research goals by conducting a hypoxia study in a hypobaric chamber. Irrespective of the arguments in the altitude literature about the validity of results from chamber studies, there were several pragmatic reasons. We judged that it would be very difficult to persuade more than 200 people to give up their holidays to sit in a metal box, be experimental subjects for three weeks, and pay for the privilege! Practically, the limited supply of chamber places and higher cost of running such studies ruled out this option.

Funding and media profile

From the beginning, we recognised that it would not be possible to finance CXE from conventional biomedical research funding sources. The MRC, Wellcome and the major charities were not going to support the infrastructure cost of conducting research in such a difficult environment. Therefore, we set out to obtain the majority of our funding from commercial sources, specifically targeting pharmaceutical and biomedical device companies who could both readily appreciate the scientific value of the research, as well as recognising the PR and marketing advantages of being associated with the charismatic pull of the Everest name. The inevitable accompaniment of this approach was the need for a substantial and sustained media profile, and this was a primary element of our strategy.

We were fortunate early on to have a handful of 'angels' who funded, advised and assisted us with marketing and PR. Together we developed a brochure and staged promotional events. Following a press launch managed by the UCL press office, we were fortunate to be featured on the BBC News at Ten, and national and local radio in the spring of 2005. The result was the commitment of our first major sponsor: BOC Medical (now part of the Linde Group) who provided a substantial grant to underpin the research portfolio. Following our first 'KnO2wledge: lessons learnt from life at the limits' conference, BBC Horizon committed to filming a documentary about the expedition. During the summer of 2006, whilst lecturing at the Cheltenham Science Festival, three of the team were approached by the director of an American science centre. Unbelievable as it seemed to them at the time he suggested that MacGillivray Freeman, makers of the blockbusting Everest film in the IMAX format, were looking for a sequel. Three months later, after a trip to Laguna beach to meet the filmmakers, the deal was sealed. In March 2009 'Return to Everest' will be released with Caudwell Xtreme Everest having a featuring role. The final piece of the jigsaw came in equal part due to serendipity and the efforts of 'Yes Consultancy' our PR agency. John Caudwell, billionaire entrepreneur and ex-owner of the Phones 4u mobile phone retailer, had signed up as a trekker early in 2006. Over the course of several months John became increasingly engaged with the medical goals of the project and in December of 2006 he donated half a million pounds to support the research. As a result, Xtreme Everest became Caudwell Xtreme Everest, our future was finally secure and John and his brother trekked to Everest Base Camp as two of our subjects.

CXE climbers high on the summit ridge with Lhotse behind

Planning and logistics

Although the Everest expedition was the centrepiece of Caudwell Xtreme Everest there were many other components. The programme of research leading up to Everest had included two previous ascents to extreme altitude (Cho Oyu, 8,201 m, sixth highest mountain in the world) in 2005 and 2006. Along with other field studies and extensive hypobaric and environmental chamber validation work, this allowed us to go to Everest with the confidence that our plans were feasible and our kit reliable. The project has been a massive logistical and organisational challenge. From the earliest days, we were very clear that our priorities were safety and science, with the summit a distant third. The team was divided into specific research, logistical and management groups with identified leaders and a clear brief. Partners with outside expertise, including our base-camp manager who organised logistics, and trekking and climbing support company 'Jagged Globe', were invaluable.

The practical obstacles to achieving the research goals were huge. Four substantial physiology laboratories had to be set up in remote, sometimes hostile, environments on the route to Everest Base Camp. Two further substantial laboratories were erected at Camp 2 (6,350 m) and on the South Col (7,950 m). In the end, we shipped more than 26,000 kilograms of equipment to Nepal. More than 400 60-litre plastic barrels, along with more than 100 'tough cases' containing more than a million individually catalogued items, were delivered to the right place at the right time: a logistical tour-de-force. In Nepal we were completely dependent on the Sherpas who became our friends and companions for the three months of the expedition. They helped co-ordinate transport up to base-camp and were completely responsible for taking expedition and research kit high on the mountain. Above base-camp they are extraordinarily strong and are able to carry big loads high on the mountain; without them, none of the high altitude science would have taken place. At the peak of activity there were more than 60 investigators, 40 Sherpas and a logistical team of five, along with up to 112 trekkers in the field at any one time. Even now, five months after our return from Everest, there are still six team members on the payroll managing data and winding down the expedition machine.

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Experimental measurements ranged from simple physiological diary data to invasive real-time monitoring of complex cardiorespiratory variables. Transcranial Doppler measurements, near infrared spectroscopy, intra-vital video microscopy and complex neuropsychological test batteries were commonplace. Pre- and post-expedition testing has included structural and functional MRI. Whilst in laboratories back home, we are undertaking everything from simple biochemical tests to light and electron microscopy, functional mitochondrial assessment and proteomic and genomic analyses. Gastrointestinal tonometry and muscle biopsy studies competed for the position of least popular study amongst the Xtreme Team!

Nigel Hart (left) and Mike Grocott on the summit

The climb

Everest is a mountain that has claimed more than 200 lives. Minimising the risks associated with climbing the mountain was a key element of CXE planning. The Khumbu Ice-Fall and the final summit ridge are the two principal hazards. The Ice-Fall has a long history of tragic deaths due to the instability of this continually moving river of ice. The summit ridge presents a different problem: the large number of

climbers on Everest means that congestion is a significant risk, with consequent delays and prolonged exposure to hypoxia, extreme cold and high winds. Our plan involved minimising exposure to the Ice-Fall by reducing the frequency and duration of trips through it, and deliberately 'holding our nerve' for the summit attempt in order to climb late in the season and reduce the risk of encountering congestion.

We also had the huge advantage of having a climbing support team. Whilst ten of the climbing team had the job of reaching the summit and obtaining the highest measurement of physiological variables, five others were specifically tasked with supporting the research and providing medical and rescue back-up for our team and any other climbers in need. We had anticipated the risk of 'moral hazard' that was likely to result from the presence of a large medical team high on the mountain: the possibility that other teams might be tempted to take greater risks in the knowledge that back-up was available. In the event the team were involved with two rescues above the South Col including a well-reported rescue of a young Nepali woman who had been abandoned by her own team.

Ultimately, the summit was reached by two teams over the nights of the 23 and 24 May. These were the last two nights that Everest was climbed from the South this spring. The balance between holding our nerve and missing the window of opportunity had been a fine one. Conditions on the summit proved too

Early evening view down to the Western Cwm from Camp three

cold and windy for safe arterial blood sampling to take place. However, 450 m lower the team were able to obtain four arterial blood samples and one venous control sample. The Sherpas once again demonstrated their astounding prowess when one of them carried the samples from 8,400 m to 6,300 m in less than two hours. A full analysis successfully completed at Camp 2 yielded, to our knowledge, the lowest measured values of PaO_2 ever recorded in non-hibernating mammals.

> Second, we sought to understand how differences in the ability of individuals to adapt to hypoxia relate to genetic variations.

The future

Back in the UK there are mountains of data to manage and analyse: more than 4,000 diary days amounting to more than a quarter of a million items of data, more than 2,000 exercise tests and 10,000 blood samples. Doing full justice to this resource will keep us busy writing papers for years to come. The aggregated data will allow us to map out the nature and time course of the physiological responses to progressive hypoxia. The genetic data along with information from blood and muscle samples will permit insights into new mechanisms. The goal then is to prove that this approach can lead to innovations in clinical care and ultimately benefit patients.

Since our return the close knit team have gone their separate ways. We have had three weddings and an engagement. Many of the team are back in their regular medical jobs, a handful are heading for medical school, and several are continuing their adventures in science.

Amongst the climbers, some have plans for further 8,000 m peaks whilst others will not go back to extreme altitude for many years, if ever.

Caudwell Xtreme Everest will, and should, be judged on the value of the science and the translational clinical studies that are to come: on the benefits to patient care that the

team hope will be achieved. We are immensely grateful to our trekkers, Sherpas, sponsors and supporters without whom none of this would have happened. For those directly involved there is the great relief of having the whole team home safe, the satisfaction of a job well done with the scientific goals achieved, and the pleasure of knowing that we have made and nurtured friendships that will last a lifetime.

Acknowledgements

The Caudwell Xtreme Everest team wishes to express their heartfelt thanks to the trekkers and Sherpas who made this study possible. Without the generosity and good humour of our trekkers and the strength and companionship of our Sherpas this experiment simply would not have taken place. We owe them a huge amount.

Caudwell Xtreme Everest (CXE) is a research project co-ordinated by the Centre for Altitude, Space and Extreme Environment Medicine, University College London, UK. The aim of CXE is to conduct research into hypoxia and human performance at high altitude in order to improve understanding of hypoxia in critical illness. Membership, roles, and responsibilities of the CXE Research Group can be found at **www.caudwell-xtreme-everest.co.uk/team**.

The research was funded from a variety of sources, none of which is public. The entrepreneur John Caudwell, whose name the expedition carries, donated £500,000 specifically to support the research. BOC Medical, now part of the Linde Group, generously supported the research early on and continues to do so. Eli Lilly Critical Care, The London Clinic (a private hospital), Smiths Medical, Deltex Medical and Rolex have also donated money to support the research and logistics. All monies were given as unrestricted grants. Specific research grants were awarded by the Association of Anaesthetists of Great Britain and Ireland, and the UK Intensive Care Foundation. The CXE volunteers who trekked to Everest Base Camp also kindly donated to support the research.

More information

www.caudwell-xtreme-everest.co.uk
www.case-medicine.co.uk
www.ucl.ac.uk/anaesthesia

Resources

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STOP PRESS!

Congratulations to Dr Jon Raphael and team at the Dudley Group of Hospitals NHS Trust for winning the Pain Medicine in Anaesthesia Award at the prestigious Hospital Doctor of the Year Awards 2007, held at London's Hilton Hotel, Park Lane, on 22 November.

Well done also to the runners up, Dr Jeremy Cashman and team from St George's NHS Trust, London and Dr Barry Newman and team from Poole Hospital NHS Trust.