gene. The HIF-1 is known to bind to hypoxia response elements, which aid in angiogenesis and metastasis.

We know that the tumor stage grade can predict hypoxia. Why is hypoxia important for the oncology community? It is important because it has several implications for imaging and therapy, including radiotherapy and chemotherapy. There have been elegant intratumoral oxygen measurements to correlate this concept of hypoxia and its clinical relevance. One of the newer imaging modalities is the positron emission tomography scan that uses the principle of increased fluorodeoxyglucose by metabolic cancer cells. In hypoxia, this modality can be misleading and warrants use of other 18F- fluoromisonidazole (FIMSA), FAZA, FETA, EF5, and Cu-ATSM that can accurately image even hypoxic tumors. The studies with FIMSA have shown that it can predict survival based on the delineation of the tumor vasculature and hypoxia. Hypoxic cells are resistant to radiotherapy, and several other techniques and the addition of hypoxic sensitizers need to be used concomitantly.

Understanding the molecular biology of the hypoxia-induced substances, we now have engineered molecules such as bevacizumab—a monoclonal antibody to target VEGF. We also have several other monoclonal antibodies and tyrosine kinase inhibitors that target this VEGF pathway and others activated by hypoxia. Thus, an understanding of hypoxia and its consequences is vital to tackle the epidemic of cancer. Although cancer is a genetic disorder involving interplay between dominant oncogenes, tumor suppressor genes, and housekeeping genes, we also understand the profound role hypoxia plays in the subsequent progression and metastasis.

How is this relevant to our community of high altitude hypoxia? We could use the knowledge gained from the oncology community to apply the same principles to fathom high altitude hypoxia. Cross-community collaboration can bring about more meaningful information. As I mentioned earlier, the cancer cell is the most evolved moiety in this universe; we could learn from it its survival tactics and apply them to the larger moiety—human beings—in their quest for adaptation and survival in extremes of conditions.

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Polyerythrocythemia and Adaptation to High Altitude

Chronic mountain sickness (CMS), found at high altitude, is a term that does not explain the etiopathogenesis of the disease in response to the effect of chronic hypoxia. There is no CMS, but rather pulmonary (mainly), cardiac, carotid, kidney, hematological, or genetic disease. All these are associated with an increase in the hematocrit, or what is now known as polyerythrocythemia. Carlos Monge Medrano originally described CMS more than 90 years ago. He was unable to find an explanation for the signs and symptoms and chose to use the term “loss of adaptation.” This term was originally accepted, but today it can be appreciated as lacking significance and should stop being used.

Undoubtedly, CMS is a chronic hypoxic process resulting in an increase of hemoglobin due to pulmonary lesions

(fundamentally) that alter the pulmonary function, thereby reducing the oxyhemoglobin saturation and stimulating the increase of red blood cells. This occurs, essentially, in pulmonary lesions that are sequelae of diverse lung disease giving rise to intrapulmonary shunts or uneven ventilation-perfusion. The term “loss of adaptation” is even semantically inadequate, because in nature, living beings tend to adapt to different environments and circumstances, which could be going to high altitude, temperature changes, solar radiation, ultraviolet radiation, diet changes, and so forth. Consequently, to insist in contemporary medicine on the use of loss of adaptation is not a mistake, but rather, foolishness!

The arterial oxygen content of blood in polyerythrocythemia appears to be increased. However, this apparent increase refers to the maximum oxygen carrying capacity of hemoglobin in blood when fully saturated. That gives rise to two conclusions: 1) that the hemoglobin in patients with polyerythrocythemia tends to be normal and is capable of full saturation when exposed to high oxygen pressures; and 2) in the majority of cases, lung disease that results in intrapulmonary shunts and uneven ventilation-perfusion with reduced alveolar pressure of oxygen or cardiac disease with reduced pulmonary perfusion—both result in the most efficient mechanism to compensate for this ventilatory or cardiac deficiency, namely, polyerythrocythemia.

The misunderstanding of these concepts has led to the wrong interpretation—such as loss of adaptation—of CMS. Throughout history, all living beings go through evolution to adapt to different environmental conditions. Even aging is an evolution that occurs to finish a vital cycle; it never goes in the reverse way. These concepts of CMS and loss of adaptation are unacceptable.

Again, “The organic systems of human beings and all other species tend to adapt to any environmental change and circumstance within an optimal period of time, and never tend towards regression which would inevitably lead to death.”

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Genome-wide analyses of Tibetan Athletes

Tibetans have successfully adapted to the hypoxic environment. Especially the high altitude tolerance and athletic ability of Tibetan mountaineers are impressive and fascinating. In order to reveal the genetic basis of hypoxia adaptation and sport ability in these athletes, we performed various types of analyses, including a genome-wide allelic differentiation scan, principal component analysis, Fst and iHS tests, and association study using whole-genome SNP data of Tibetans living in various regions as well as 36 Tibetan mountaineers who successfully reached the top of Mount Everest. A total of 1204 SNPs were selected from the shared 452,456 SNPs in the comparison between non-athlete Tibetans and Han groups by GWAS ($p < 0.001$), of which 121 significant SNPs from

171,108 SNPs in the comparison between Tibetan mountaineers and Dingri Tibetans were annotated in 37 genes ($p < 0.001$); 124 out of 135,542 SNPs were annotated in 57 genes within the athletic group and Weizang people.

In addition to reported genes related to hypoxia adaptation such as EPAS1, ANGPT1, etc., several candidate genes involved in cellular energy metabolism and myogenesis appear to contribute to mountaineers' physical performance including a member of sodium/calcium exchanger. The frequency of its major alleles increased with the altitude elevation. Furthermore, calcium signaling shows to be the most significant pathway in Tibetan athletes when pathway enrichment analysis was performed in all candidate genes. Fst analysis also indicated a significant overrepresentation of genes involved in calcium related pathway. Our results suggest a potential mechanism in Tibetan athletes to cope with double stress of hypoxia and high-intensity exercise.

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Acute Mountain Sickness—Can it be Predicted?

Introduction.—Acute Mountain Sickness (AMS) is a syndrome complex seen in people reaching altitudes unaccustomed to earlier. AMS is frequently associated when the gain in altitude is rapid with an improper acclimatization schedule. AMS, has a synonym in High Altitude Sickness, as it was thought to occur only at high altitude. AMS and its related problems are of great concern to us because an increasing quantum of people is flocking to the mighty Himalayan ranges;

thus getting exposed to unaccustomed altitudes. The problems of AMS can be a considerable drain on the time, resources and morale of the whole team. It is therefore necessary to evaluate the possibility of a methodology to predict the subset of people prone to develop AMS.

Aim.—To evaluate the role of capillary fragility and serum electrolytes as a predictor in AMS.

Materials and Methods.—The study was done on three groups. Group 1 consisted of a team of 12, trekking and climbing in the Ladakh Himalaya. Group 2 had 15 students and 5 instructors attending the mountaineering course at the Nehru Institute of Mountaineering. Group 3 had 6 climbers and 7 highlanders (Porters) on an expedition to peak Kamet. The capillary fragility was checked as described by Stirrups et al which consists of placing a plastic cup of 1 cm diameter over the lower lip mucosa and applying a negative pressure of 200mm of mercury for a period of 1 minute. This was done with an airtight syringe, calibrated with provision thus produced were counted and recorded.

Results.—The initial physical evaluation of all 3 groups was normal, based on which all were cleared for the expeditions. Analysis of the data shows that all those who were positive for the test of capillary fragility developed AMS at some altitude during the ascent.

Conclusions.—With respect to the development of AMS, the test of capillary fragility that is deranged or down regulated. Sensitive predictive tool. Thus the bottom line in the pathogenesis of AMS seems to be capillary fragility that is deranged or down regulated.

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