Abstracts

7th Chronic Hypoxia Symposium

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Dedicated to the Late Danish Prof. Poul-Erik Paulev

THE 120-TH ANNIVERSARY OF ACADEMICIAN N.N. SIROTININ

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The generator of scientific ideas N.N.Sirotinin along with his research school, have been a great contribution to the different spheres of physiology – mountain, extreme, ecological, evolutionary, comparative, aerospace, age physiology; in radiation and sports medicine; in allergology, immunology, hypothermia, reanimatology. His achievements were outlined in: P.V.Beloshitsky "Annals of biomedical research at Elbrus region (1929 - 2006)".

Investigations of the hypoxic states was especially important for N.N.Sirotinin. He started his hypoxia investigations in 1929, first in expeditionary conditions, then – at stationary Elbrus Medical–Biological Station (EMBS, established on 1972; Professor P.V.Beloshitsky was EMBS Director from 1972 to 2006). EMBS included buildings for space physiology laboratory, clinical department, unique thermobarocamera, temporary laboratories at different mountain altitudes up to 5621m. EMBS was an International Center for studying mechanisms of hypoxic states development – not only their destructive mechanisms, but also constructive ones with the purpose of improving the health, the organism resistance to extreme factors and different diseases' treatments. Sirotinin had published a book "Life on Heights and Disease of Heights" (1939, in Ukrainian), it had no analogues in the world at that time.

The studies of hypoxic states and their mathematical modelling carried out by N.N.Sirotinin scientific school became the basis for new methods of hypoxytherapy for the first time in world practice; they contributed to transformation of hypoxia from descriptive-experimental science into an exact one. Thanks to these studies of hypoxic states and their mathematical modeling, concepts were developed in regards to "optimal stepwise adaptation to conditions of mountain heights", "changes in reactivity and resistance in phylogenesis and ontogenesis"; "Elbrus". Likewise, classification of the hypoxic states was proposed and genesis of hypoxia during irradiation and hypothermia were invented. Peculiarities of pharmacological substances' influence in hypoxia were determined and as a result of this the necessity of a new science – space (ecological) pharmacology was substantiated on 1964.

Today, due to the number of objective reasons, investigations of hypoxia in my Ukraine have lost their leading positions. Therefore I – Professor P.V.Beloshitsky, direct successor of Sirotinin's investigations, would like to pass the "Crown" of "Capital of Hypoxia" from Kyiv, Ukraine to La Paz, Bolivia to the High Altitude Pulmonary and Pathology Institute of Professors Zubieta (father and son) and now Dr. Natalia Zubieta (grandaughter) who also follow the same scientific traditions.

CHRONIC HYPOXIA AND BIOSPACEFORMING: ADAPTATION AND SURVIVAL BEYOND EARTH

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Humans cannot expect to go to high altitude cities and continue to be sea level residents. Adaptation is a fundamental process in order to secure survival of the species. And it implies change, but with adequate functionality. The same concept applies to space travel. One of the transcendental mechanisms of adaptation to high altitude is the increase of red blood cells. This is the biological response to chronic hypoxia that allows for a most efficient and less energy consuming mechanism of oxygen transport to the tissues. And it should never be considered a negative effect, even within disease. One of the key issues is that Chronic Hypoxia becomes a fundamental tool. It gives humans and other species an advantage of survival, on earth and even beyond earth. There are time frames for an adequate and suitable adaptation. This is explained with the Adaptation to High Altitude Formula. Additionally and actually paradoxically, there is more tolerance to hypoxia, the higher one goes in altitude. On the summit of Mt. Everest at 8842m, humans are 6 fold more tolerant to hypoxia than at sea level. These fundamental observations show us that as we go high in a mountain, we are actually reducing the barometric pressure and we are getting closer to space, where the pressure is 0. And our adaptation is perfect, being the cities of La Paz and El Alto, examples with 2 million people carrying out normal lives. Exposure to acute hypoxia is altitude and time related. The faster one goes, and the higher one goes, the possibility of suffering Acute Mountain Sickness is greater. However, if enough time is given, to carry out a smooth adaptation, and the subject remains at a fixed altitude, the biological systems adapt, in a most efficient way to chronic hypoxia. Even at the summit of Mt. Everest.

Hence why try to remain with the optimal body for earth habitation?. Why use so much oxygen pressure? Why expect to live surrounded by an atmosphere with a barometric pressure similar to that of the earth? Why expect the future habitable planets to be like earth?

Humans have to understand that it is not the planets that have to be terraformed, like Mars. It is us that have to change and adapt to other worlds i.e. BioSpaceforming, and continue life and intelligence in totally different conditions.

BioSpaceForming is the adaptation of all living beings on earth to outer space. Humankind with the highest intelligence, evolving into the future beyond earth.

Bio = life, Space = Universe, Forming = Adaptation

It is our brains that have to travel. not so much our limbs. Those were designed for planet Earth, for gravitational pull. But Earth is just a station, possibly that we inhabited temporarily, and now the future lies ahead. It is the neurons that have to evolve. They have to learn to live with less oxygen. like we do at high altitude. High altitude residents are more prepared for space habitation. They have already taken the first big step: greater tolerance to hypoxia.

MOLECULAR MECHANISM UNDERLYING THE CARDIOPROTECTIVE EFFECTS CONFERRED BY ADAPTATION TO CHRONIC CONTINUOUS AND INTERMITTENT HYPOXIA

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Adaptation to continuous hypoxia (CH) confers protection against lethal myocardial injury caused by acute ischemia/reperfusion (I/R) insult. The salutary effects can be demonstrated both in the open-chest model of myocardial infarction and in freshly isolated ventricular myocytes subjected to simulated I/R. However, a single daily interruption of the hypoxic exposure with a brief normoxic episode can abrogate the CH-induced cardioprotection. Regarding chronic intermittent hypoxia (IH), the duration and frequency of daily hypoxic and normoxic episodes are critical determinants of cardiac ischemic tolerance. While chronic IH consisting of repeated cycles of hypoxia/normoxia lasting several minutes each (hypoxic conditioning) or a single daily hypoxic episode lasting several hours is cardioprotective, chronic exposure to fast (seconds) cycles of severe hypoxia/normoxia simulating obstructive sleep apnea syndrome aggravates heart injury caused by I/R. Although many factors have been shown to play a role in the ischemia-tolerant phenotype of hearts adapted to protective modes of CH or IH, the detailed underlying mechanism remains incompletely understood. We have shown that the induction of cardiac ischemic tolerance requires signaling via moderate levels of reactive oxygen species (ROS) and pro-inflammatory cytokines such as TNFα during adaptation period resulting in increased capacity of myocardial antioxidant systems and activation of cytoprotective pathways involving mitochondrial ATP-sensitive as well as large-conductance calcium-activated potassium channels. These adaptive responses are absent in the non-protective mode of CH associated with brief daily reoxygenation, which leads to excess formation of ROS and oxidative stress during I/R insult.

IMPACT OF ERYTHROPOIETIN IN THE NEURAL CONTROL OF HYPOXIC VENTILATION

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Erythropoietin (Epo), the main regulator of red blood cell production, has several functions in addition to classical erythropoiesis. Epo, its receptor (EpoR) and its endogenous antagonist (soluble EpoR) are present in a broad range of tissues, including the brain. Several elegant research performed during the last decade reveled that Epo has a complete new role: Epo exerts a protective function upon hypoxic and ischemic injury. Our studies have also contributed to this new concept of Epo. We demonstrated that Epo prevents the respiratory depression by activating the brainstem respiratory neurons and the carotid body glomus cells. By using transgenic mouse lines overexpressing Epo in brain only (Tg21), and in brain and plasma (Tg6), we demonstrated that cerebral Epo enhances the ventilatory response to acute and chronic hypoxia by interacting with brainstem respiratory centers. Furthermore, as changes in arterial Po_2 and Pco_2 are as well sensed by peripheral chemoreceptors to adjust lung ventilation to the metabolic demand, in a recent study we tested the hypothesis that Epo have an impact in the modulation of carotid body (CB) chemoreceptors in response to hypoxia and hypercapnia. To this aim, we used isolated and perfused *ex vivo* CB preparations from adult male Sprague Dawley rats. Our results strongly suggest that the plasma Epo concentration determines the CB chemo-response to hypoxic and hypercapnic conditions. All together, these novel findings are relevant to better understand respiratory disorders, including those occurring at high altitude.

ACID IMBALANCE BORDERING BASE IN A PUBLIC HOSPITAL OF MEXICO AT 2238 M.S.N.M.

CASE REPORT
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History of present illness:
Female patient (Weight 58 Kg, height: 1.50 m.), Has a history of marked decay, sensory alterations in time, space and person, polypnea, decreased visual acuity. Without pulmonary rales, with abdominal pain in left hemiabdomen, abundant diarrhea without blood or mucus, frequent vomiting, with abdominal peristalsis, with anuria, without fever. At admission at emergencies he presented CF: 120 per min, AT: 90/60 mmHg, RF: 27 / min, Temp 36.6 °C. With a history of Diabetes Mellitus of 11 years, hypothyroidism without taking levothyroxine for 1 month, hypertension from 1 year, treated with losartan 50 mg / 24 h. The patient was taking the following medications: metformin 850 mg / 8 hours, glibenclamide 5 mg / 12 hours, linagliptin 5 mg / 24, Pioglitazone, lozartan 50mg / 12 h.

Discussion:
The patient entered the hospital with severe decompensation that endangered her life, despite the metabolic variables she was conscious but with important neurological deterioration, without data of structural coma or focalization. With extreme metabolic acidosis that according to NEJM (1), would not be compatible with life by pHa, HCO3 and paCO2. These last two gasometric variables correspond to an extreme compatible with a sample taken at 8,800 meters above sea level.

Treatment:
Sustained treatment with mechanical ventilation, vasopressors, sodium bicarbonate, fluid intake in the emergency department and initial stage in intensive care did not improve the patient's evolution, even prolonged acidosis, until 13 hours from November 30th. The renal support did not favor the development of hemodynamic instability, therefore it has a main indication in these cases. Finally, the replacement of hormones hydrocortisone, insulin and levothyroxine contributed to stabilize the depressed metabolism.

Conclusion
Acidosis not compatible with life reverted with the treatment used. Objectively for this case the therapeutic gasometric parameters according to altitude above sea level, for sea level, Mexico City, La Paz el Alto and Bajo with respect to bicarbonate can be standardized based on clinical response, improvement in systemic perfusion, regardless of the value.

POLY-ERYTHROCYT-HEMIA, A SIGN OF MULTIPLE PATHOLOGIES CONFUSED AS CHRONIC MOUNTAIN SICKNESS:THERE IS NO LOSS OF ADAPTATION. A PRESENTATION BEYOND LIFE

Gustavo Zubieta-Castillo

1926-2015

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Some high altitude residents can present higher hematocrits and hemoglobin than normal residents. This was originally described as Chronic Mountain Sickness (CMS) and was mistakenly referred to as a "loss of Adaptation". In my criteria, during over 63 years medical of practice at 3600m of altitude in the city of La Paz, where thousands of patients were observed, it became evident over time, that there were great mistakes in the interpretation.

First, the denomination Chronic Mountain Sickness implied "one disease" at high altitude, where, in reality, it is multiple pathological entities located in the different organs, with priority in lung and heart disease, but also in kidney, carotid body, central nervous system, in the gonads, and perhaps in the bone marrow and the blood.

Second, the wrong use of the terminology referred to as polycythemia, increased polycythemia, erythrocytosis and excessive erythrocytosis. These terms are not accurate in medical epistemology, where for something to be considered as knowledge, it must be true in nature. I created the precise term: PolyErythrocytHemia (PEH) where: Poly=many, Erythrocyt=Red Blood Cells and Hemia=in blood. This is precisely what the sign of increased red blood cells is, in all these pathological entities at high altitude.

Third, it is always associated to hypoxemia. As far as current knowledge goes, hypoxemia can be due to: hypoventilation, pulmonary shunts, diffusion alterations and uneven ventilation/perfusion. And this is where all investigation and diagnosis should lead, in these pathologies at high altitude.

Fourth, therapy should never be focused on the unphysiological idea of reducing the number of red blood cells to a "normal level". This wrong and primitive concept has led to erroneous strategies such as bleeding, destroying red blood cells with toxic and prohibited drugs such as Phenylhydrazine and even radioactive substances, that only led to death due to complications in the endothelium and multiple organ failure, including liver and kidneys. Additionally, the wrong idea of reducing the ingestion of red meats, and even red vegetables, with the idea that the organism should not have the nutrients that red blood cells require, as though it were a hematological disease, comparable to a blood cancer.

Finally, the term "Loss of Adaptation" seemed totally illogical and we stood within the International Consensus Group on the Definition of Diseases at High Altitude with a dissenting point of view, thereby disagreeing with the wrong use of this term. Living organisms never loose adaptation. This is an antithesis of life: Adaptation of deficient organic function due to diverse diseases must maintain cellular function, in the hypoxic environment at high altitude through PolyErythrocytHemia. I wrote, during my life, on July 22, 2010 "FOREVER: LOSS OF ADAPTATION" DOES NOT EXIST!", which is easily accessed through the web.

"CMS or rather PolyErythrocytHemia is found in residents at high altitude with some abnormal pulmonary function (increased shunt, impaired diffusion, uneven ventilation and/or hypoventilation), sequelae of diseases of diverse etiopathogenesis. These lead to a sustained (and variable) low oxygen saturation and cyanosis, giving rise to pulmonary hypertension and increased polycythemia as compensatory mechanisms of adaptation to the disease under chronic hypoxic conditions. The symptoms and signs are reversible by descent to sea level or by increasing the PIO2."

Once again, next to my ashes, in my mausoleum at the IPPA High Altitude Museum, remembering my scientifically productive 90 years of existence, I affirm forever that: *"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 (loss of adaptation) which would inevitably lead to death"*

THE INCIDENCE OF CEREBRO-VASCULAR ACCIDENTS IN CMS

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At high altitude there is lower barometric pressure and hence lower Partial Inspired Oxygen Tension (PIO2). High altitude residents have higher hematocrit and hemoglobin values, than sea level residents in the Andes. This is a natural adaptation process, being the most energy efficient mechanism of adequate oxygen supply to the tissues in a hypobaric environment.

Some people at high altitude, however, present higher hematocrits above those of the normal residents. This has been described as Chronic Mountain Sickness. The overall fear is that this higher hematocrit with a high viscosity blood, can give rise to thrombus and a series of multiple obstructive circulatory pathologies, being the most feared, the Cerebro-Vascular Accidents (CVA). These are a most serious event that can bring about diverse types of paralysis or even death.

In our Institution at 3500m of altitude, we consider a hematocrit higher than 58%, a value above the normal healthy subjects. The incidence in the city of La Paz, obtained from a hospital laboratory records is 28% for males and 11% in females. According to current beliefs, these patients are at risk of suffering CVAs. We suspected from many years back, based on clinical experience, that these patients don't suffer much CVAs.

Records of all patients diagnosed as CVAs were reviewed during a 3 year period, from Jan 2015 to Nov 2017, at the Hospital Arco Iris located at 3700m of altitude in the city of La Paz. Of 96 people found to have been diagnosed as suffering from CVA, only 10 had a concomitant Poly-Erythrocyt-hemia, (which would be classified as Chronic Mountain Sickness).

Upon careful review of the diagnosis of all these 10 patients, it became evident that 9 suffered likewise Arterial Hypertension. The last one had multiple pathologies including renal insufficiency, electrolyte imbalance, and a history of convulsions.

It becomes clearly evident that although these 10 patients, had an increased hematocrit, one could not attribute the AVC solely to it, but rather to the most common cause: Arterial Hypertension. An event that happens not only at high altitude but also, recurrently, at sea level.

These findings suggest that a high hematocrit is not the cause of CVAs at high altitude, as there are always other pathological entities involved, that seem to be the primordial alteration. The fear of "thick" blood producing CVAs also seems unfounded. More extensive studies, will, most probably, confirm this observation.

COULD HIGH ALTITUDE AFFECT THE PROSTATE HEALTH?

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Many physiological responses to high altitude (HA) exposure have been studied. Different hormones, including sex hormones are involved in process of high altitude adaptation. Testosterone, the main androgen which participates in male reproduction, also is one of the erythropoiesis regulators.
Epidemiological studies showed that HA exposure are associated with higher prevalence of cancer and increase the risk of death by this disease. However, there is only limited evidence available for the effect of this exposure in prostate health, even though it is well-known that this organ is androgen-dependent. Based on the literature, it is assumed that this effect of androgens on prostate illness at sea level could be worse at HA.
In addition, common factors and biomarkers such HIF-1, SENP1, IL-6, CRP, including testosterone, are related in both high altitude diseases and prostate illness.
In conclusion, better understanding and future research of physiological and pathological prostate illness in HA conditions need be considered.

NEURONAL MECHANISMS UNDERLYING CENTRAL AND OBSTRUCTIVE SLEEP APNEA

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Apnea, the cessation of breathing, is a physiological and pathophysiological phenomenon common in the pediatric and adult patient community. Indeed, with the increased prevalence of obesity, sleep apnea has become a problem of epidemic proportions. Among the different forms of apnea, obstructive sleep apnea (OSA) is clinically the most prominent manifestation. OSA is characterized by repetitive airway occlusions that are typically associated with peripheral airway obstructions. Yet, even though peripheral airway obstruction may be initial cause of OSA, the manifestation of the disease involves dynamic interactions between chemo- and mechanosensory reflexes, behavioral state, neuromodulation, and the differential activation of the central respiratory network and its motor outputs. An important driver of the disease is the Chronic exposure to Intermittent Hypoxia (CIH). CIH directly affects the central respiratory network which triggers a vicious cycle: CIH- induced desynchronization among the respiratory neurons leads to hypoglossal apneas that in cause further episodes of intermittent hypoxia. CIH itself will affect the cardiorespiratory coupling leading to autonomic consequences, that become major contributors to morbidity and mortality. Not only OSA, but also central apneas (CA) have multiple, and partly overlapping mechanisms. Thus, we conclude that the mechanisms underlying OSA and CA are neither "exclusively peripheral" nor "exclusively central" in origin.

FUNCTIONAL FOODS FOR INFLAMMATORY DISORDERS SUCH AS METABOLIC SYNDROME AND INFLAMMATORY BOWEL DISEASE

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Functional foods provide health benefits in chronic diseases such as obesity, hypertension, diabetes and inflammatory bowel disease, in addition to nutrition. The metabolic syndrome of central obesity, insulin resistance, elevated blood pressure, impaired glucose tolerance, non-alcoholic fatty liver disease and dyslipidaemia is due to chronic low-grade inflammation. A diet high in fructose and saturated/trans fats induces these cardiovascular, liver and metabolic signs in rats and components of foods can reverse all these symptoms in diet-induced obese, hypertensive and glucose-intolerant rats. In particular, anthocyanins from tropic Australian native fruits such as Davidson's plums, polyphenols from Garcinia fruits such as achacha and mangosteen, and algae lowered blood pressure, prevented inflammatory cell infiltration into the heart, liver and fat pads, improved plasma lipid profiles and decreased plasma inflammatory biomarkers. All these interventions could be produced commercially, sustainably and cost-effectively in many regional areas of Australia and South America with the aim of reducing the incidence of metabolic syndrome and inflammatory bowel disease, and decreasing the risk of costly cardiovascular and metabolic disorders, especially in regional areas. Further, the effectiveness of indigenous fruits and vegetables have rarely been defined

WHAT IS THE CRITICAL BAD PROGNOSIS PCO2 LEVEL AT HIGH ALTITUDES?

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Discussion of population dynamics, its effect on healthcare, analysis of cost and development of cost effective measures of continued care. The concept of prognostication and giving complete information to the patient so they can make adequate decisions towards end of life. Discuss how in COPD patients at sea level chronic PCO2 levels >50 mmhg carries bad prognostic index. Question would be at what level of PCO2 would carry a bad prognosis in high altitudes environments.

PROTECTIVE ROLE OF EPO AGAINST CONSEQUENCES OF INTERMITTENT HYPOXIA IN NEWBORN AND ADULT RODENTS : APNEA OF PREMATURITY VS SLEEP APNEA

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Owing to the immaturity of the brain, apnea of prematurity (AoP) occurs in more than 85% of infants born with less than 34 weeks of gestational age. AoP is associated with severe and repeated episodes of arterial oxygen desaturation (intermittent hypoxia – IH), which in turn increases the respiratory instability and the number of apneas. While AoP and IH are frequent in preterm boys and girls, there is no data addressing whether IH leads to sex-specific respiratory consequences, neither if drugs targeting AoP are more effective in males or females. In this work, we used rat pups for investigating whether IH-mediated increase of apneas is sex-specific. Furthermore, we investigated whether caffeine (treatment of choice of AoP, but ineffective in about half of the cases), erythropoietin (Epo - a neuroprotective factor and potent respiratory stimulant at neonatal ages), and both drugs together (caffeine+Epo) prevent the IH-mediated formation of apneas in a sex-dependent manner. Newborn rats exposed to IH during postnatal days (P) 3-10 were used in this work. During this time, animals were daily gavage with a vehicle, Epo, caffeine, and Epo+caffeine (10-12 pups/group). At P10 the frequency of apneas at rest were measured (by plethysmography), as an index of respiratory dysfunction induced by IH plethysmography. Our results showed that IH induces 40% more apneas in male than female rat pups. Moreover, results in males evidenced that caffeine and Epo significantly prevent the increase of apneas induced by IH, and that the administration of both drugs together do not provides a cumulative beneficial effect. Results in females showed that nor caffeine, Epo, neither both drugs together prevent from the IH-mediated augmentation of apneic events. We concluded that IH in newborn rats leads to sex-specific respiratory consequences. Our data suggest also that caffeine and Epo have similar effects to reduce the IH-induced apneas in male but not in female animals.

PEDIATRIC MEDICAL PRACTICE AT 2800M IN THE UNITED STATES

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The population living at moderate altitude in the US is small but has tripled in Colorado over the last 30 years. These people are considered acclimatized, not adapted like the populations in Nepal, the Andes, and other mountainous countries where people have lived for hundreds of years. The presenter began treating children at 2800m in 2000 after practicing at sea level for 20 years. Children frequently presented with severe hypoxia and cough but were not ill-appearing and had no recent travel. They are told they have pneumonia or asthma and treated with drugs when most do well with oxygen alone. This entity became known at HARPE: high altitude resident pulmonary edema, as reported in two articles published in 2017 and 2018. Other cases of severe rapidly reversible hypoxia are reported after pulmonary contusions and return to altitude and hip surgery with return to altitude. Physicians treating patients at lower altitude who will be ascending should consider the possiblity of HAPE when they reach their home, and not consider acclimatization protective for everyone.

The presenter also noted that twice as many mountain resident children were below the standard CDC or WHO growth charts for height and weight. An initial analysis of over 10,000 data points showed that these little ones recovered after age 2 and were on the standard charts. Currently more data is being organized into an altitude specific growth chart to save parental and professional anxiety leading to unnecessary testing and accusations of malnutrition.

COLONIZING HIGH ALTITUDE HYPOXIC ENVIRONMENTS: STRATEGIES TO DEAL WITH METABOLIC NEEDS

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The aptitude of mammals to colonize high-altitude environments is limited by their ability to tolerate decreased oxygen availability. Previous research in our lab showed that rats and mice display divergent physiological and molecular responses after acute exposure to hypoxia. This response is traditionally linked with the regulation of metabolism, in consequence, we aimed to identify the strategies underlying the metabolic response of rats and mice to acute and chronic exposure to hypoxia.
SD rats and FVB mice were exposed to hypoxia (12% O_2) for different periods of time. The metabolic rate (VO_2 and VCO_2) and minute ventilation (VE) were measured by indirect calorimetry and plethysmography. The hematological response was evaluated by the quantification of hematocrit and hemoglobin concentration. As the brain is highly dependent on oxygen, we assessed the mitochondrial respiration in brain cortex using the high-resolution respirometer O2k (Oroboros Inc.).
In comparison to normoxic controls, mice showed a higher metabolic rate after 7 days of hypoxia. No change in rat's metabolism was observed. In line with the increased V_{O2}, mice showed a continuous augmentation in V_E with a peak at 7 days of exposure. Rats showed a weaker rise in the V_E at 6h with no further increase. In brain, mice showed an increased mitochondrial respiration after 24 hours of hypoxia, while those exposed to 7 and 21 days were similar to the controls. Though in rats only weak changes in the ventilation and no response in brain-mitochondrial respiration were observed, they showed a strong hematological response. The hemoglobin concentration and hematocrit increased in a sustained way starting at 24 hours, reaching a plateau at 21 days of exposure to hypoxia. Hematological adjustments occurred in mice only after 21 days.
Our results suggest that mice privilege an increase of their ventilatory activity to cope with hypoxia resulting in an enhanced metabolic rate and preserved mitochondrial activity in brain cortex. In rats, whereas the ventilatory response is weak, they favour a rapid and sustained hematological response. We propose that the process of acclimatization to hypoxia ultimately relies on the strategy of capture, distribution and use of available oxygen for metabolic use.

ERYTHROPOIETIN: A SPACESHIP SHIELD FOR TRAVELING EVOLUTION?

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Erythropoietin (Epo) is a hypoxia-responsive molecule that acts on erythroid progenitor cells to promote their survival and differentiation to mature erythrocytes. Apart from this canonical role, Epo also promotes adaptive cellular responses to hypoxic environmental challenges and tissue-damaging insults in various non-hematopoietic tissues. In the mammalian brain, Epo and its receptor (EpoR) are expressed by glia and neurons and exert important functions during neural development and in the protective response against diverse types of injuries. Such commitment in the increase of the robustness and tolerance of the nervous system has led to the proposal that, rather than regulation of red blood cell production, Epo's original evolutionary function was providing unspecific and unconditional neural protection. In line, the demonstration that the human recombinant Epo induces neuroprotection and neuroregeneration of brain cells from orthoptera insects (grasshoppers and locust) proved that Epo evolved about 550 million years from an urbilaterian (common to vertebrates and invertebrates) ancestor. However, how Epo is integrated with a highly evolutionary conserved O_2-dependent molecular mechanism is yet unknown. Recent evidence in the literature demonstrates that Epo in the brain (and other tissues) increases mitochondrial energy production, regulates oxidative stress, controls mitochondrial calcium homeostasis, and promotes mitochondrial biogenesis. Because: 1) mitochondria are main O_2 sensitive organelles that play a crucial role in the brain development, maturation, and function, and 2) because these organelles are known for having shaped the fabric of life and its evolution, we propose the hypothesis that the endosymbiosis between mitochondria and eukaryotic cells necessitated "chaperone" molecules to monitor the mitochondrial functions and to correct/repair dysfunctions. Specifically, we propose that Epo's original evolutionary function was to support mitochondrial function during shortage of O_2 availability. The aim of this talk is exploring the scientific bases supporting this hypothesis.

MATHEMATICAL MODELS OF SYSTEM MECHANISMS OF ORGANISM ADAPTATION TO HYPOXIA

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The process of adaptation to hypoxia and the mechanisms that provide it are necessary prerequisites for a high reliability of an organism functioning in various modes of its vital activity.

For a mathematical analysis of the organism's adaptive capacity to hypoxia of various etiologies we used the model of functional respiratory system (FRS). FRS is a controlled dynamic system; it describes the transport and mass transfer of respiratory gases in respiratory tracts, alveolar space, blood, tissue reservoirs and organs (brain, heart, respiratory and skeletal muscles, etc.) The model is represented by ordinary nonlinear differential equations; in it, the regulation is carried out on the basis of compromise resolution of conflict situations that appear between tissues and organs during their fighting for oxygen in conditions of its deficit. It was assumed that the decision about the choice of characteristics' values for compensating influences is made by the decision centre based on the information about the level of functional activity, degree of oxygen deficiency, excessive accumulation of carbon dioxide in all tissue compartments of the organism. This decision was transmitted to executive organs of self-regulation and it increased their functional activity, ensuring the realization of a basic respiratory function.

Analysis of FRS model demonstrated that short-term perturbations of the system which caused hypoxia development could be compensated by the reaction of self-regulation mechanisms that appeared in organism in an evolutionary way — due to intensification of activity of external respiration system, cardiac muscle and vascular smooth muscles. During the medium-term hypoxia influence on organism (weeks) some functional mechanisms that change organism sensitivity to hypoxia might be formed; they increase the efficiency of tissue mass transfer and stimulate erythropoiesis. During the long-term (months, years) influence of hypoxic states on organism, it could no longer compensate this through functional capabilities only. This caused structural changes - hypertrophy of executive regulatory organs and, first of all, to hypertrophy of the left heart ventricle.

In our model the individualization was foreseen taking into account the weight and growth of individual person; the coefficients of organism sensitivity to hypoxia and carbon dioxide excess were used — and these coefficients decreased during a training process.

STUDYING OF SPORT MEDICINE PROBLEMS AT THE ELBRUS MEDICAL AND BIOLOGICAL STATION (EMBS)

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Professor N.N.Sirotinin suggested the concept of gradual stepwise adaptation to mountain heights' conditions in 1950. Since 1960, we started athletes' training in the mountains; and there we found that simultaneous influences of mountains' conditions on organism and individual dosed exercises, accelerate and improve the adaptation process. Therefore we had proposed to use active rest in mountain conditions as a method for improving the health of working people and a means for effectively improving sport achievements.

Inspection of alpinists: We obtained a unique experience in the selection and training of high altitude climbers at Elbrus Medical and Biological Station (EMBS), examining almost all Himalayan expeditions' members known in the former USSR, Russia and Ukraine. Selection and training of climbers under hypoxibaric conditions were carried out through several stages: 1. clinical examination, 2. special clinical, physiological examination during "ascent" in baro-chamber and stress tests, 3. clinical, physiological examination of adaptation processes to mountain height conditions, 4. use of mathematical models of hypoxic states to estimate the speed and efficiency of oxygen transport. Special attention was paid to mental and physical work capabilities, stability for cold, adaptive states and adaptability.

Thermoregulation and sport: This is the problem of temperature homeostasis maintainance in athletes who fulfill intensive physical work in conditions of hypoxia and cold. We found that hypoxic environments reduced heat generation, changing the physical and chemical structures of thermogenesis. During the team of climbers' preparation we also took into account the fact that high adaptability to cold reduced the organisms' adaptability to hypoxia, therefore, training procedures were recommended to be carried out at sea level.

Problems of sports longevity of sports' veterans: We paid particular attention to development of optimal ways to continue active life in sport, especially with hypoxytherapy methods. The "Regulation on the open championship of Ukraine among veterans of mountaineering" was approved in 1997. We found that mountaineering veterans, who train every year in the mountains, have greater capacity of safety when exposed to hypoxic environment and cold. With age, organism ability for adaptation to hypoxia decreased, however, it is not completely lost - older people can adapt to mountain heights up to 5000 m.

USO DE HIDROCORTISONA EN SHOCK NO REFRACTARIO EN PACIENTES CRÍTICOS DE ALTURA

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La sepsis grave y el shock séptico no refractario se encuentran entre las principales causas de ingreso a la UCI y, a pesar de las recientes mejoras en los resultados clínicos, las tasas de mortalidad siguen siendo elevadas. Se investigó el efecto del tratamiento con hidrocortisona en pacientes con diagnóstico de shock no refractario, específicamente sobre la mortalidad por cualquier causa a los 30 días, debido a que no está claro si la hidrocortisona reduce la mortalidad entre los pacientes con shock séptico. Es importante mencionar que esta población de estudio estuvo caracterizada por vivir en condiciones de altura.

Se encontró un mayor número de casos de muerte en aquel grupo que recibió hidrocortisona (7 frente a 2). Es importante destacar que la literatura científica sobre la eficacia de la hidrocortisona en pacientes con shock séptico sigue siendo controversial. Si bien la literatura menciona una posible influencia de la altura en el metabolismo del cortisol (hidrocortisona endógena), no se han encontrado estudios que evalúen el efecto de la altura sobre la eficacia de la administración exógena de hidrocortisona, mucho menos en el contexto de shock séptico no refractario.

En este sentido, se puede inferir que se necesitan de más estudios clínicos aleatorizados extensos y bien diseñados para poder apoyar o negar el uso de hidrocortisona en pacientes con shock séptico no refractario. Es necesario admitir que los hallazgos de la presente investigación no permiten confirmar o negar los beneficios del uso de hidrocortisona para la reducción de la mortalidad y de la duración de la estancia hospitalaria en pacientes ingresados por shock séptico no refractario.

FACTORES ASOCIADOS A POLICITEMIA EN TRABAJADORES MINEROS DE GRAN ALTURA

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Objetivo: Identificar los factores asociados a policitemia en trabajadores mineros de gran altura. Métodos: Fue un estudio observacional, descriptivo, retrospectivo y transversal. La muestra fue conformada por 37 trabajadores de la compañía minera Castrovirreyna S.A. los cuales fueron diagnosticados con policitemia.

Resultados: Se observó que 54.1% de los trabajadores eran empleados de Castrovirreyna Cia mientras que el otro 45.9% lo conformaban trabajadores de otras empresas contratas, los trabajadores de la compañía en su mayoría se encuentran entre los 51 a 60 años (60%), mientras que en las empresas contratas la edad predominante en los trabajadores fue de 51 a 60 años (71.4%), el mayor porcentaje de trabajadores tanto de la compañía como de las empresas contratas tienen una vivencia en altura de entre 11 a 20 años con una frecuencia de 70% y 85.7%, respectivamente. Por otro lado, se pudo apreciar que todos los trabajadores de la compañía reciben tratamiento, sin embargo, dicha realidad difiere en los obreros contratas donde sólo un 42.9% recibió tratamiento. Conclusión: La edad y el tiempo de vivencia pueden ser considerados como factores asociados a la policitemia.

MOON FACE DUE TO SUDDEN EXPOSURE TO HIGH ALTITUDE : POSSIBLE CAUSES AND THE SOLUTIONS

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Many of us tell that “Each subsequent day of the same trip gaining altitude in a short period of time, my face gets puffier and puffier. By day four, my face is so puffy, my eyelids are all gross and I'm certain strangers can tell something is wrong with me” what is this phenomenon? Is it endocrine disorder? Is it seen in all who go to high altitude with sudden gain in height? And many more questions still remain.

The only predictor of acute mountain sickness (AMS) is having had it previously, but anyone can get it at any time. The definition in addition to moon face headache after recent ascent plus at least one of the following due to altitude causes water retention, hard time sleeping apart from, (i) tummy troubles (loss of appetite, nausea, vomiting, (ii) tired (fatigue/weakness), (iii) tipsy (dizzy/lightheaded) and (iv) the terrible insomnia (not just frequent waking). These are the four T's. Not sure how to counteract, except to keep sodium levels down, drinking water, maybe some diuretics. This may not be "serious", but it clearly troubles all of us and detracts from our generally feelings of wellbeing.

The moon face syndrome mimicking Cushing is associated with salt retention apart from short term adjustments to new hypoxic environment by altering endocrine system. The drug of choice the Acetazolamide (Diamox), is often prescribed for high altitude problems for excreting sodium and sparing potassium.

Since it is actually a diuretic it might be just the ticket, if not contraindicated for you for any reason. Altitude sickness is caused by hypoxia, which up regulates prostaglandins, that leads to sympathetic stimulation and pain. Probably aspirin blocks this. There have been a few small placebo-controlled studies that show that it works, but that's about it. I say if it works, why not? Except one trip I took so much aspirin I got nosebleeds. The possible hypothesis and preventive measures will be presented during the talk.