Background.—Cerium dioxide nanoparticles (CeO₂ NP) have antioxidant properties and also can alter membrane potential in mitochondria influencing cell respiration. In this study we check the idea that CeO₂ NP adsorbed on the silicon base has counter inflammatory, antioxidant and metabolic effects and can be possibly applied in pneumonia treatment.

Methods.—Thirty-six Wistar male rats, 5 months old, 250-290 g were divided in five groups: 1) intact animals; 2) i/p saline injection; 3) CeO₂ NP treatment; 4) experimental pneumonia (i/p LPS injection, 1 mg/kg); 5) experimental pneumonia treated by CeO₂ NP (2.5 mg/kg). Pulmonary ventilation and gas exchange were measured four times: before and 1, 3 and 24 h after LPS injection. The mRNA of TNF- α , IL-6, and CXCL3 were determined by RT-PCR. ROS-generation in blood plasma and lung tissue homogenate was measured by means of lucigenin- and luminol-enhanced chemiluminescence.

Results.—Endotoxaemia in the acute phase was associated with essential inhibition of metabolism: gradual decrease of V_E (by 72%) and VO₂ (by 62%) 24 hour after LPS injection; pathological changes in lung morphology; enhanced expression of CXCL3 (by 68%); increase of ROS generation in blood (by 660%) and lungs (in 33%).

LPS-injected rats treated with CeO₂ NP did not demonstrate any V_E and VO₂ reduction 1 hour after LPS-injection and increase of V_E (by 25%) and VO₂ (by 20%) 3 hours after injection; this effect remained 24 hours after injection.

It should be noted that CeO₂ NP treatment of control rats increased V_E by 20% and VO₂ by 45% in comparison with first measurement after each introduction of the substance.

Treatment of LPS-injected rats with CeO₂ NP has led to diminishing in lung morphology pathological deviations; significant decrease of the expression of inflammatory markers: CXCL33 (in 7.1 times, $p < 0.01$), IL-6 (in 3.5 times, $p < 0.05$) and TNF- α (in 2 times, $p = 0.05$); significant reducing of ROS generation in blood (in 2.7 times, $p < 0.05$), and lung tissue homogenate (in 1.3 times $p < 0.05$).

Conclusions.—CeO₂ NP significantly reduces morphological and functional pulmonary damage in course of experimental acute pneumonia. Discussing mechanism of this effect we propose two suggestions. First: CeO₂ NP is powerful antioxidant, which protects lung tissue and, possibly, inhibits synthesis of cytokines. Second: treatment with CeO₂ NP significantly accelerate metabolism and gives additional vigor to cells suffering with pneumonia.

Life in High-Altitude Conditions

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I have always accepted and endorsed both Prof. Dr. Gustavo Zubieta-Castillo (Sr) and Prof. Dr. Gustavo Zubieta-Calleja (Jr) whenever they mentioned that life is possible on top of Mt Everest. I never doubted. I have a lot of supporting evidence which I wish to share with the rest of the world, during this meeting at very high altitude in Chacaltaya (5230 m) where I deliver my talk for the second time. Life does exist at extreme conditions of heat, pressure, temperature, radiation etc. We have functional life at the deepest part of the sea and at very high altitude. Life started at the bottom of the sea and birds fly for long hours at very high altitudes during their migration. People migrated to live and reproduce at high altitudes. The secret of life adaptation is not well understood. Scientists have designed their studies to find out the problems faced during their adaptation. Limited efforts are made to realize how life has sustained for long periods of time at extreme conditions. The most common household pests, cockroaches, have survived severe radiation, heat, and cold and even toxic pesticides, to which they adapt and can therefore not be eliminated. Plants which normally grow at a particular rate under normal conditions, are found growing at a higher rate when their life is threatened, as noted in young mango plants when pruned, they flower and yield fruit earlier. We are aware of the longevity in plants when they are bonsaied. Similar life prolongation is noted in humans and animals under hypoxic conditions. Longevity of life under hypoxic conditions is well established and it seems evident that high altitude residents have a healthy form of life. Lowlanders under hypoxic conditions and highlanders under hyperbaric conditions, as presented by Prof. Dr. Gustavo Zubieta-Calleja, will have initial problems (peripheral edema, somnolence and other changes), which get adjusted. On long stays, with generations living in those environments, there will be a genetic adaptation, which is applicable to all forms of life. Physical and mental performance improves at higher altitudes. Hypoxia makes other dormant parts

of the human brain function, and hence great philosophers and religious giants frequently visited high altitudes. When these environments are altered by any manmade developments, it hampers the process of natural adaptation. Many toxins are now found causing environmental damage at various levels. This is evidenced by the unreasonable usage of medication. Living in harmony with nature seems to be the ultimate solution. The effect seems to be more evident on life at high altitudes. Let us preserve high altitude conditions for better health, for quality longevity. Let the dream of the Parvatha Guru (Mountain Guru), Gustavo Zubieta-Castillo Sr., come true.

Rearrangement of Neuroendocrine Systems in the Mountains

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The aim of this research was to study the functional state of the anterior pituitary, thyroid, adrenal, and reproductive glands and their relationship with chronic exposure to high altitude. Studies were conducted in high altitudes inhabitants of the Tien-Shan (1200 m, 2800 m, 3600 m). Adrenocorticotrophic hormone (ACTH), cortisol, catecholamines, thyroid, and sex hormones were determined by immunosorbent and spectrofluorometric methods. Normal hormone levels for sea level inhabitants were used for comparison.

Increased cortisol levels in mountaineers (M) (2800 m) may reflect a reduction in reserve capacity of the pituitary-adrenocortical system and the formation of their chronic condition or incomplete adaptation, or the continuing adaptation to the environment in a number of successive generations. Reduced activity of the pituitary-adrenocortical system in high altitude residents (HAR) at 3600 m is a consequence of the harsh weather conditions, narrowing the boundaries of the organism's adaptation and facilitating economical and appropriate regulation.

High altitude residents at 2800 m and 3600 m (when compared to the normal hormone levels and data of low mountain residents at 1200 m), presented a predominance of the mediator activity of the hormone sympathetic-adrenal system, showing an increased secretion of norepinephrine and dopamine, and a decreased secretion of epinephrine. Increased levels of norepinephrine are associated with its decreased metabolism and reserves, providing constant catecholamines that create the preconditions for a stable and long-term work of the body, providing an adequate state of physiological function. Feeding habits (prevalence of carbohydrates and fats in food M and HAR) also lead to the activation secretion of norepinephrine, which leads to intensive use of the biological mediator precursor, dopamine, as evidenced by its high level in residents at both altitudes. This change in optimum reserve of catecholamines promotes an accelerated restoration of catecholamine levels.

Prolonged exposure to high altitude hypoxia induces contrasting changes in thyroid hormone levels. The mountaineers (2800 m) are found close to the low values of normal TSH levels, whereas thyroid hormones tend to increase. The increase in T₃ and T₄ levels, while maintaining the basic concentration of TSH or small hyperthyroidism, seem necessary to adapt to the extreme conditions of high mountains. Increased levels of T₄, TSH and norepinephrine, with a decreased secretion of T₃ in HAR (3600 m), reflect an additional reaction on the PTS factor constant exposure to cold in the mountains. Low values of T₃ without changes in TSH and T₄ levels are explained by the influence of cold.

The detected levels of testosterone in male HAR (3600 m) show the adverse effects of environmental factors, and reduced levels of progesterone (89%) indicate a hard endocrine function of women M (2800 m), on the mobilization of the strategic reserve endocrine system. However, the decreased functional activity of the sex glands does not exceed the boundaries of conventional indicators, which are a reflection of the body's resistance.

Conclusion: Features of endocrine systems in high-population of Tien-Shan include reduced activity of the pituitary-adrenocortical system in the organism, and economical operation, which allows for normal life, work and heavy physical activities in the specific conditions of the mountains. The parameters of endocrine status should be assessed only in relation to normal population values.

Why is it Not Possible to Predict, Through Tests at Sea Level, Who Will Develop AMS?

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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