Some people do not present AMS on several altitude exposures, however, unexplainably, they may have it occasionally. Several tests have been tried in order to determine who will have AMS, however, none to date are able to achieve with absolute certainty who will get AMS. Some tests include having subjects breathe a hypoxic mixture. Others have created exercise protocols with exposure to hypoxia and some other techniques. However, none have been successful. We have successfully diagnosed and treated patients with AMS of different intensity, over many years of work at high altitude, some having undiscovered pathologies that became evident on exposure to high altitude. For example, interauricular communications, nephropathies, leading to essential hypertension, cardiac arrhythmias, presence of a kidney stone that did not block the urine pathway completely, abnormal arteries in the kidney, sequelae of pulmonary disease with localized fibrosis, relative anemia due to poor bone marrow response, falciform anemia, and many others. However, those that apparently have no evident disease can present with severe cases of dehydration, particularly while doing exercise at high altitude. This of course, can be quite debilitating and if pushed beyond rationale can lead to severe complications. Performing a very precise diagnosis is difficult and there is still much to study in order to understand hypoxia thoroughly. One of the explanations for the occasional presence of AMS could be the presence of subclinical viral infections. We live with viruses, and when the virus is not so aggressive and not present in sufficient quantities, the organism has an internal struggle that uses up the energy. If the person ascends a mountain in this condition, his reserve to face hypoxic stress is limited and hence complications may appear. Likewise, if the person prior to the ascent had an different type of food, with unusual spices, or with unusual bacteria, then there is an inflammation of the bowels and the endothelial cells of the gastrointestinal tract, particularly at the colon level, may not be able to absorb water as efficiently as they would under normal circumstances. This could lead to a more severe case of dehydration and hence AMS. There are probably many other factors which include stress from other psychological difficulties, or even exposure to toxics that are inhaled and produce inflammation in the respiratory tract. Furthermore, those training at high altitude can overdo the exercise efforts, with great willpower, leading to very increased pulmonary artery pressure and hence a dilated right heart. This overcharged effort of the muscle cells in the right heart can give rise to inflammation and microlesions that render the heart mildly insufficient in its capacity for pumping blood. On going higher in a sports competition, the optimal heart function is diminished and hence AMS can appear. This is due to the fact that the Adaptation to High Altitude Formula has not been respected in relation to time, where an adequate and timely increase of red blood cells is essential thereby generating subacute high altitude heart disease.

Low Altitude Peripheral Edema (LAPE): The Opposite of HAPE or HACE

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Millions of permanent high-altitude residents, born at high altitude, living normal lives, practicing sports, sleeping well, reproducing, and enjoying entertainment, occasionally descend to sea level, for work or leisure. This is a change where the organism perfectly adapted to chronic hypoxia is suddenly exposed to a hyperoxic environment and needs to adapt to the new circumstance. Although no alarming symptoms and signs such as those that can be seen in acute mountain sickness exist like headaches, nausea, or vomiting, there are signs that show evident changes in the body. One of the most striking is edema of lower limbs that can become more pronounced at 2 weeks of stay. Although there may be an initial edema due to long airplane travel times, this usually goes away within one or two days. However, after around 2 weeks, a positive Godet sign develops in both legs that can be quite impressive. The Godet sign, found by pressing during a few seconds on the skin in front of the tibia, displaces excessive fluid found in the interstitial subcutaneous spaces and gives rise to the formation of an evident concave impression. This sign is usually found in patients suffering from cardiac insufficiency, renal insufficiency, anasarca with low blood protein levels, or inflammation. If a sea level physician would evaluate one of the high-altitude residents, at that moment, he would surely think of cardiac insufficiency, and may even start treatment with diuretics or digitalis. Possible mechanisms involve an increase of sialic acid, found above or borderline of the normal maximum limits found during tests, in 4 subjects. Urine tests also showed an acid pH = 6.0, in spite of vegetarian diets, on a recent trip to India. Upon ascent to high altitude, there is central edema and that is why acute mountain sickness, high altitude pulmonary edema and high altitude cerebral

edema occur. Conversely, on descending to sea level, peripheral edema occurs. Going higher, oxygen needs to be transported preferably to the life-sustaining organs: brain, heart, and lungs, whereas going lower there is "excessive" amounts of oxygen and peripheral edema occurs possibly as a defense mechanism to reduce oxygen transport to the life sustaining organs, as it is sensed toxic. The hematologic adaptation with a decrease of the hematocrit to sea level values, is linear and takes around 20 days, going from 3500 m. Hence, once the hematocrit is at the optimal values for sea level, the peripheral edema decreases and is not as evident. Consequently, the Altitude Adaptation Formula stands valid even going down and hence it is best to include the altitude change in the denominator:

$$\text{Adaptation to altitude} = \text{time/altitude } \Delta$$

Rebuilding of Carbohydrate and Lipid Metabolism Under Hypoxia: Regularities and Therapeutic Possibilities

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Previously, we have found that the effects of chronic (staying in midlands) or moderate periodic hypoxia as well as hypoxic preconditioning is accompanied by beneficial rebuilding in lipid and carbohydrate metabolism in human and animals: a reduction of total cholesterol and its fractions in blood plasma, a hypoglycemic reaction or normalization of elevated blood glucose, and a decrease of impaired glucose tolerance. This metabolic rebuilding has a phase character during the adaptation to hypoxia and following deadaptation. Changes in metabolism during hypoxia occur in a consecutive manner and mediate by induction and repression of target genes following activation of hypoxia responsible signal ways and transcription factors. In particular, we showed the alternate transactivation of HIF-1 α and -3 α subunits, and the restructuring of glucose transport by consecutive induction of GLUT-4 and -1 in rat myocardium and lungs. Mitochondrial respiration is consequentially shifted from down - to up-regulation, and from carbohydrate to mainly lipid substrate using. In human, we found attenuation of transcriptional regulator of cholesterol synthesis SREBP-1, leptin and insulin-like growth factor IGF-1 levels in blood plasma under prolonged hypoxic conditions, as well as positive correlation with HIF-dependent protein IGF-1 and HDL-cholesterol level. In middle-aged people with metabolic disorders (metabolic syndrome, diabetes mellitus, dyslipidemia), a favorable influence of staying in midlands, moderate acute or periodic hypoxia was found, but metabolic pathology was associated with altered patterns of regulatory protein expression. The data suggest the close relationship between carbohydrate and lipid metabolism under hypoxia, and evidence the possibility of hypoxic correction of metabolic disorders as diabetes, dyslipidemia and metabolic syndrome based on phase processes of metabolic rebuilding.

Modification and Further Applications of the Adaptation to High Altitude Formula

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Adaptation to high altitude is fundamental for life to go on. It is a time and altitude dependent phenomena, because the organism needs the adequate time to build the defense mechanisms to face environmental changes. Quoting the late Gustavo Zubieta-Castillo: "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."

$$\text{Adaptation to altitude} = \text{time/altitude } \Delta$$

It is important to note that altitude changes require adaptation going both ways: going up in altitude or for high altitude residents, going down. This formula was originally developed using the changes in altitude going higher, because it was thought worldwide that the normal physiology of the body was developed at sea level, only. However, high altitude residents are perfectly adapted to life in their own environment. Hence it has been found convenient to include in the formula, in the denominator "altitude Δ " i.e. altitude change, instead of only the term