Some factors—such as birth weight, maternal anemia, pre-eclampsia, and existence of congenital diseases—have been clearly defined as prognostic for surviving birth. Pregnancy at high altitude is associated with a reduction in birth weight of approximately 100 g per 1000 m of ascent. Low birth weight affects mostly children from mothers without high altitude ancestry, but not native babies, and evidence of endoplasmic reticulum stress and protein synthesis inhibition in the placenta of nonnative women at high altitude have been found. Children from natives may be protected by the augmented uterine artery flow described for this group. Also, there is the possibility that elevated enzymatic antioxidant activity contributes to the Andean protection against altitude-associated small for gestational age infants. Hemoglobin concentrations in mothers at high altitude are well studied. When appropriate adjustments were used, maternal anemia was associated with lower infant Apgar scores at both 1 minute and 5 minutes after birth, as well as complication of labor, lower gestational age at birth, and higher parity. Little is reported about congenital heart diseases, their natural history, especially regarding pulmonary hypertension, and the unique physiology of indigenous high altitude residents in this context.

Our investigation team has been working on this last topic since 2003. We report the results of 4000 echocardiographic studies performed in 3500 patients born at 3600 m in La Paz, Bolivia, not older than 3 months. The patient group was selected by pediatricians and referred because of heart murmur, cyanosis, syndromal phenotype, heart failure, oxygen dependency, and enhanced cardiac size in the Rx. Of these, 20.1% of the children showed no abnormal finding, 18.1% showed pulmonary hypertension (defined as systolic pulmonary pressure of more than 40 mm Hg or more than two thirds from the systemic pressure) in the absence of congenital heart disease, 14.6% showed ventricular septal defect, 20% presented with patent ductus arteriosus, 14.2% atrial septal defect, 5.1% tricuspid atresia, 2.6% complete atrioventricular channel, 2.5% tetralogy of Fallot, 2.5% Shone complex, and 0.4% others.

We assume that the high incidence of pulmonary hypertension in this group, with oxygen dependency and right ventricle hypertrophy for weeks, is due to a prolonged postnatal adaptation period. The most important reason for this phenomenon is the late remodeling of the pulmonary artery branches, which implies the persistence of a thick muscular media. The persistent elevation of the pulmonary pressure and hypoxia are predisposing factors to patency of the ductus arteriosus. Right-sided congenital heart diseases like tricuspid atresia are 3 times more frequent in our patient cohort than at sea level; being left-sided significantly lowers their incidence. Environmental and genetic circumstances may both play a role in the pathogenesis of congenital heart disease at high altitude.

Alexandra Heath, MD, PhD
La Paz, Bolivia

How the Central Nervous System Copes With Hypoxic Challenges

All mammals developed effective strategies to cope with reduced oxygen availability or other metabolic, environmental,

and behavioral challenges. An important prerequisite for survival is the necessity to maintain functional integrity during times of extreme challenges. Mammals accomplish this task through a highly coordinated, systems- and cellular-level reconfiguration involving the partial shutdown of some but not all organs. This reconfiguration is controlled through a similarly complex reconfiguration at the cellular and network level within the central nervous system. During hypoxic exposure, for example, active cellular networks must continue to control vital functions, such as cardiorespiratory coupling. In this lecture, I will discuss the ability of the cardiorespiratory network to assume multiple states that adapt the organism to continuously changing external and internal conditions.

Jan Marino-Ramirez, PhD
Seattle, WA, USA

Cardiorespiratory Coupling in Health and Disease: From Bench and Wilderness to the Bedside

The heart beating and breathing are intricately linked, both functionally as well as anatomically. Within the central nervous system, we find highly overlapping brainstem networks that control these autonomic physiologies. Both of these activities are essential for survival, and the cardiorespiratory coupling has many potential benefits, creating synergies that promote healthy physiology. When this coupling deteriorates, autonomic dysautonomia ensues. In this lecture, I will discuss the neuronal control of this coupling in health and disease and describe how hypoxia can significantly alter these interactions as well as the modulatory control. I will describe how reactive oxygen species act on the neuronal network that provides the biological basis of respiratory sinus arrhythmia. I will also discuss how intermittent hypoxia alters the modulatory state of neuronal networks that ultimately drives these networks into instability.

Jan Marino-Ramirez, PhD
Seattle, WA, USA

Hypoxia and Cancer

Cancer is a heterogeneous group of disorders linked by unregulated growth of abnormal cells characterized by several genetic aberrations. Hypoxia is a phenomenologic concept produced by lack of oxygen. It depends on the demand of the cells and tissues of the organ. Approximately 90% of cancers are solid tumors; the rest are hematologic cancers. Hypoxia seems to play a major role in most solid tumors in their characteristic behaviors.

A cancer cell is the most evolved, rapidly adapting moiety, probably in the universe. The evolutionary abilities of the cancer cell program it to continue to grow and multiply even under adverse conditions. Hypoxia occurs in a tumor even when it is as small as 5 mm. The genetic alterations in the hypoxic cell are several. Equally important are the production and release of cytokines such as vascular endothelial growth factor (VEGF), hypoxia-inducible factor-1 (HIF-1), and mutation in the p53

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.

Govind Babu, MD
Bangalore, India

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.”

Gustavo Zubieta-Castillo Sr, MD
Gustavo Zubieta-Calleja Jr, MD
La Paz, Bolivia

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