Review

Gustavo Zubieta-Calleja*

Redefining chronic mountain sickness: insights from high-altitude research and clinical experience

https://doi.org/10.1515/mr-2024-0036
Received May 5, 2024; accepted July 31, 2024;
published online August 27, 2024

Abstract: Chronic Mountain Sickness (CMS), characterized by increased red blood cells above average values traditionally attributed to chronic hypobaric hypoxia exposure, is being redefined in light of recent research and clinical experience. We propose a shift in perspective, viewing CMS not as a singular entity but as Poly-erythrocythemia (PEH), as the Hematocrit/Hemoglobin/Red Blood Cells (Ht/Hb/RBCs) increase constitutes a sign, not a disease reflecting a spectrum of oxygen transport alterations in multiple diseases in the chronic hypoxia environment in high-altitude populations. Drawing on over five decades of experience at the High Altitude Pulmonary and Pathology Institute (HAPPI-IPPA) in Bolivia, we advocate for altitude-specific blood parameter norms and emphasize the importance of correct etiological diagnosis for effective management. This updated understanding not only aids in managing chronically hypoxemic patients at various altitudes but also offers valuable insights into global health challenges, including the recovery from COVID-19.

Keywords: polycythemia; high altitude; EPO; hemoglobin; excessive erythrocytosis; hematocrit

Introduction

Through many years of clinical practice, we have observed that the interpretation of Chronic Mountain Sickness (CMS) is not adequately focused. The time has arrived to write this review, based on our extensive experience on-site practice. First, it is essential to mention that Drs. Zubieta and Dr. John Triplett, with the support of the International Society of Mountain Medicine and its standing President, Dr. Bengt Kayser, were the pioneers carrying out the 1st World Congress of Altitude Medicine and Physiology. It was held in our hometown, La Paz, Bolivia, in 1994 at 3,500 m [1]. Later, in the follow-up 2nd World Congress held in Cuzco, Peru, we published in the Peruvian journal Acta Andina "New concepts on CMS" [2]. This publication essentially questioned how CMS could be considered a "loss of adaptation". Pryor to the 3rd World Congress of Mountain Medicine and High-Altitude Physiology and the 18th Japanese Mountain Medicine Symposium held in Matsumoto, Japan (May 20–24, 1998), an international committee was formed to establish a consensus on CMS. The idea was to define subacute and chronic high-altitude disease [3]. It is worth mentioning in an anecdotal way that Drs. Gustavo Zubieta-Castillo and Gustavo Zubieta-Calleja (Jr) were the members of this committee with permanent high-altitude medical practice treating CMS patients in La Paz and its neighboring city of El Alto (3,100–4,100 m). Therefore, it was unsurprising that our views differed from those of the rest of the committee, who primarily resided at sea level. The result was that many of our observations were not fully understood [4–6] and, therefore, not taken into account. Subsequently, we published our findings in several articles, which have been systematically ignored for not being in line with the "Consensus Statement" [7, 8]. In this review, we want to highlight the importance of revisiting the basic concepts and presenting a new guide to studying the physiology and pathophysiology of CMS, focusing on clinical practice.

In 1928, the Peruvian Carlos Monge Medrano reported the first historical reference of CMS. Some high-altitude residents presented a hematocrit (Ht) above the residents' average value [9]. He initially thought it was Polycythemia Vera (PV), which was later ruled out. The terminology varied because nobody understood what it was. Originally, it was referred to, in English, as "polycythemia" and later "increased polycythemia" and in Spanish in Peru and Bolivia as "poliglobulia". Subsequently, it was referred to as "erythrocytosis" and later as "excessive erythrocytosis". This last term is inappropriate because, in "erythrocytosis", the suffix "osis" (from the Greek etymology) means disease (of the red blood cells [RBCs]), something nonexistent in CMS from the microscopy

***Corresponding author: Gustavo Zubieta-Calleja**, Pulmonary, High Altitude Pulmonary and Pathology Institute (HAPPI-IPPA), Av. Copacabana – Prolongación # 55, La Paz, Bolivia, E-mail: gzubietajr@gmail.com. https://orcid.org/0000-0002-4283-6514

in these cells. Some examples of morphological alterations of RBCs in other diseases are: poikilocytosis (inequality or variability in the shape of RBCs), anisocytosis (extremely variable dimensions), microcytosis, macrocytosis, or megalocytosis (decrease or increase in diameter) [10], and other variants such as dacryocytosis, dianocytosis, sickle cell disease, spherocytosis [11]. Likewise, "excessive" denotes a value above what is necessary, which is generally not the case with CMS. Physiologically, any organism settles on the most effective (and least energy expenditure) oxygen transport mechanism to the tissues in a hypobaric environment, compensating for an organ functional insufficiency [7]. Consequently, from our point of view, the presence of higher than the average Ht/Hemoglobin (Hb)/RBCs is erroneously categorized as being "excessive". Fear of thick blood that is thought to produce cerebrovascular accidents is understandable but not accurate [12]. If this were true, we would have an enormous quantity of strokes at high altitude, however, it is not so as evident in clinical practice.

Furthermore, there is a misconception that the "adequate amount" of Hb for humans is only found at sea level. It disregards that as the altitude of residence increases, Hb increases as an efficient energy-saving mechanism of oxygen transport in a hypobaric chronic hypoxia environment (Figure 1). Erythrocytes, with Hb within, are the nucleus-free cells of the body with the life-enabling role of oxygen transport. Both those born in the highlands, as well as newcomers to the Andes (who stay long enough to reach their adequate blood Hb levels necessary to live at a certain altitude), have elevated Hb levels [13]. Interestingly, rats exposed to hypobaric chambers at 8,000 m for over one month and a half presented a Hb of 27 gm % [14], which perfectly fits the calculated value for Mt. Everest at 8,842 m (shown in red) in Figure 1, from a trend analysis of average Hbs in different high altitude populations.

There is a common belief that "adaptation" is defined solely by genetics in specific populations over many generations. Whereas physiologic changes due to altitude shifts are considered "acclimatization". We believe hypobaric hypoxia falls outside climate change variables such as temperature, humidity, precipitation, and wind. Consequently, we do not use the term "acclimatization". We consider adaptation to high altitude a physiological adaptation. "Genetic adaptation" takes many millions or thousands of years, whereas "physiologic adaptation" includes short to long-term in one lifetime essential survival functional changes [15]. Epigenetic expressions are within the physiological adaptation scope in our criteria, as they are "functional adaptations" [16]. As Frisancho pointed out in 2013, there is also a developmental functional adaptation to high altitude [17], which is interpreted as a physiological adaptation. Storz and Scott also write about "physiological adaptation to high altitude hypoxia" [18].

We, likewise, consider the increase of Ht/Hb/RBCs a "physiological adaptation" upon exposure to chronic hypoxia even without altitude change, i.e., hypoxic secondary polycythemia as in chronic obstructive pulmonary disease (COPD) at sea level. Moreover, this increase tends to be more significant at high altitudes as hypobaric hypoxia increases, and following the oxygen dissociation curve, saturation decreases accordingly. High altitude residents have adapted to a low barometric hypoxic condition involving many physiological and molecular changes, that allow a normal life under chronic hypoxia. Their organisms become very efficient in managing

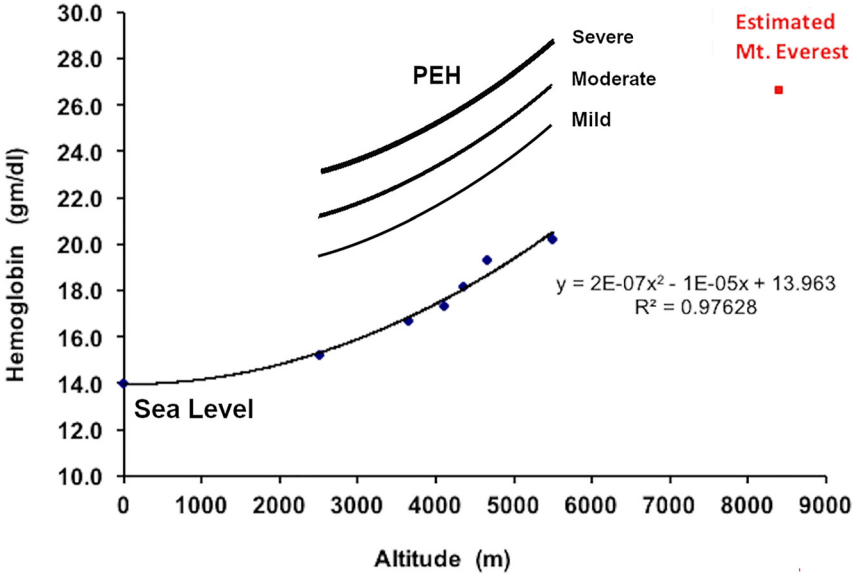

Figure 1: As altitude increases the normal adaptation hemoglobin in Andeans is depicted in different populations (squares) with a trend line projecting the estimated Mt. Everest calculated level. Following this increase, Poly-ErythrocytHemia (PEH: formerly known as CMS), would be expected to have different altitude threshold values responding to the different environmental chronic hypoxia levels. It is not right to have a fixed hemoglobin value to define multiple pathologies (CSM) at different altitudes and define what is, erroneously called, "excessive erythrocytosis".

the reduced pressure of inspired oxygen pressure (PIO_2), which in the city of La Paz is 94 mmHg. This becomes particularly evident when high-altitude residents descend to sea level (PIO_2=150 mmHg). Under those circumstances, the body is exposed to a relatively "excessive" amount of environmental oxygen pressure that, in a highly efficient high-altitude adapted oxygen transport biological mechanism, is beyond what is necessary. On going to sea level, physiological adaptation reduces "excessive" RBCs, i.e., "excessive" in the new environment at sea level. Such is the case when a CMS patient descends in altitude or when a regular healthy highlander does [13]. In the case of normal residents at 3,500 m, going down to sea level there is a linear decrease in Ht/Hb/RBCs, lasting 20 days. The explanation has to be no more RBC production and perhaps neocytolysis [19] or hemolysis [20], as described in astronauts during space travel. Astronauts present anemia in space and we consider it due to a less physiological oxygen requirement as the lack of gravity does not require the constant use of orthostatic muscles [21].

The increase of RBCs in some subjects above that of normal high-altitude residents was accurately denominated by Prof. Dr. Gustavo Zubieta-Castillo (Sr) as in poly-erythrocythemia (PEH), where poly=many, erythrocyt=RBCs, and hemia=in the blood [8]. From this point on, we will refer to the abbreviation "PEH" or Mountain Sicknesses (CMSs) instead of CMS. This is because PEH (formerly referred to as CMS) is not due to one isolated and distinctive sickness but rather multiple diseases at high altitude that trigger PEH. It is essential to define these disorders in high-altitude cities clearly. Multiple diseases are not only misdiagnosed but are consequently inadequately treated at high altitudes worldwide [2]. The current scientific world literature is biased and inaccurate, leading to many ineffective and/or detrimental treatments like excessive phlebotomies [22, 23], red meat food restrictions (creating nutritional deficiencies), and even the use of prohibited hemolytic drugs like Phenylhydrazine [24], with the idea of destroying "excessive" RBCs resulting in the loss of life. In the city of La Paz and El Alto (3,100–4,100 m), patients with PEH are regularly subjected to bleeding, and this has to stop. Sea-level medical doctors and scientists perform short-time research visits at high altitudes, classifying all subjects with elevated Ht without adequate screening or based on a rather superficial diagnosis based on sea-level standards of normality, excluding serious lung function testing.

We have often observed that spirometry is used to determine normal pulmonary function and this is a simplistic erroneous generalization. This causes multiple pathologies to be included under the same name, "CMS" (singular), which consequently erroneously mixes and blends numerous diseases as an independent and single entity. "Sickness", as defined by the Merriam-Webster dictionary, is considered to be a specific disease. For this reason, an adequate denomination would be Chronic Sicknesses in the Mountains (CSM) or perhaps CMS**s** in plural instead of CMS, or better yet: PEH.

The term PEH, denoting the presence of a clinical sign, is analogous to jaundice in hepatic and hematologic disease, where the latter denotes a clinical sign resulting from liver compromise in many diseases or hemolysis and not a disease in itself. This also has some similarities with cyanosis (bluish color of the skin resulting from poor circulation or inadequate oxygenation of the blood), which is also a clinical sign and not a disease.

The present article is based on our clinical experience gained during over more than half a century of medical practice and research at our High Altitude Pulmonary and Pathology Institute (HAPPI-IPPA https://altitudeclinic.com) at 3,500 m, in the bowl-shaped mountain city of La Paz (the highest capital city in the world) and its neighboring city in the high plateau El Alto (Bolivia), ranging from 3,100 to 4,100 m. All this is based on the teachings of the late Gustavo Zubieta-Castillo, the founder of our institute.

Definition of the disease

What has been described as "CMS" is a set of signs and symptoms (that should be considered a syndrome PEH, not a disease) found in some residents above 2,200 m as a result of one or several underlying illnesses associated with a sustained (and variable) decrease in oxygen saturation in blood or tissues, and above normal Ht/Hb/RBCs [8]. The underlying diseases include primarily pulmonary function disorders (increased intra-pulmonary or cardiac shunt, diffusion alteration, non-uniform ventilation/perfusion, and/or hypoventilation) or sequelae of various pathologies: heart, renal, paraganglioma (carotid body tumor or chemodectoma) [25], Hb alterations, neuroendocrine disorders, among others [8]. These diseases lead to cyanosis, pulmonary hypertension in some, and subsequent PEH as a compensatory mechanism of physiological adaptation of several underlying hypoxic conditions under the hypobaric chronic hypoxia environment. PEH generally results from a sustained (and variable) decrease in oxygen saturation (SpO_2) due to multiple pathologies. It is important to point out that it is not the increase of Ht/Hb/RBCs that gives rise to a low SpO_2. The diseases may appear silent or insidious at sea level or lower altitudes but become evident under overlapping environmental hypobaric hypoxia. At sea level, oxygen pressure is abundant at 760 mmHg of barometric pressure, and the SpO_2 of the oxygen Hb dissociation curve is in the flat upper plateau (close to 100 %) even despite hypoxicating diseases. In other words, symptoms and signs are aggravated upon ascent to higher

Table 1: Normal male and female values of Hb values, and anemia and PEH) values for different altitudes.

Sex	Altitude in m	Anemia	Normal Hb	Mild PEH	Moderate PEH	Severe PEH
Males	2,500	<12	12–19	19–21	21–23	> 23
	3,500	<13	13–20	20–22	22–24	> 24
	4,500	<15	15–21	21–23	23–25	> 25
	5,500	<17	17–23	23–25	25–27	> 27
Females	2,500	<10	10–17	17–19	19–21	> 21
	3,500	<11	11–18	18–20	20–22	> 22
	4,500	<13	13–19	19–21	21–23	> 23
	5,500	<15	15–21	21–23	23–25	> 25

PEH, poly-erythrocythemia; Hb, hemoglobin.

altitudes and are reversible when descending to sea level or by increasing the Inspired Partial Oxygen Pressure (PIO_2) [13, 26]. PEH is the physiological adaptation (the process of adjustment) of hypoxic diseases to a chronic hypoxia hypobaric environment. It is not a "loss of adaptation" or "maladaptation" [27]. In fact, for preciseness, it must be considered that PEH results from "organ dysfunction" of multiple diseases in the chronic hypoxic environment at high altitude. It is crucial to classify PEH as mild, moderate, and severe quantitatively (Table 1) [8, 28], which varies according to the altitude of residence (Figure 1). In other words, it cannot be a fixed Hb value (Hb>21 gm % in men and Hb>19 gm %) above which many scientists classify them as CMS *at any altitude* as expressed in the international consensus statement [3].

Pathogenesis

CMS is not a single entity. It involves multiple diseases, mainly respiratory, within an environment of chronic hypobaric hypoxia. It can present with pulmonary shunts, pulmonary diffusion disorders, hypoventilation and/or non-uniform ventilation-perfusion, sequelae of old pneumonia, pulmonary thromboembolism, pulmonary micro-thromboembolism, and many other alterations [29–31]. It also includes other diseases: cardiac (some arrhythmias), Glomus (Carotid Body tumor) and other carotid body disorders [32], hormonal disorders, metabolic disorders such as gout [33], sleep apnea, possibly but minimally nonspecific hemoglobinopathies [34, 35], and other underdiagnosed diseases, all generating hypoxemia (Figure 2).

Several of these patients have varicose veins in the lower limbs, a cause (and not a consequence) of PEH, as insidious pulmonary micro-thromboembolism is known to be a hypoxia-inducing pathology [36]. Any acute pulmonary pathology at high altitude generates hypoxemia (low SpO_2), much like sea-level residents ascending to high altitude [37]. It is initially compensated by hyperventilation and tachycardia, concomitantly stimulating hematopoietic erythropoietin (EPO) production in the kidney and lungs [38]. We have defined this as the Oxygen Transport Triad [39]. In this model, oxygen transport is based on three pillars: The pneumodynamic pump (vacuum pressure pump movement of air from the environment to the alveoli in the lungs), the hemodynamic pump (a blood compression pump moving blood through the circulation), and Hb (the molecule that captures oxygen for its transport to mitochondria). RBC production is increased in the bone medulla, evolving to PEH. Furthermore, EPO promotes adaptive cellular responses to hypoxic pathological challenges and tissue-damaging insults in various non-hematopoietic tissues [40], including the brain [41], lung [42], kidneys [43], vascular system [44], and heart [45]. It also has anti-inflammatory, anti-oxidant, anti-apoptotic, and proangiogenic effects [46]. Furthermore, it protects vessels and the brain [47]. The late Prof. Dr. Gustavo Zubieta-Castillo originally mentioned the direct effect of EPO on the heart in his conference on Respiratory Disease, CMS and Gender Differences at high altitude in 1998 in Matsumoto, Japan [6] (Figure 3).

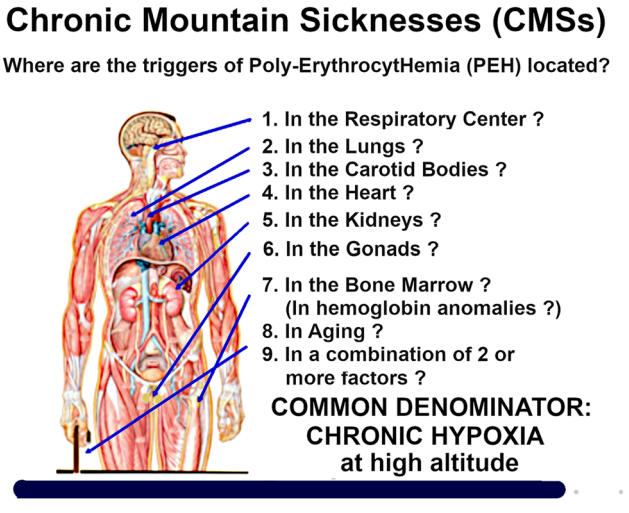

Figure 2: Diagram showing the different sites in the body where there could be triggers of poly-erythrocythemia (PEH), previously referred to as CMS.

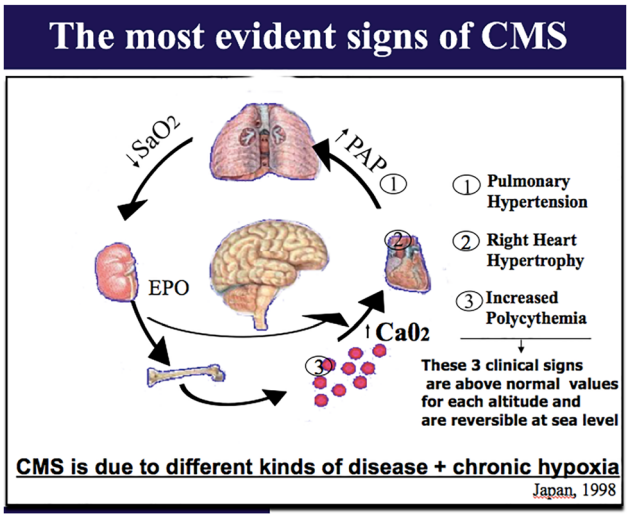

Figure 3: Slide presented by Prof. Dr. Gustavo Zubieta-Castillo during the 3rd World Congress on mountain medicine and high altitude physiology in Matsumoto, Japan 1998. The effect of EPO on the bone medulla and likewise directly on the heart is shown SaO_2=arterial hemoglobin oxygen saturation, PAP=pulmonary artery pressure, EPO=erythropoietin, CaO_2=arterial oxygen content.

The increased number of RBCs is the most energy-efficient form of transporting enough oxygen for tissue oxygenation, thereby reducing hyperventilation and tachycardia, representing the initial physiological responses that require high energy consumption [48]. However, pulmonary hypertension and resulting right heart hypertrophy jointly constitute normal physiological adaptation remodeling. Chronic smokers tend to have PEH [49, 50], particularly when they cough and present permanent expectoration (which increases uneven ventilation-perfusion and, to some degree, increases shunts). Other patients can present unilateral diaphragmatic paralysis, renal artery stenosis, ventilation disorders in the upper airways, central hypoventilation disorders, Hb abnormalities, and so on [8]. Therefore, multiple diseases result in a diminished arterial partial pressure of oxygen (PaO_2) due to functional insufficiencies in one or several organs. Future studies will discover new causes for a few unexplainable PEH. Since this low PaO_2 is on the Hb saturation curve's descending slope, the only way of possible subsistence at high altitude is PEH and possibly mitochondrial changes (mitochondrial plasticity). We have termed this "increased mitochondrial efficiency" at high altitude [51]. Any pathology associated with secondary polycythemia at sea level could also look like CMS at high altitude. This is because PEH increases (above normal levels) with time as PaO_2 decreases with rising altitude: High Altitude Adaptation Formula [13]. Underlying chronic hypoxemia becomes more evident when exposed to an additional hypobaric hypoxia in the steep portion of the oxygen Hb dissociation curve. A phenomenon similar to the Triple Hypoxia Syndrome [52, 53].

Individuals with excessive erythrocytosis (PEH) living at 3,500 m in La Paz, Bolivia according to Zubieta, and 5,100 m, at Cerro de Pasco, Peru, according to Hancco present fewer symptoms than usually reported as compared to those with lower Ht values [8, 54]. Hence, to survive at a high altitude with an oxygen transport deficiency, we consider a higher PEH a beneficial physiological adaptation.

Our point of view is supported by research performed on EPO over the past 20 years [40–42, 45, 46, 55–57]. We now know that EPO, in addition to being synthesized in the kidneys and regulating erythropoietic function, is endogenously synthesized in almost every organ in the body. It has been determined that EPO is a protective, anti-apoptotic, anti-inflammatory, anti-cytotoxic, antioxidant factor in all these organs, which also favors cell regeneration and vascularization [47]. PEH due to a lower PaO_2 triggering a higher EPO is a physiological adaptation even within disease. Hypoventilation at high altitude is often related to PEH. Alterations of the respiratory center play a fundamental role and require further studies.

Population incidence

Contrary to the popular (but erroneous) belief that CMS is a progressive disease secondary to living long enough in a hypoxic environment [58], not everybody living at high altitude develops it, regardless of their ancestry (native, lowlander ancestry, or newcomer) or their length of stay at high altitude. There are many confusing reports about the true incidence as they are based on the altitude of residence, where at a higher altitude there are more cases going from 1.05 to 11.83 % [59]. In India, no cases were found below 3,000 m but 13.3 % above [60]. This results from the fact that the threshold defined as the maximum normal Ht or Hb is not well represented in the different populations at high altitude. Furthermore, high altitude residents often change altitude because of work, leisure, or other daily activities that impact their hematocrit levels [13]. The Ht reduces linearly to optimal sea level values in around 20 days [13].

For example, when setting a maximum normal Ht of 58 % threshold for La Paz, at 3,500 m, a study of all pathologies according to hematology laboratory records of a hospital at 3,510 m reported an incidence of PEH in 28 % of men and 11 % of women. Applying the same threshold to a hospital in the neighboring city of El Alto at 4,100 m (600 m higher), the incidence increased to 35 % in men and 20 % in women [6]. The problem with these incidences is that they included dehydration cases and multiple other pathologies in a

hospital, as all hematological records were included. Nevertheless, it becomes evident that around 600 m of difference at those altitudes significantly changes the normal thresholds (Table 1). The 2005 international consensus statement referring to CMS and high altitude pulmonary hypertension (HAPH) states that "… when dealing with the definition, diagnosis, treatment, and prevention of these sicknesses, the altitude of residence of the patients must be taken into account". The altitude of residence is in fact mentioned, but we are talking about the normal levels of Hb or Ht at different altitudes. Whereas the consensus group (that included ourselves as a minority but not listened to) has set a fixed level of Hb to define CMS for any altitude, which from our point of view is wrong. It is important to take into consideration that there is variability of normal blood parameters according to altitude, and it is not correct to define a single level of Hb>21 gm % in men and Hb>19 gm % in women for CMS patients for all altitudes [3]. This translates into a lack of understanding of the exponential variation of barometric pressure with altitude and the optimal physiological compensatory systems to sustain life at each different altitude (Figure 4). Using those fixed values, PEH incidence in China is estimated to be 17.8 % [61]. In Qinghai, China in Han immigrants, averaging all cases found from 2,261 to 5,226 m, it was found to be 5.59 % [59]. In high altitude districts of the Indian Himalayas, in Himachal Pradesh above 3,000 m, it was found to be 13.3 % [60].

The international consensus statement likewise affirms: "Hb levels are not the only clinical signs of CMS, and the scoring system indicates that a patient presenting with high Hb but without any other signs (breathlessness, cyanosis, sleep disturbances, …) is not a CMS patient". This is confusing as it presumes that CMS has to be symptomatic. Nevertheless, those that are asymptomatic with a higher Hb are probably not suffering from the temporary condition "Triple Hypoxia Syndrome" which makes them symptomatic [52] (see below). The fact of the matter remains that many papers [58, 62–64] erroneously include many pulmonary pathologies, as they only base their diagnosis on chest X-rays and spirometry.

In some countries, such as in the USA, high altitude is considered to be above 2,500 m since their geography does not allow them to study higher altitudes with significant populations within their territory. In contrast, Bolivia, Peru, China, India, Iran, and others possess populated lands at almost double that height. These differences in altitude challenge the parameters of normality established at sea level.

Therefore, following the traditional classification mentioned, if the threshold is not independently set for every altitude, the incidence of CMS increases as the altitude increases. Consequently, it would presumably, make sense that the highest incidence of CMS would be at La Rinconada, Peru, at 5,100 m. In reality this is not true since PEH's limits require a new definition at every specific altitude. This could also explain why according to [54], PEH can actually be asymptomatic, i.e. it includes normal Hts for that altitude. More than a decade before, this same concept was already expressed in our papers [2, 8]. The incidence is not necessarily greater at higher altitudes, and should be similar at all altitudes, as the multiple diseases that generate PEH are mostly the same at all altitudes (i.e., Pulmonary shunt, if present, exists regardless of the altitude) [6]. Exceptions can be found based on the exposure to other risk factors that could compromise the respiratory system, such as mining activities at high altitude known to produce silicosis, cobalt

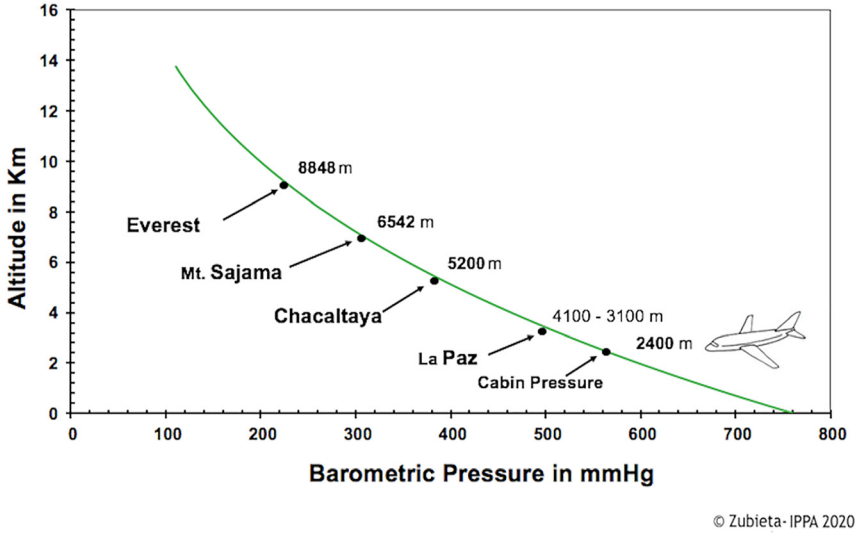

Figure 4: Exponential decrease of barometric pressure in relation to altitude. Note that the city of La Paz has a 1,000 m altitude differences, being in the high plateau the city of El Alto at 4,100 m. Chacaltaya is the location of the glass Pyramid laboratory 2 h from La Paz, by car. Mt. Sajama is the highest mountain in Bolivia where the world's highest soccer game was played on July 7th, 2001.

toxicity [65], and other lung diseases. This may be an essential confounder as several high altitude towns tend to be related to mining, such as La Rinconada, in Peru at 5,100 m or La Oroya at 3,745 m. Poor quality of living conditions in La Rinconada as it is an improvised mining town, also plays a role.

Normal Hb levels should be defined for every altitude (Table 1). The Chipayas in Bolivia, a native resident group, living for more than 2,000 years at 4,000 m, would be suspected to be free of PEH if they had been perfectly adapted to high altitude. However, they can present PEH due to their multiple diseases, lung and heart diseases, as expected [66]. We examined them and found several cases of PEH. Despite their 3,000 or 4,000 years of residence at high altitudes, the Tibetans have PEH likewise [67]. The Chinese Han living in Lhasa have a higher incidence of PEH [61] because high altitude is a test of cardio-pulmonary fitness, and they are well known to smoke very much, a common cause of COPD and hypoxemia [28]. Conversely, healthy sea level foreigners can come live to high altitude and never develop CMS or rather PEH.

Symptoms and signs of CMSs

The symptoms described in multiple articles regarding CMS (claimed to be characteristic), do not correspond to the true clinical scenario. We proceed to analyze each symptom as described in [68], items 1–13, below. It becomes evident that signs and symptoms are present in multiple diseases at sea level and hence likewise at high altitude. Unfortunately, they are commonly attributed to CMS in patients who can be suffering from many other diseases.

1) Clock glass nails and drum stick fingers

At least from what we observe in La Paz, this sign is very rare and we have only appreciated it rarely in our routine clinical practice, in over 50 years. These were patients with serious lung diseases during development (growth stages) and of course with sustained chronic hypoxia. They had, of course, PEH, but that was a compensating physiological response that allowed them to survive. Could these cases be classified as CMS, with respiratory and/or cardiac pathologies since childhood? The vast majority of patients with PEH may have distal cyanosis, as expected but with fingers without malformations (Figure 7). If this was a sign derived from sustained hypoxia during adulthood, one could assume that it would be also present in COPD patients at sea level.

2) Dilatation of veins

According to medical terminology, a vein dilatation occurs in many individuals due to low adipose subcutaneous tissue and is perfectly normal in skinny subjects at any altitude e. g. elderly. The author has this characteristic in the hands and has a normal Ht of 50 % throughout his life at high altitude. But there are also pathologies such as varicose veins in the lower limbs that may associated to thrombophlebitis. Actually, it is well known, varicose veins are the cause of constant pulmonary thromboembolism and/or micro-thromboembolism [36, 69–72] that in many cases gives rise to Poly-Erythrocythemia, and are not (as frequently expressed) the consequence of CMS. Increased blood viscosity does not necessarily produce varicose veins. Quite the contrary, chronic pulmonary thromboembolism reduces the useful area of gas exchange in the lung [73] blocking perfusion which associated to HAPH, is also aggravated by a reduced arteriolar vaso-constriction reflex [28]. Hypoxemia increases and is biologically compensated through an increase in RBCs (and Hb and Ht, concomitantly). It is important to note that most PEH patients have normal mean cell volume (MCV), mean cell Hb (MCH), MCH concentration (MCHC). This is because their RBCs are normal, although some may actually have iron deficiency. It is interesting to note that high-altitude Tibetans have been found to have a higher MCV than their sea-level 50 year residence counterparts [74], but having a higher Hb at high altitude can be an explanation.

The patient in Figure 7D presents a Ht 74 % for many years and does not present varicose veins. This is proof that PEH does not evolve into varicose veins as repeatedly affirmed in several CMS articles. That patient had a process of pulmonary diffusion limitations, secondary to his work in mining for many years in Potosi at 4,100 m and consequently sustained pneumoconiosis. In other words, chronic lung disease, reduces the area of functionality of the lung rendering it insufficient. The body responds generating an increase in RBCs, as a mechanism of physiologic adaptation of hypoxemic disease to the hypoxic environment.

3) Headache

The causes of headaches are multiple even at sea level: high blood pressure, migraine, excessive alcohol consumption, processed food containing nitrates, poor posture, stress, concussion, dehydration, glaucoma, influenza, panic attacks, cerebro-vascular accidents (CVA), and many more [75, 76]. Any of these multiple causes of headache are also naturally found at high altitude. And if a study of all the population is performed, it is possible that at high altitude, such as at sea level, there is a 14 % incidence, just as at sea level [77].

Migraine is found in 5–9 % of men and 12–25 % of women in the United States [78]. The incidence of tension headache is 11 % in Singapore [79], 20–40 % in the USA [76] and greater than 80 % in Denmark [76]. This translates to a pathological disorder, not necessarily linked to an increased Ht. It would seem that the fact that Acute Mountain Sickness (AMS) can produce headaches in around 25 % of those traveling to 3,600 m, it has been adopted as a "chronic" malaise at high altitude linked to CMS.

4) Tinnitus

Tinnitus is the sound in the ears that can be pulsating or constant. This is frequently associated with advanced age, as well as with arterial hypertension. Hypertension, nevertheless is not present in most patients with PEH [54]. At sea level, tinnitus has the incidence of 8–30 % in adults [80].

5) Sleep disorders

Sleep disorder is another symptom commonly described in CMS, and in reality, at sea level it is a constant problem, with an incidence of 32.1 % [81]. Of course, when a subject initially ascends to high altitude there may be interrupted sleep, particularly during the first night [82]. Interrupted sleep may be present for several days until RBCs increase and normalize SPO_2 for that specific altitude. However, in that case, it seems evident that the same study would need to be performed after 40 days of adaptation at 3,600 m [13]. Some permanent high-altitude residents affirm that they do not sleep well at high altitude, but most of these do not have polyerythrocythemia. It is a complex, multifactorial issue that, with a proper diagnosis, can be improved. Some CMS patients have sleep apneas and Sleep-Disordered Breathing (SDB), with low saturations [83] but due to their high Hb they have a pool of oxygen that serves as a reserve. This is deduced from the fact that they have very long breath-holding times Figure 10 [5].

6) Shortness of breath

Shortness of breath is a symptom present in many cardiac and respiratory pathologies at sea level. 4.7 %, of adults in Rotterdam have COPD [84]. Many people at sea level are on supplementary and/or portable oxygen because they are short of breath. Why would those conditions be considered different for residents at high altitude? Interestingly, tolerance to hypoxia increases with higher altitudes [85].

7) Deep Cyanosis in the mucosae of the mouth and throat

Again, this is common in pulmonary disease [86]. All high-altitude residents have a mild degree of cyanosis due to high altitude, and much more so in patients with a low SpO2 (due to different diseases) at high altitude (Figure 8). Some authors affirm that "There is also a characteristic complaint of dyspnea, insomnia, dizziness, headache, paresthesias, and mental confusion" [68]. Again, most symptoms are temporary and transitory in most people. Particularly during the triple hypoxia syndrome, described below. Does no other disease have these symptoms? Perhaps even most readers will have suffered those symptoms quoted above sometimes, particularly during the COVID-19 pandemic.

8) Moderate hemoptysis and epistaxis episodes

It is affirmed, likewise, that moderate hemoptysis and epistaxis episodes are also common. Many other diseases have these symptoms. Hemoptysis is the production of blood from acute bleeding in the lung [87, 88]. This is a serious pulmonary condition that requires urgent medical care. The causes are multiple: lung cancer, infections such as tuberculosis, bronchitis, or pneumonia, pneumolysis as in COVID-19, and certain cardiovascular conditions. Likewise, Sarcoidosis, Aspergilloma, Histoplasmosis, Pulmonary edema, Foreign body aspiration and aspiration pneumonia, Goodpasture's syndrome, granulomatosis with polyangiitis, epsinophilic granulomatosis with polyangiitis (Churg-Strauss syndrome), Bronchiectasis, Anticoagulant use, Trauma, Lung abscess, Mitral stenosis [89]. One of the most important causes is Pulmonary embolism and definitely that would be a thromboembolic disease.

Epistaxis is in fact relatively common in CMS, but it is generally due to rhinitis, viral localized inflammation or bacterial infection, nose-picking particularly in a low-humidity high-altitude atmosphere and toxic gas or Diesel exhaust inhalation among others [90].

9) Fatigue

This symptom can be due to multiple causes at sea level such as: cardiac insufficiency, electrolyte alterations due to diarrhea, poor diet, lifestyle factors, physical health conditions, even mental health issues, being overweight or obese, periods of emotional stress, boredom, grief, taking certain medications, such as antidepressants or sedatives, using alcohol on a regular basis, using illicit drugs, such as cocaine, consuming

too much caffeine [91]. Furthermore during diseases: anemia, arthritis, fibromyalgia, chronic fatigue syndrome, infections, such as cold and flu, Addison's disease, hypothyroidism, hyperthyroidism, insomnia, anorexia, autoimmune disorders, congestive heart failure, cancer, diabetes, kidney disease, liver disease, COPD, emphysema, among others [92]. Most people that do not sleep well due to multiple causes, being the foremost, psychological worries, can be tired during the day.

10) Burning in the palms of hands and soles of feet

Anyone having looked after patients at high altitude, has heard this complaint in people without PEH. The causes can be: circulation problems, neurologic alterations, and perhaps others like vitamin deficiencies.

11) Loss of appetite

This is quite a common symptom is several health alterations and everyone has temporarily had it due to: colds, gastric disorders and even psychological disorders. Furthermore, CMS patients tend to be overweight and they definitely mostly are well fed, unless they are in an acute triple hypoxia syndrome episode [52].

12) Muscle and joint pain

Many people around the world have muscle pain due to excessive exercise or multiple pathologies [93]. Joint pain can be due to arthrosis, viral diseases (such as COVID-19) and multiple autoimmune diseases.

13) Lack of mental concentration and lack of memory

Old age, Alzheimer, stress, worries are commonly associated with this symptom. Quite the contrary to what is believed, patients with PEH, do not regularly complain of this syndrome, unless they are well advanced in age. Modern, hectic life, full of cell phones and distractions have even children and young adults suffering from these memory alterations. Interestingly, a greater vascularity in the brain has been described at high-altitude as in many other organs, like the placenta [94] and the retina [95]. The Vascular Endothelial Grow Factor (VEGF) is increased at high altitude as an adaptation mechanism [51, 96].

It becomes clearly evident that many of the symptoms and signs referred to commonly in the scientific literature on CMS can have multiple causes that should not be solely attributed to the increase of RBCs. This also poses a conflict when trying to gather so many different diseases in descriptive and quantitative data regarding specific symptoms. For example, a patient with cardiac arrythmia may not present loss of apetite or muscle and joint pain, or burning sensation of the palms and feet.

Definite signs and symptoms in CMSs based on our highland experience

Quite the contrary to those expressed above, it is evident that there are some frequent signs and symptoms in most (CMSs) that contrary to CMS, should not be regarded or treated as a single disease but rather as multiple diseases:

1) **Hypoxemia.**

Low SpO_2 and low PaO_2.

2) **Pulmonary hypertension.**

Secondary to hypoxemia as a compensating factor.

3) **Increased Ht/Hb/RBCs specific for each altitude.**

At each altitude there is a different cut-off level where patients can be classified as having PEH Table 1 and Figure 1.

4) **Hyperpigmentation of the parts of the skin exposed to the sun.**

In other words, an exaggerated "sun tan" possibly resulting from the increase of Hb and iron in the blood. That is the opposite of what happens in the yellow Asian races, which have different types of anemia and poor exposure to sunlight. At high altitude, there is an abundance of sunlight and hence high ultra-violet radiation in general in our longitude and latitudes (Figure 8) [97, 98].

5) **Hyperhemic conjuntivae.**

The patients with PEH, often worry about their cyanotic looks and their eye hyperhemic conjuntivae (Figure 8).

6) **Cyanosis of lips, oral mucosae and fingernails.**

A cardinal symptom in PEH. The lips and the fingernail look cyanotic.

7) **Daytime Somnolence.**

People with PEH tend to fall asleep easily during the day.

8) **Sleep apnea.**

Breathing at night may be interrupted due to sleep apnea episodes (presenting irregular respiration during sleep), particularly in some patients with PEH with overweight tendencies.

9) **Long breath-holding times.**

Characteristically, and due to the increased Hb, following a deep inspiration these patients are able to hold their breaths longer than average normal residents [5].

Laboratory exams, normal ranges, and classification of PEH

For an adequate etiological diagnosis, multiple tests are required. These should be performed according to individual requirements. Routine hemogram, chest X-rays or CAT scan, electrocardiography, echocardiography, abdominal imagining, urine and kidney function tests, arterial blood gases, pulmonary lung function tests including spirometry, hyperoxic shunt tests, diffusion tests, ventilation studies and fast nitrogen analysis, breath-holding SpO_2 should be performed [5]. Likewise, carotid body chemosensitivity to oxygen (Dejours test), evaluation of the circulating level of soluble EPO receptor (the natural "antagonist" of EPO), EPO and iron transporting studies, Hb studies, sleep studies, otorhinolaryngology studies, testosterone studies, mitochondrial and genetic studies, among others, need to be taken into account to properly determine the cause of PEH, i.e. CMS [2]. EPO-induced increased Ht values and erythrocyte mass have been suggested as altering the integrity of vascular smooth muscles, leading to the deregulation of endothelial vasodilatory factors like NO and aggravating hypertension at sea level [99]. However, CMS patients tend to be hypotensive, which would rule out this effect, although vascular endothelium studies are needed as they may play an important role in the high-altitude pathologies.

Following the graph of the average Hb for each altitude, it can be defined in a pragmatic way that an increase of 2 gm/dl above the maximum standard value for men and women at every specific altitude is where PEH could be diagnosed. For example, in the city of La Paz, at an altitude of 3,500 m (average), a value of Ht>58 % and Hb>20 gm % in men and Ht>55 % and Hb>19 gm % in women can be considered the thresholds to define the presence of PEH (Figure 5). The PEH's severity is classified as Mild, Moderate, and Severe, increasing 2 gm/dl per level for all altitudes. Following this same line of reasoning, the classification of PEH for males and females at different altitudes is shown in Table 1.

This is based on the distribution of Hb observed in 3,688 patients at the High Altitude Pulmonary and Pathology Institute. It refers to all the patients we treated in our Institute at 3,500 m of altitude of residence (although La Paz, is situated between 3,100 m and 4,100 m of altitude, our Institute is at 3,500 m precisely).

Distribution by age, degree of lung compromise, and altitude is available along with the relation to PaO_2 in one of our old papers published at the Bolivian Academy of Sciences in 1970, [100]. Distribution by sex is presented in Figure 6. The distribution by the age of patients with Ht>54 % and Hb>18 gm % is shown in Figure 7. This data is from 2,263 miners who presented silicosis and silicotuberculosis

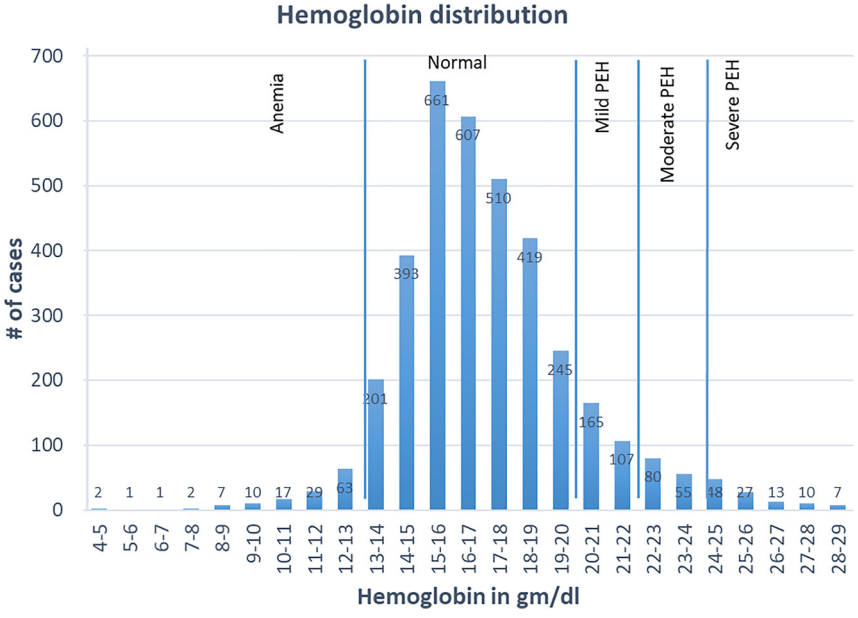

Figure 5: Hemoglobin distribution of 3,688 patients both male and female at 3,500 m of altitude in the high altitude pulmonary and pathology institute, showing the normal range, anemia and mild, moderate and severe PEH.

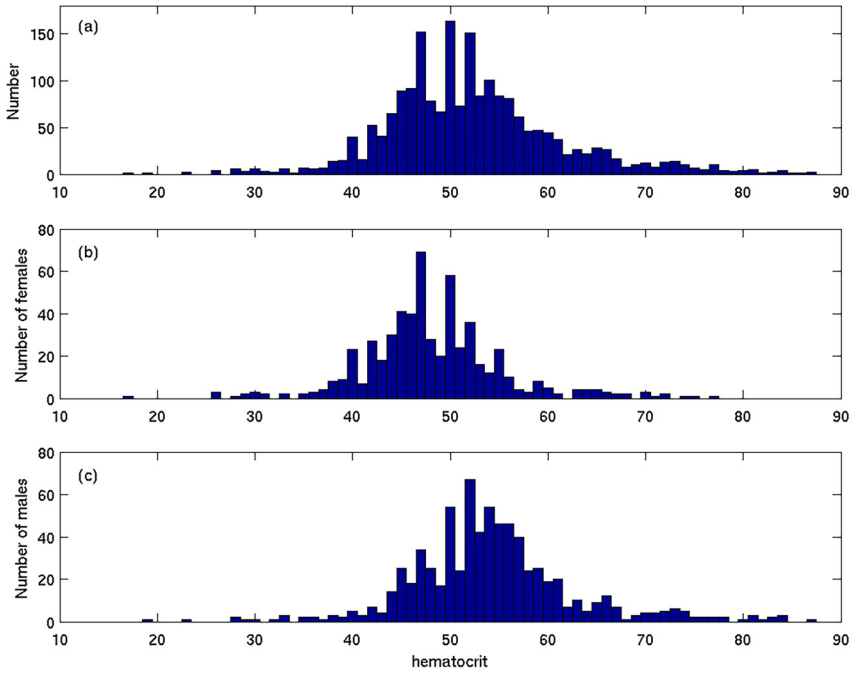

Figure 6: Distribution of hematocrit levels from the IPPA laboratory database at 3,500 m including 1955 samples blood tests for (a) adults, (b) females and (c) males. Courtesy of Michael Moretti.

evaluated at 3,500 m in the Caja Nacional de Seguridad Social by the first author of the article entitled CMS and Miners published at the Bolivian Academy of Sciences in Spanish [100]. It is important to note that although those patients had an increased Ht (Erythrocytosis, or instead defined as poliglobulia in 1985) the age distribution did not differ from those that had normal Hts. From our point of view, this clearly shows that life expectancy is the same and is not altered by an increased Ht, provided that the underlying disease is regularly treated.

Clinical picture

These multiple PEH-inducing pathologies at high altitude can present with cyanosis in the lips and the nail beds (Figure 8) and sometimes with bloodshot sclerotics. As these patients look congested, they are often confused with being an alcoholic, and it profoundly affects them aesthetically, socially, and psychologically, inducing them to seek medical assistance [8]. Apart from these characteristics, subjects are often asymptomatic, and some notice the presence of PEH as a

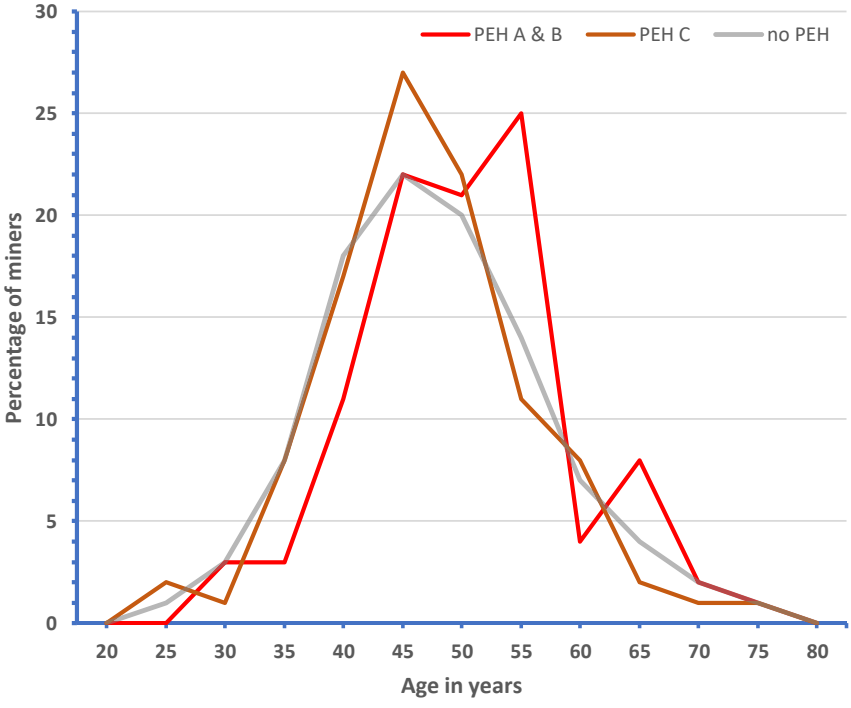

Figure 7: Distribution by age (Edad in Spanish) of 2,263 miners residing at high altitude 3500 m or more with type A: Ht>70 %; Hb>23 gm %, type B: 70 %>Ht>62 %; 23 gm % >Hb<20 gm % and type C: 62 %>Ht>54 %; 20 gm %>Hb>18 gm %. Sin Eritrocitosis (without erythrocytosis): Ht<54 % and Hb<18 gm %. From (Zubieta-Castillo, G. & Zubieta-Calleja, 1985).

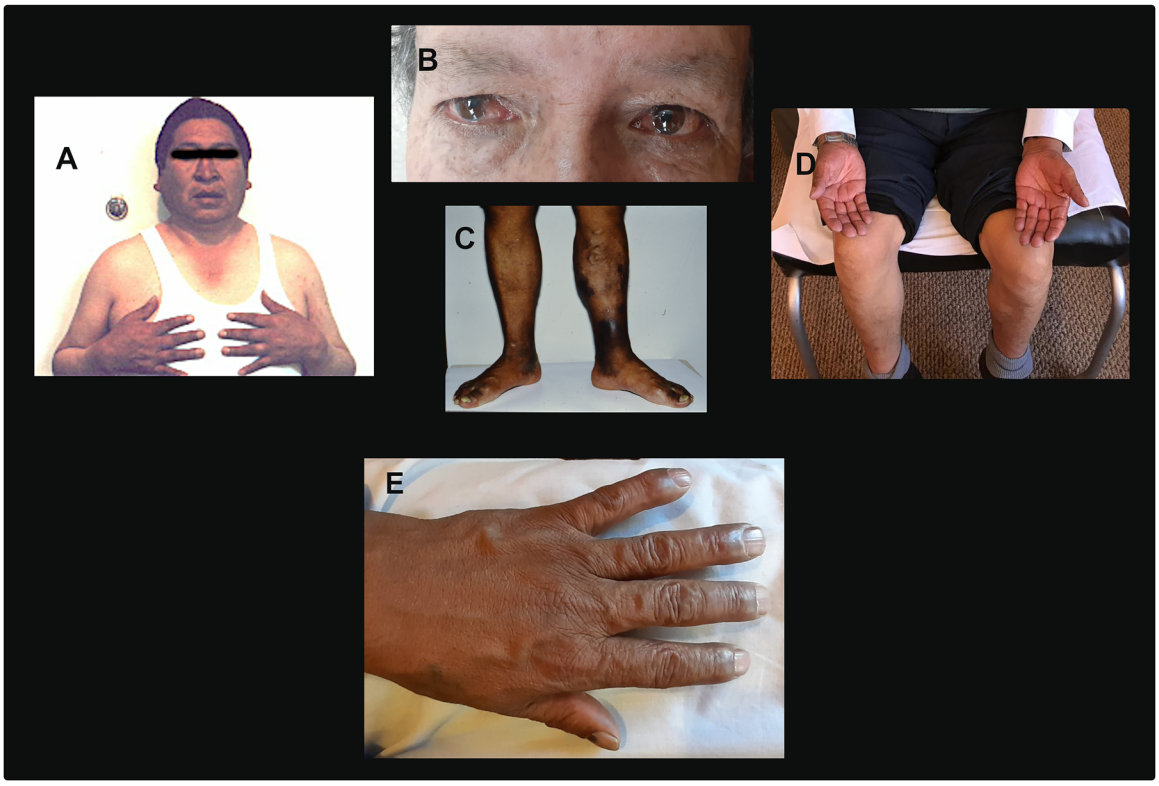

Figure 8: Signs in CMS. (A) A patient with poly-erythrocytHemia (PEH) where distal cyanosis in lips and nail beds can be observed. Additionally, distal skin hyperpigmentation in areas exposed to the sun, due to increased presence of iron. Notice that there is no finger clubbing or glass fingernails (B) Red sclera (C) Unilateral varicose veins and formation of thrombus, are an important cause of PEH, resulting from pulmonary thromboembolism. Some also present trophic skin changes due to trauma secondary to itching and subsequent scratching resulting from dry skin in a low humidity, low temperature high-altitude environment. They are often associated with an increased pigmentation of the skin secondary to a long-term traumatic local inflammatory process, extravasation and presence of high iron due to PEH (D) Cyanosis in hands, with no finger clubbing (also known as drum stick fingers). (E) No clock glass nails or drumstick fingers.

result of a medical consultation or a routine or casual hematological study, as often expressed in the past [8], and now confirmed [54]. It is important to note that the severity of hypoxemia varies in every patient regarding the severity of their underlying conditions, and PEH values will, therefore, vary accordingly as well. These patients can likewise suffer from the Triple Hypoxia Syndrome from time to time (originally described by Prof. Dr. Gustavo Zubieta-Castillo), when "the classic CMS symptomatic description" could become more evident, as patients become temporarily symptomatic [28, 52]. In this condition, their hypoxemia is temporarily aggravated due to the overlapping sum of three types of hypoxia that can further give rise to these unusually high Ht and Hb values:

The first (1st) hypoxia results from the hypobaric hypoxia that all high-altitude residents live with, with a decreased PIO_2, depending on the altitude of habitat. This is due to the environmental exponentially decreased oxygen pressure with respect to sea level. Healthy people living in these conditions are physiologically adjusted with a higher Ht/Hb/RBCs compared to those living at sea level [13], where normality varies depending on the altitude (Table 1).

The second (2nd) hypoxia, which further lowers PaO_2, is secondary to any hypoxemia present as a result of any of the multiple chronic hypoxia-inducing pathologies described above. Patients with the first and second hypoxia are those who tend to show an asymptomatic PEH as a result of their underlying hypoxemia. They have an individual alteration associated with decreased PaO_2. This can be from a transport deficiency from the environment to the lungs, or from the lungs to Hb in the pulmonary circulation, or in Hb itself, or due to deficiencies in the heart, kidneys, abnormalities in neural signaling of the central respiratory system, or carotid body, hypoventilation, etc., as described in the pathogenesis section, above.

The third (3rd) hypoxia presents when a patient with PEH at a high altitude gets an acute superimposed condition (on top of the other two). This third hypoxia is temporary and results from transitory acute pathologies or infections (i.e., any pathology that anyone at sea level could present but would not

impact SpO_2 significantly since they are at low altitude in the flat upper plateau of the oxygen Hb dissociation curve). These could be allergies, dehydration, seasonal flu or colds with nasal congestion, viral diseases, acute bronchitis, cough, expectoration, and/or others. More severe complications such as pneumonia, pulmonary thromboembolism, bronchitis, asthmatic processes (though not common), transient myocarditis, and others, which further reduce PaO_2, are likewise implicated. Under these circumstances, some walk-in patients arrive for consultation with very low PaO_2 values approaching even 30 mmHg (Normal=60 mmHg, in the city of La Paz at 3,600 m). That PaO_2 happens to be similar to extreme values found on the summit of Mount Everest [101, 102]. However, these patients can report only minor discomforts such as headaches, daytime sleepiness, palpitations, and/or fatigue when climbing stairs or going uphill. This 3rd hypoxia is treatable with oxygen (via nasal prongs), antibiotics if required, bronchodilators, platelet anti-aggregation therapy, hypotensive drugs, antihistamines, rehydration, and rarely corticosteroids, depending on the disease [103]. As this temporary condition is reversed, the subjects return to the 2nd permanent hypoxia stable level and symptoms subside. This second hypoxemia is generally irreversible because of the permanent pulmonary lesions, sequelae, or other chronic cursing pathologies as those described above.

Interestingly in CMS, apoptosis of RBCs is decreased [104] because RBCs are the fundamental part of the oxygen transport triad [39, 53]. The patients with PEH also have prolonged breath-holding times [5, 105, 106], because there is a higher "oxygen reserve pool (ORP)" due to increased Hb levels [39]. These subjects are also able to perform exercise normally [107]. It has been reported that they present higher pulmonary arterial hypertension during exercise as compared to that of normal [108]. Nevertheless, this condition does not constitute a physical limitation [109], as misreported in several studies. As CMS is generally (and mistakenly) considered an isolated unique pathology, questionnaires such as the International Consensus on the definition of Sub-Acute and Chronic Diseases at High Altitude and also the Quinghai were developed (paralleling the Lake Louise Score for AMS) setting punctuation on signs and symptoms [61]. But being CSM, multiple pathologies in a chronic hypoxia environment, frequently misdiagnosed, the scores do not optimally reflect reality. Recent studies had to stop using the questionnaire for not adequately corresponding to clinical observations. Furthermore, during the International Consensus [3], we, Zubieta-Castillo and Zubieta-Calleja objected against using the misleading concept of "loss of adaptation" and "maladaptation" [8, 27, 110]. Indeed, the late Prof. Dr. Gustavo Zubieta-Castillo, a world pioneer in defending hypobaric hypoxia physiology, affirmed that "The organic systems of human beings and other species tend to adapt to any environmental

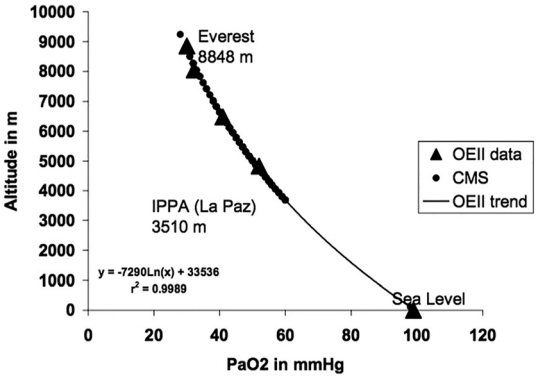

Figure 9: PaO_2-altitude graph developed from operation Everest II (OEII) carried out by Charles Houston in a hypobaric chamber [139]. Tendency line (OEII trend) determined from the OEII PaO_2 values (triangles) at different simulated altitudes. Real CMS patients living between 3,100 m and 4,100 m (La Paz) with PaO_2 values below 60 mmHg (dots), obtained from IPPA, are placed on the trendline to show their relative theoretical living altitude [100].

change, within an optimal time, and never tend towards regression which would inevitably lead to death". Regression would be "loss of adaptation". The presence of PEH is expected when there are hypoxic diseases at high altitude. This is an "adaptation to hypoxia within the disease", not a loss of adaptation or maladaptation. When PEH is present in high altitude residents, it is as if these patients were not living at their altitude of residence but at a higher altitude (Figure 9) [101]. This is one of the reasons behind Prof. Dr. Gustavo Zubieta-Castillo's proposal in 2003 that man could adapt to live even on the summit of Mt. Everest [111]. As diseases are being overlooked by non-physician researchers who do not live and work at high altitude, the hypoxic environment has been systematically blamed as the origin of CMS as a single entity.

Actually, in PEH (resulting from hypoxemia), there is a type of silent hypoxemia. Interestingly in COVID-19 silent hypoxemia has come into world literature [112]. In CMSs, patients live with underlying low oxygen levels, yet completely undiagnosed and unaware of it. PEH should be regarded as a sign denoting the presence of hypoxia, as fever is regarded as a sign of infection or hyperbilirubinemia as a sign of liver disease. The etiology of the hypoxia-inducing disease is commonly underdiagnosed, and frequently associated solely with high altitude instead of looking for other confounders. When searching for the origin of PEH, diagnosis is associated with "inadequate function" or insufficiency of some organ due to disease. This is predominantly in the lungs (pneumo-dynamic pump) and/or in the heart (hemo-dynamic pump)), or in any other organ, sending a subliminal alarm of this, resulting in an increase of EPO, and the subsequent increase of the number of oxygen

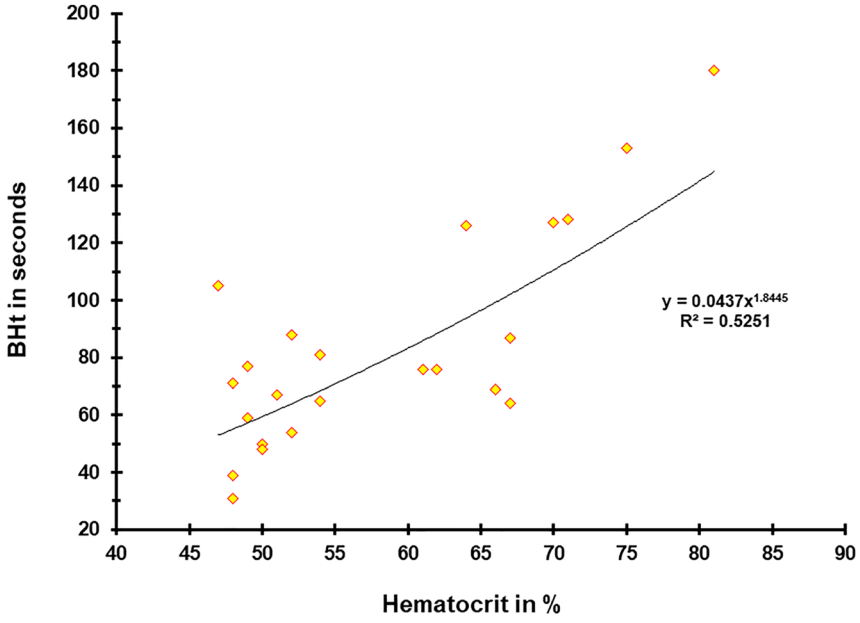

Figure 10: The relation between hematocrit and breath-holding time after a deep inspiration at 3,500 m. BHT=breath-holding time.

transporters (RBCs). This can be better understood by reading about the Oxygen Transport Triad [8, 39, 53].

Differential diagnosis

Differential diagnosis is also a source of confusion. PEH (a clinical sign resulting from high altitude hypoxemia + organ insufficiency) is often thought to differ from common secondary polycythemia, assuming that the latter would present with "very obvious" or "macroscopic" underlying diseases or injuries such as those seen radiologically in patients with silico-tuberculosis or silicosis [100, 113]. This is an outdated concept. It is interesting to point out that there was no correlation between the severity of lung radiographic anomalies and the degree of PEH in miners [100]. Often, there is not a very evident cause of hypoxemia in most patients. Indeed, recently it has been shown that the sensitivity of the erythropoietic system is so high that there is a resetting of the RBC level at every 300 m of altitude [85, 114]. Thus, this misunderstanding has led to the belief that populations (such as Tibetans) living at high altitudes do not develop PEH (although it exists). It was assumed that PEH would be a hematological disorder directly caused by high-altitude hypoxia, the time of high altitude permanence, and individual susceptibility. As such, some have denominated it as "High altitude Pathological Erythrocytosis". This is redundant as the suffix "osis" and pathological both signify disease. Perhaps it refers to hematological disease at high altitude.

The precise diagnosis of the underlying disease requires exhaustive tests to reach the differential diagnosis among the causes of hypoxemia. Unfortunately, these tests are not performed in routine check-ups and examinations fundamentally due to inadequate comprehension of chronic hypoxemia. This is due to the sustained assumption that PEH being a high-altitude hematological disorder, has to be treated mostly by hematologists. A profound respiratory, cardiac and other organ study is needed to rule out many pathologies.

PEH should be essentially distinguished from other causes of Ht elevation and well-known non-hypoxic causes of secondary polycythemia at sea level. As the normal hematological threshold values increase with altitude, the disease should also be distinguished accordingly. These include hemoconcentration or dehydration, renal tumors, and myeloproliferative disorders, including PV. In the latter, there is not only an increase in RBCs but also in white blood cells and platelets, with a mutation in the JAK tyrosine kinase gene (V617F) in 90 % of cases which would sensitize blood precursors to EPO. Clonal erythrocytosis is the diagnostic feature of PV and should be distinguished from non-clonal erythrocytosis [115]. PEH must also be distinguished from other causes without hypoxemia, such as excessive production of EPO in hematologic tumors and hormonal changes (testosterone elevation). Likewise, the Chuvash Polycythemia, a genetic disorder with a specific mutation in the *VHL* gene resulting in an R200 W amino acid substitution, in an area of Russia [23]. Eventually, very rare hemoglobinopathies should be considered [35, 116]. It should be noted that the use of the term "polycythemia" is inadequate when only the RBCs increase, even at sea level, and should be replaced by PEH, as the increase of the RBCs only (and not

the platelets or white blood cells) when associated to hypoxemia, is a compensatory mechanism at all altitudes.

Prognosis

The prognosis depends on the origin that triggered the rise of RBCs and the form of treatment performed. First, it is fundamental to identify if the underlying cause is treatable, and in the event it is, PEH can disappear. For instance, when a pacemaker is placed due to cardiac arrhythmia (unpublished data). Patients with PEH should have regular check-ups and be treated promptly. If not, there are four possibilities to face these pathologies: 1) moving the patient to a lower altitude [117]; 2) providing permanent supplemental oxygen; 3) using CPAP during sleep (based on the diagnosis); or 4) letting the RBCs increase to an optimal level of compensation [8]. When patients follow the first three options, PEH should decrease. Nevertheless, it is evident that there are complications in going to reside at a lower altitude because the underlying pathology continues. In very humid environments, they may be more prone to pneumonia or asthmatic reactions aggravating their health. Upon administering permanent oxygen, the patient becomes oxygen-dependent and can evolve negatively due to the underlying disease, not being correctly diagnosed, and possibly due to deleterious effects of hyperoxia and oxygen itself [118]. Additionally, the quality of life in those on permanent oxygen is severely reduced.

The third option (above) is positively responsive in some patients, as sleep apnea is common. It represents a sort of intermittent hypoxia possibly associated with inflammation [83]. Further studies are needed in this area, as the higher Hb in PEH represents a more elevated "ORP" for apnea episodes (as evidenced with the extended breath-holding times Figure 10) [5], which is favorable in our criteria. The fourth option is the most practical, economical, and physiological solution, provided the underlying causes of hypoxemia are treated. They are free to move around and even do exercise. EPO is elevated in these patients. This hormone becomes an additional protective factor by stimulating the increase of the RBC count, by its neuroprotective properties, and by heart muscle protection factors [55, 56]. Likewise, EPO elevation is associated with increased Nitric Oxide and angiogenesis [119], which could explain why several of these patients tend to have normal to low blood pressures even while living in Cerro de Pasco 5,100 m. No relationship was found between PEH and a higher incidence of hypertension [120]. Apparently, most patients with PEH who developed a stroke at high altitude also had high blood pressure, and all patients with PEH who developed a stroke presented comorbidities well known to cause stroke at sea level [121]. As such, high blood pressure is a known cause of stroke at all altitudes but with a lower incidence at high altitude [122]. A recent study has shown a lower incidence of stroke in the general population at high altitudes [123]. Although more data is required, it seems that several feared complications from having a higher blood viscosity are actually questionable. Heart disease may actually be the source of hypoxia instead of the consequence, as seen in cardiac arrhythmia, in some patients with PEH. The evolution towards a picture of heart failure depends on the underlying disease but is not frequent. Our observations are confirmed in a recent study at the La Rinconada, Peru 5,100 m, where no correlation between the degree of PEH and cardiac insufficiency was found [120].

Circulation time in PEH patients does not differ from the healthy [105]. Longevity was found to be higher as altitude increases in Bolivia [98]. With an adequate treatment of the underlying diseases, PEH patients usually live a long time and do not present progressive deterioration unless the baseline disease progresses. It is well known in our city of La Paz, Bolivia, that chronic cigarette smokers can have a Ht of 75 % for over 30 years. They continue to live normal lives, several despite avoiding quitting smoking. It may be that as lung cancer is less frequent at high altitude, chronic smokers live long enough and do not find a reason to quit [124].

Treatment

Regarding treatment, there are different concepts but they have to be taken carefully on an individual basis. Adequate treatment is dependent upon adequate diagnosis. As long as CMS is erroneously regarded as a single disease secondary solely to life in the hypoxic environment, treatment will be focused on reducing the Ht and Hb, as they are seen as harmful and deleterious side effects. As such, some suggest following a red-meat-free diet as meat is considered a source of "excessive" vitamin B-12 and iron in an attempt to prevent the increase in RBCs. The naïve logic behind this is that if the organism is deprived of the essential nutrients for RBC formation, RBCs will decrease, assuming the environment triggers an excess of EPO. This position can lead to a certain degree of malnutrition and weakness that eventually complicates the condition, just as it does in patients with COPD [125]. Furthermore, it reduces the oxygen transport capacity and the blood "ORP", which are fundamental during sleep apnea at high altitude a expressed before.

Other colleagues follow the old concept of periodic phlebotomy to reduce RBCs due to increased blood viscosity, which would generate a series of theoretical and unproven complications such as heart failure and varicose veins, CVA, gout, etc. It is important to note that these patients do not

necessarily seem to have a higher incidence of CVA [121]. However, without diagnosing the cause of hypoxemia, if high altitude is considered the only variable responsible for this RBC rise, the fear of PEH-derived complications gives rise to the systematic "need" to decrease the detrimental "excess RBCs". Therefore, phlebotomy is thought to be a symptomatic non-curative treatment. In reality, it induces an organism imbalance, increasing ventilation and producing tachycardia, assuming an analogy to physiological responses to hemorrhagic shock as lifesaving compensating mechanisms to fight bleeding. In the later, it is a desperate biologic attempt to provide oxygenation to the tissues. Following the phlebotomy a few weeks afterward, there is an eventual, inevitable return to the increase of RBCs, seeking the organism a constant optimal balance [13]. Frequent phlebotomies cause stress, dyspnea, metabolic disorders, discomfort, adynamia, fatigue, poor tolerance to exercise, and even a peculiar greenish skin color. Sadly, these medieval period practices still continue in several places at high altitudes due to the poor understanding of the vital role of increased RBCs in multiple diseases [126]. This has to be stopped.

Some patients in Bolivia, quite unfortunately and despite regulations, continue to be prescribed phenylhydrazine, an internationally banned hemolytic drug that generates continuous hemoglobinuria [24]. The latter stains their underwear with brown color urine, inducing nephropathy, toxic hepatitis, and eventual inflammation of the endothelium. Those patients are checked periodically for the Ht, which is reduced (temporarily pleasing the patients and physicians), unfortunately resulting in severe consequences. The Pan American Health Organization (PAHO) banned this toxic medication because it can lead to death. Death is not commonly a consequence of the initial PEH pathology, but instead, secondary to the therapy itself and, as such, it has been defined as iatrogenic [24, 28]. In the past, some have even used radioactive phosphorus as used in the treatment in PV [127] in an attempt to destroy RBC with unfortunate consequences in Bolivia. Other suggested treatments included: progesterone with the idea of inducing hyperventilation [128], but it resulted in some males acquiring female traits and reducing their libido, so it was discarded or did not seem to improve the condition. Acetazolamide, commonly prescribed by others in AMS, has also been proposed, but this inhibitor of carbonic anhydrase taken regularly due to its diuretic effects can lead to dehydration and increase the risk of stroke. A recent study of prolonged use of acetazolamide showed a reduction of the Ht. However, it also produced metabolic acidosis and several side-effects, including death after the 2nd day of treatment in one subject, which was assumed to be another cause by the authors [129]. We believe these types of treatments are a desperate attempt to reduce the Ht due to the lack of understanding of the underlying pathology and the compensating effect of PEH. As far as we know, we do not know of the regular use of acetazolamide at high altitude, most probably due to its side effects and no long-term studies. We would never use such treatments as they are mostly theoretical and lack evidence-based publications.

The acid-base status with a perfect balance at any altitude maintaining a pH of 7.4 for optimal cellular function is absolutely essential [130]. A perfect Acid-Base balance allows climbers to reach even the summit of Mount Everest [131]. Some have also suggested using Sildenafil to reduce pulmonary hypertension, giving rise to reducing RBCs, but this was never proven. Others have suggested the use of Atorvastatin along with phlebotomies [132], hoping to reduce the RBCs count, but in our experience with several patients who had followed this treatment, it had not been effective, as the underlying causes were not treated and they continued to present hypoxemia. In any case, if PEH is a sign and not a disease by itself, attempting to treat it is like trying to treat jaundice instead of hepatitis or obstructive cholelithiasis, or the newborn blood incompatibility.

The treatment in other pathologies at sea level in studies with carbamylated EPO (CEPO) and Asialo EPO, which are EPO derivatives with loss of hematopoietic function, but fully organ-protective properties has been suggested [47]. Furthermore, EPO crosses the blood-brain barrier, and they demonstrated, by using rodent animal models, that EPO in the brain is a potent stimulator of ventilation, both under normoxic and hypoxic conditions [40, 47].

Other treatments such as Yoga and breathing exercises were also suggested. Consequently, the treatment should be focused on a precise diagnosis of the underlying hypoxemia-inducing disease. The disease needs to be treated, and this could be with the use of antibiotics, good hydration, antiplatelet aggregation factors (if hypercoagulability would be proven), adequate nutrition based on a sufficient amount of vitamin B-12, and iron. The latter can be achieved with a red meat diet, seeking to improve the quality and function of the RBCs. Exercise is fundamental as it stimulates circulation. Varicose veins should be treated, as well as vasculitis. Pulmonary rehabilitation with an increased Positive End Expiratory Pressure (PEEP) to induce opening of nonfunctioning alveoli, likewise. Adequate oral hydration should be stressed as dehydration is an important cause of coagulation disorders. Smokers should quit smoking. Patients suffering from renal artery constriction can be candidates for arterial bypass surgery. For those with uneven ventilation, a pulmonary surgery in order to extract shunting areas should be considered. However, this requires advanced technology to diagnose and treat properly. Cardiac pacemakers can be implanted in those with PEH-inducing arrhythmias. Cardiac surgery can be performed in those suffering from intracardiac shunts. Patients

who have diaphragmatic paralysis should do exercise. A case we treated went to live to a lower altitude of 2,500 m to improve and continues to be alive at over 90 years of age. Jobs with an increased risk of lung toxicity should be avoided or controlled adequately through the use of masks and other biosecurity measures.

Prevention

Quitting smoking decreases polycythemia at sea level [133]. These multiple pathologies at high altitude do not necessarily evolve into congestive heart failure [120]. Knowing the causes of Ht/Hb/RBCs elevation is essential for the diagnosis of the underlying pathologies. These should be diagnosed and treated as complications as they are rarely due to Ht elevation solely. The diagnosis and efficient treatment of pulmonary pathologies can prevent the presentation of scar sequelae (localized fibrosis) that lead to diffusion disorders and alteration in ventilation/perfusion. Certain cardiac arrhythmias can be corrected with the implantation of a pacemaker. Ventilation disorders of the upper respiratory tract may improve with appropriate treatment (e.g., nasal surgery, uvula surgeries, weight loss). Central hypoventilation disorders with sleep apnea can improve with CPAP. The subjects that present poly-erythrocythemia in the family carry genetic characteristics that need to be studied. Still, nevertheless, most patients adapt to life at high altitude with their elevated Ht/Hb levels. Regular exercise, avoiding malnutrition, and inhalation of dust particles and/or exposure to allergens arising from plants, animals, or chemicals are transcendental strategies to prevent these disorders' progression and negative evolution. These patients, if properly treated, can expand their life span. A healthy lifestyle, nutrition, and avoiding jobs or hobbies that compromise oxygen transport should be prioritized. Using adequate airway filter protection to prevent lung toxicity, i.e., mining (dust and metals; silicosis), painting and aerosols (chemicals), metal or ceramic pottery, sowing (inhaled fabrics), and avoiding other jobs that increase the risk of developing pneumoconiosis, and those where the airways are not protected from toxic particles, are recommended. Anesthesiologists should avoid inhalation of anesthetics which can lead to interstitial pulmonary fibrosis and even lung cancer.

The application of the knowhow of PEH to COVID-19

In the COVID-19 pandemic, the pneumolysis (destruction of alveoli) produced by the CoV-2 alveolar attack and intense inflammation can result in the formation of pulmonary fibrosis [53]. This reduces the gas exchange area and will require the most efficient compensation for a pulmonary insufficiency through PEH following the Oxygen Transport Triad mechanism [39]. Most of those who have received invasive ventilation through mechanical ventilators, due to the poor understanding of the disease, presented significant lung damage if they were able to survive. To use increased PEEP pressures in fragile lung tissue due to pneumolysis (described as the destruction of the lung) was most deleterious [53, 134]. Those patients should not have phlebotomies as PEH is the most energy-efficient compensation of disease with chronic hypoxemia. Sea-level patients with the post-COVID-19 disease are subjects no longer breathing at sea level but rather at a simulated high altitude due to the reduction of the gas exchange surface area (Figure 9). Hence, following the physiological response to chronic hypoxia, we hypothesized they would present PEH. This is not bad for them; it is merely a physiological survival mechanism and should be well understood. Pulmonary insufficiency gives rise to a compensating increase of the Ht/Hb/RBCs in the same way that going to high altitude induces erythropoiesis [13]. Dehydration should be systematically controlled. It is interesting to note that low EPO levels are predictors of poor prognosis of COVID-19 at high altitude [135]. It is also noteworthy to point out that several of our patients at high altitude increase their Ht, post COVID-19. Phlebotomies should definitely not be practiced, and they should be well hydrated.

Furthermore, it is noteworthy that there are lower death rates due to COVID-19 at high altitude, in Bolivia and Peru [136] and for us, this is due in part to the favorable effects of higher Ultra-Violet radiation and many other factors (including and increase of Ht/Hb/RBCs) at high altitude [137, 138]. However, those higher Hts, and higher EPO levels during the critical hypoxemia due to pneumolysis, represent a jewel as a higher Hb implies an increased "ORP", as a resource for survival while inflammation decreases [53, 112]. Noteworthy is the advantage of a higher baseline Ht during hyperoxic treatment, which gives rise to a higher CaO_2 [53]. In a recent paper, it is confirmed that in the high-altitude cities in the Andes in four countries and Mexico there was a significantly lower Case Fatality Rate due to COVID-19 [139].

Limitations of this article are the lack of space in order to include many comments and observations regarding many findings in CMS molecular and physiological articles, but these will be dealt with in a forthcoming publication. Additionally, some PEH pathologies of unknown cause can be found, but with time those will be properly diagnosed as scientific knowhow improves. CMS is a complex subject due

to its multiple presentations in a chronic hypoxia environment. The limitations of the adequate interpretation of these multiple pathologies are related to the possibilities of diagnosis. It would be ideal to have an advanced laboratory at a high altitude to search for Hb variations, for respiratory center and carotid body disfunction and alterations in oxygen and carbon dioxide sensors in respiratory center malfunctions. A further limitation is the possibility of diagnosis of a possible alteration of the mitochondrial function within the carotid sensors.

Conclusions

This article is born as an absolute necessity to present a different standing of CMS with the hope of improving the quality of life of those suffering these alterations in the chronic hypoxia environment found at high altitude. Based on the clinical practice, the terminology used to describe these multiple pathologies (not a single entity) is analyzed arriving to the conclusion that the increase of Hb/Ht/RBCs, PEH is fundamentally a "sign" in medicine, analogous to jaundice (that results from multiple hepatic and hematologic alterations), and is not a disease in itself. The normal values of the increase of Hb/Hb/RBCs have to be altitude specific with different degrees such as mild, moderate or severe, rejecting the idea of a fixed value for males and females to diagnose as CMS at any altitude as is the current trend. It is proposed that it should not be referred to CMS but rather as CMSs. Finally, the symptomatology is presented in order to simplify and further understand chronic disease in a hypoxic environment and its future application of the know-how of PEH in multiple diseases, even at sea level, as is the case of COVID-19.

Future perspective

With this article, the outlook for the improved understanding and medical care of those suffering from CMSs around the world, can improve significantly. Advanced diagnostic centers can be set up and patients will no longer be submitted to phlebotomies or different treatments that in the end are ineffective and even can reduce their lifespan. It will further serve humanity boosting the understanding of tolerance to hypoxia for healthy individuals and also for those with disease at high altitude. It will also help understand the physiological response to a reduced oxygen pressure and even help in the establishment of colonies in space, where a chronic hypoxia environment has many advantages in reducing energy expenditure and boosting biological survival possibilities.

Supplementary Materials

The following supporting information can be found: Figure S1: The Triple Hypoxia Syndrome.

Acknowledgments: The author is greatly indebted to the late Prof. Dr. Gustavo Zubieta-Castillo, founder of the High Altitude Pulmonary and Pathology Institute in La Paz, Bolivia, the first high altitude clinic globally, 52 years ago (July 9th, 1970). We transmit his ideas and pathophysiological concepts of Poly-ErythrocytHemia (PEH), a term he invented as a product of his extensive experience. He was a physiologist and clinician was born, lived, and worked at high altitude during practically all his 90 years of highly productive and creative life, treating patients with these diseases [105]. He started as an evaluator of pulmonary incapacity in the Bolivian tin miners at the Caja Nacional de Seguridad Social. The author specially thanks Natalia Zubieta-DeUrioste for all her analysis, critical thinking, suggestions, and writing advice. She could not be a co-author as she is doing her Ph.D. in neuroscience and has no time to contribute to the final form. To Lucrecia De Urioste and Rafaela Zubieta for their encouragement and support.
Research ethics: Not applicable.
Informed consent: Not applicable.
Author contributions: The author accepts responsibility for the entire content of this manuscript and approved its submission.
Competing interests: The author states no conflict of interest.
Research funding: None declared.
Data availability: Not applicable.

References

1. Zubieta-Calleja G. 1st world congress on high altitude medicine and physiology [Internet]. International Society for Mountain Medicine Newsletter. 1994. Vol. 4 Number 4. Available from: https://www.altitudeclinic.com/congress.html.
2. Zubieta-Castillo G, Zubieta-Calleja G. New concepts on chronic mountain sickness. Acta Andin 1996;1.
3. León-Velarde F, Maggiorini M, Reeves JT, Aldashev A, Asmus I, Bernardi L, et al. Consensus statement on chronic and subacute high altitude diseases. High Alt Med Biol 2005. https://doi.org/10.1089/ham.2005.6.147.
4. Zubieta-Castillo G, Zubieta-Calleja G. Chronic Mountain sickness discussion part 1 [Internet]; 2010 [cited 2021 Mar 20]. Available from: http://altitudeclinic.com/blog/2010/07/chronic-mountain-sickness-discussion-part-1/.
5. Zubieta-Castillo G, Gustavo, Zubieta-Calleja G, Zubieta-Calleja L. Pulse oximetry in chronic mountain sickness – long breath holding time & oscillation at lowest saturation. In: Ohno H, Kobayashi T, Masuyama S, Nakashima MI, editors. Progress in Mountain Medicine and high altitude physiology. Matsumoto, Japan: Press Committe of the 3rd

World Congress on Mountain Medicine and High Altitude Physiology; 1998:349–54 pp.
6. Zubieta-Castillo G, Zubieta-Calleja GR, Arano E, Zubieta-Calleja L. Respiratory disease, chronic mountain sickness and gender differences at high altitude. In: Ohno H, Kobayashi T, Masuyama S, Nakashima M, editors. Progress in Mountain Medicine and high altitude physiology. Matsumoto, Japan: Japanese Society of Mountain Medicine 3rd World Congress on Mountain Medicine and Physiology; 1998:132–7 pp.
7. Zubieta-Calleja GR, Paulev PE, Zubieta-Calleja L, Zubieta-Calleja N, Zubieta-Castillo G. Hypoventilation in chronic mountain sickness: a mechanism to preserve energy. J Physiol Pharmacol 2006;57:425–30.
8. Zubieta-Castillo GR, Zubieta-Calleja GR, Zubieta-Calleja L. Chronic mountain sickness: the reaction of physical disorders to chronic hypoxia. J Physiol Pharmacol 2006;57:431–42.
9. Monge MC. La enfermedad de los Andes (Síndromes eritrémicos). An la Fac Med 1928;14.
10. England JM, Ward SM, Down MC. Microcytosis, anisocytosis and the red cell indices in iron deficiency. Br J Haematol 1976;34:589–97.
11. An X, Mohandas N. Disorders of red cell membrane. Br J Haematol 2008:367–75. https://doi.org/10.1111/j.1365-2141.2008.07091.x.
12. Faeh D, Gutzwiller F, Bopp M. Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. Circulation [Internet] 2009 [cited 2021 Jun 29];120:495–501.
13. Zubieta-Calleja GR, Paulev PE, Zubieta-Calleja L, Zubieta-Castillo G. Altitude adaptation through hematocrit changes. J Physiol Pharmacol 2007;58:811–8.
14. Papoušek F, Sedmera D, Neckář J, Ošťádal B, Kolář F. Left ventricular function and remodelling in rats exposed stepwise up to extreme chronic intermittent hypoxia. Respir Physiol Neurobiol 2020;282. https://doi.org/10.1016/j.resp.2020.103526.
15. Zubieta-Calleja G. Adaptation, genetic adaptation, physiological adaptation, intelligence, and Biospaceforming [Internet]; 2020. Available from: http://altitudeclinic.com/blog/2020/12/adaptation-genetic-adaptation-physiological-adaptation-intelligence-and-biospaceforming/.
16. Julian CG. Epigenomics and human adaptation to high altitude. J Appl Physiol 2017;123:1362–70.
17. Frisancho AR. Developmental functional adaptation to high altitude: review. Am J Hum Biol 2013;25:151–68.
18. Storz JF, Scott GR. Life ascending: mechanism and process in physiological adaptation to high-altitude hypoxia. Annu Rev Ecol Evol Syst 2019;50:503–26.
19. Alfrey CP, Rice L, Udden MM, Driscoll TB. Neocytolysis: physiological down-regulator of red-cell mass. Lancet [Internet]. 1997 [cited 2022 Aug 31];349:1389–90.
20. Trudel G, Shahin N, Ramsay T, Laneuville O, Louati H. Hemolysis contributes to anemia during long-duration space flight. Nat Med 2022 [Internet]. 2022 Jan 14 [cited 2022 Aug 31];28:59–62.
21. Zubieta-Calleja G. Human adaptation to high altitude and to sea level: acid-base equilibrium, ventilation and circulation in chronic hypoxia. Saarbrücken, Germany: VDM Verlag Dr. Müller; 2010.
22. Rosove MH, Perloff JK, Hocking WG, Child JS, Canobbio MM, Skorton DJ. Chronic hypoxaemia and decompensated erythrocytosis in cyanotic congenital heart disease. Lancet 1986;328:313–5.
23. Gordeuk VR, Key NS, Prchal JT. Re-evaluation of hematocrit as a determinant of thrombotic risk in erythrocytosis. Haematologica 2019;104:653–8.
24. Zubieta-Calleja GR, Zubieta-Castillo G, Zubieta-Calleja L. Inadequate treatment of excessive erythrocytosis. Acta Andin 1995;4. [Internet]. Available from: https://www.altitudeclinic.com/fenilhi2.html.
25. Pacak K, Jochmanova I, Prodanov T, Yang C, Merino MJ, Fojo T, et al. New syndrome of paraganglioma and somatostatinoma associated with polycythemia. J Clin Oncol 2013;31:1690–8.
26. Peñaloza D, Arias Stella J. Corazón y circulación pulmonar en grandes alturas: nativos normales y mal de montaña crónico. Rev Peru Cardiol. 2011;37:38–56.
27. Zubieta-Castillo, G & Zubieta-Calleja G Loss of adaptation and Maladaptation: two terms inadequately used – Conversely – "Adaptation": a fundamental law of biology that at high altitude, even permits life at the hypoxic levels of Mt. Everest. In: The Lung at high altitude: from cellular acclimatization to clinical disease [Internet]. 2012. p. 6. Available from: https://www.researchgate.net/publication/313560385_loss_of_adaptation_and_maladaptation_two_terms_inadequately_used.
28. Zubieta-Calleja GR, Zubieta-Castillo G. High altitude pathology at 12,000 ft. La Paz, Bolivia: Papiro; 1989.
29. Zubieta-Calleja GR. High altitude residents in Bolivia. In: Progress in Mountain Medicine and high altitude physiology [Internet]; 1997: 185–9 pp. Available from: https://www.researchgate.net/publication/236259964_High_altitude_residents_in_Bolivia_Progress_in_Mountain_Medicine_and_High_Altitude_Physiology.
30. Cafaro RP. Hypoxia: its causes and symptoms. J Am Dent Soc Anesthesiol 1960;7:4–8.
31. Sarkar M, Niranjan N, Banyal PK. Mechanisms of hypoxemia. Lung India 2017;34:47–60.
32. Iturriaga R, Del Rio R, Idiaquez J, Somers VK. Carotid body chemoreceptors, sympathetic neural activation, and cardiometabolic disease. Biol Res 2016;49. https://doi.org/10.1186/s40659-016-0073-8.
33. Jefferson JA, Escudero E, Hurtado ME, Kelly JP, Swenson ER, Wener MH, et al. Hyperuricemia, hypertension, and proteinuria associated with high-altitude polycythemia. Am J Kidney Dis 2002;39:1135–42.
34. Kalotychou V, Tzanetea R, Konstantopoulos K, Papassotiriou I, Rombos I. Erythrocytosis due to a combination of the high oxygen affinity hemoglobin variant, Hb olympia [β20(B2)Val→Met] with β- and α-Thalassemia mutations: first case in the literature. Hemoglobin 2010;34:383–8.
35. Deyell R, Jackson S, Spier S, Le D, Poon MC. Low oxygen saturation by pulse oximetry may be associated with a low oxygen affinity hemoglobin variant, hemoglobin Titusville. J Pediatr Hematol Oncol 2006;28:100–2.
36. Hasegawa H. Current status of pulmonary thromboembolism incidence, diagnosis, classification, pathogenesis, and treatment. Jpn Circ J 1984;48:100–10.
37. Naeije R. Physiological adaptation of the cardiovascular system to high altitude. Prog Cardiovasc Dis 2010;52:456–66.
38. Savourey G, Launay JC, Besnard Y, Guinet A, Travers S. Normo- and hypobaric hypoxia: are there any physiological differences? Eur J Appl Physiol 2003;89:122–6.
39. Zubieta-Calleja G, Zubieta-DeUrioste N. The oxygen transport triad in high-altitude pulmonary edema: a perspective from the high Andes. Int J Environ Res Publ Health 2021;18:7619, Available from: https://www.mdpi.com/1660-4601/18/14/7619/htm.
40. Marti HH. Erythropoietin and the hypoxic brain. J Exp Biol 2004;207. https://doi.org/10.1242/jeb.01049.
41. Arcasoy MO. Non-erythroid effects of erythropoietin. Haematologica 2010;95. https://doi.org/10.3324/haematol.2010.030213.
42. Kakavas S, Demestiha T, Vasileiou P, Xanthos T. Erythropoetin as a novel agent with pleiotropic effects against acute lung injury. Eur J Clin Pharmacol 2011;67:1–9.

43. Zhang Y, Zhu X, Huang X, Wei X, Zhao D, Jiang L, et al. Advances in understanding the effects of erythropoietin on renal fibrosis. Front Med 2020;7. https://doi.org/10.3389/fmed.2020.00047.
44. Brito J, Siqués P, León-Velarde F, De La Cruz JJ, López V, Herruzo R. Chronic intermittent hypoxia at high altitude exposure for over 12 years: assessment of hematological, cardiovascular, and renal effects. High Alt Med Biol 2007;8:236–44.
45. Joyeux-Faure M, Godin-Ribuot D, Ribuot C. Erythropoietin and myocardial protection: what's new? Fundam Clin Pharmacol 2005. https://doi.org/10.1111/j.1472-8206.2005.00347.x.
46. Heitrich M, García DMde los Á, Stoyanoff TR, Rodríguez JP, Todaro JS, Aguirre MV. Erythropoietin attenuates renal and pulmonary injury in polymicrobial induced-sepsis through EPO-R, VEGF and VEGF-R2 modulation. Biomed Pharmacother 2016;82:606–13.
47. Soliz J, Joseph V, Soulage C, Becskei C, Vogel J, Pequignot JM, et al. Erythropoietin regulates hypoxic ventilation in mice by interacting with brainstem and carotid bodies. J Physiol. 2005;568:559–71.
48. Zubieta-Calleja GR, Paulev PE, Zubieta-Calleja L, Zubieta-Calleja N, Zubieta-Castillo G. Hypoventilation in Chronic Mountain Sickness: a mechanism to preserve energy. J Physiol Pharmacol 2006;57:425–30.
49. Malenica M, Prnjavorac B, Bego T, Dujic T, Semiz S, Skrbo S, et al. Effect of cigarette smoking on haematological parameters in healthy population. Med Arch 2017;71:132–6.
50. Aitchison R, Russell N. Smoking – a major cause of polycythaemia. J R Soc Med 1988;81:89–91.
51. Zubieta-Calleja GR, Zubieta-DeUrioste N. High altitude pulmonary edema, high altitude cerebral edema, and acute mountain sickness: an enhanced opinion from the high Andes – La Paz, Bolivia 3,500 m. Rev Environ Health [Internet] 2022. [cited 2022 May 31];0(0). Available from: https://www.degruyter.com/document/doi/10.1515/reveh-2021-0172/html.
52. Zubieta-Castillo G, Zubieta-Calleja G. Triple hypoxia syndrome. In: High altitude pathology at 12000 ft [Internet]. Imprenta publicidad Papiro; 1989:41–50 pp. Available from: https://www.altitudeclinic.com/thsart.htm.
53. Zubieta-Calleja GR, Zubieta-DeUrioste N, Venkatesh T, Das K, Soliz J. COVID-19 and pneumolysis simulating extreme high-altitude exposure with altered oxygen transport physiology; multiple diseases, and scarce need of ventilators: andean Condor's-eye-view. Rev Recent Clin Trials 2020;15:347–59.
54. Hancco I, Bailly S, Baillieul S, Doutreleau S, Germain M, Pépin JL, et al. Excessive erythrocytosis and Chronic Mountain Sickness in dwellers of the highest city in the world. Front Physiol 2020;11:773.
55. Ehrenreich H, Weissenborn K, Begemann M, Busch M, Vieta E, Miskowiak KW. Erythropoietin as candidate for supportive treatment of severe COVID-19. Mol Med 2020;26:58.
56. Soliz J, Schneider-Gasser EM, Arias-Reyes C, Aliaga-Raduan F, Poma-Machicao L, Zubieta-Calleja G, et al. Coping with hypoxemia: could erythropoietin (EPO) be an adjuvant treatment of COVID-19? Respir Physiol Neurobiol 2020;279:103476.
57. Wajcman H, Galactéros F. Hemoglobins with high oxygen affinity leading to erythrocytosis. New variants and new concepts. Hemoglobin 2005;29:91–106.
58. Painschab MS, Malpartida GE, Dávila-Roman VG, Gilman RH, Kolb TM, León-Velarde F, et al. Association between serum concentrations of hypoxia inducible factor responsive proteins and excessive erythrocytosis in high altitude Peru. High Alt Med Biol 2015;16:26–33.
59. Wu T, L W, Y L, Rl G, Q C, Z W, et al. Epidemiology of chronic mountain sickness: ten years study in Quingai–Tibet. In: Ohno H, Kobayashi K, Masuyama SNM, editors. Progress in Mountain Medicine and high altitude physiology. Japan: Press Committee of the Third World Congress; 1998:120–5 pp.
60. Sahota IS, Panwar NS. Prevalence of Chronic Mountain Sickness in high altitude districts of Himachal Pradesh. Indian J Occup Environ Med 2013;17:94–100.
61. Jiang C, Chen J, Liu F, Luo Y, Xu G, Shen HY, et al. Chronic mountain sickness in Chinese Han males who migrated to the Qinghai-Tibetan plateau: application and evaluation of diagnostic criteria for chronic mountain sickness. BMC Publ Health 2014;14. https://doi.org/10.1186/1471-2458-14-701.
62. Healy K, Labrique AB, Miranda JJ, Gilman RH, Danz D, Davila-Roman VG, et al. Dark adaptation at high altitude: an unexpected pupillary response to chronic hypoxia in Andean highlanders. High Alt Med Biol 2016;17:208–13.
63. Vyas KJ, Danz D, Gilman RH, Wise RA, León-Velarde F, Miranda JJ, et al. Noninvasive assessment of excessive erythrocytosis as a screening method for Chronic Mountain Sickness at high altitude. High Alt Med Biol 2015;16:162–8.
64. Rivera-Ch M, León-Velarde F, Huicho L. Treatment of chronic mountain sickness: critical reappraisal of an old problem. Respir Physiol Neurobiol 2007;158:251–65.
65. Jefferson JA, Escudero E, Hurtado ME, Pando J, Tapia R, Swenson ER, et al. Excessive erythrocytosis, chronic mountain sickness, and serum cobalt levels. Lancet 2002;359:407–8.
66. Zubieta-Castillo G, Moretti M, Zubieta-Calleja GR. The P-50 of the hemoglobin oxygen dissociation curve of the Chipayas: a 2000 year high altitude dweller bolivian ethnic group. In: Wilderness and environmental medicine selected abstracts from the Symposium on the effects of chronic hypoxia on diseases at high altitude, 2008, La Paz, Bolivia. 2008. [Internet]. Available from: https://www.researchgate.net/publication/284349622_The_P-50_of_the_hemoglobin_oxygen_dissociation_curve_of_the_Chipayas_A_2000_year_high_altitude_dweller_bolivian_ethnic_group.
67. Buroker N, Ning XH, Zhou ZN, Li K, Cen WJ, Wu XF, et al. SNPs, linkage disequilibrium, and chronic mountain sickness in Tibetan Chinese. Hypoxia 2017;5:67–74.
68. Villafuerte FC, Corante N. Chronic Mountain sickness: clinical aspects, etiology, management, and treatment. High Alt Med Biol 2016;17:61–9.
69. Wolinsky CD, Waldorf H. Chronic venous disease. Med Clin 2009;93:1333–46.
70. Kline JA, Courtney DM, Kabrhel C, Moore CL, Smithline HA, Plewa MC, et al. Prospective multicenter evaluation of the pulmonary embolism rule-out criteria. J Thromb Haemostasis 2008;6:772–80.
71. Malik AB. Pulmonary microembolism. Physiol Rev 1983;63:1114–207.
72. Pagnamenta A, Vanderpool R, Brimioulle S, Naeije R. Proximal pulmonary arterial obstruction decreases the time constant of the pulmonary circulation and increases right ventricular afterload. J Appl Physiol 2013;114:1586–92.
73. Lyhne MD, Kline JA, Nielsen-Kudsk JE, Andersen A. Pulmonary vasodilation in acute pulmonary embolism – a systematic review. Pulm Circ [Internet]. 2020 [cited 2024 May 5];10:1–16.
74. Basak N, Norboo T, Mustak MS, Thangaraj K. Heterogeneity in hematological parameters of high and low altitude Tibetan populations. J Blood Med [Internet]. 2021 [cited 2024 May 5];12:287–98.
75. Levin M. Classification and diagnosis of primary headache disorders. Semin Neurol [Internet]. 2022 [cited 2024 May 5];42:406–17.
76. Manzoni GC, Stovner LJ. Epidemiology of headache. Handb Clin Neurol 2010;97:3–22.

77. Stovner LJ, Hagen K, Jensen R, Katsarava Z, Lipton RB, Scher AI, et al. The global burden of headache: a documentation of headache prevalence and disability worldwide. Cephalalgia 2007;3:193–210.
78. Burch RC, Loder S, Loder E, Smitherman TA. The prevalence and burden of migraine and severe headache in the United States: updated statistics from government health surveillance studies. Headache 2015;55:21–34.
79. Ho KH, Ong BKC. A community-based study of headache diagnosis and prevalence in Singapore. Cephalalgia 2003;23:6–13.
80. Bhatt JM, Lin HW, Bhattacharyya N. Prevalence, severity, exposures, and treatment patterns of Tinnitus in the United States. JAMA Otolaryngol – Head Neck Surg. 2016;142:959–65.
81. Kerkhof GA. Epidemiology of sleep and sleep disorders in The Netherlands. Sleep Med 2017;30:229–29.
82. San T, Polat S, Cingi C, Eskiizmir G, Oghan F, Cakir B. Effects of high altitude on sleep and respiratory system and theirs adaptations. Sci World J 2013;2013:241569.
83. Sun S, Oliver-Pickett C, Ping Y, Micco AJ, Droma T, Zamudio S, et al. Breathing and brain blood flow during sleep in patients with chronic mountain sickness. J Appl Physiol 1996;81:611–8.
84. Terzikhan N, Verhamme KMC, Hofman A, Stricker BH, Brusselle GG, Lahousse L. Prevalence and incidence of COPD in smokers and non-smokers: the Rotterdam study. Eur J Epidemiol 2016;31:785–92.
85. Zubieta-Calleja GR, Ardaya G, Zubieta N, Paulev PE, Z-C G. Tolerance to hypoxia [Internet]. J Fisiol 2013;59:65–71. Available from: https://zuniv.net/pub/TolerancetoHypoxiaFiziol.pdf.
86. Engelfriet PM, Duffels MGJ, Möller T, Boersma E, Tijssen JGP, Thaulow E, et al. Pulmonary arterial hypertension in adults born with a heart septal defect: the euro heart survey on adult congenital heart disease. Heart 2007;93:682–7.
87. Earwood JS, Thompson TD. Hemoptysis: evaluation and management. Am Fam Physician 2015;91:243–9.
88. Larici AR, Franchi P, Occhipinti M, Contegiacomo A, del Ciello A, Calandriello L, et al. Diagnosis and management of hemoptysis. Diagn Interv Radiol 2014;20:299–309.
89. Bidwell JL, Pachner RW. Hemoptysis: diagnosis and management. Am Fam Physician 2005;72:1253–60.
90. Gifford TO, Orlandi RR. Epistaxis. Otolaryngol Clin 2008;41:525–36.
91. Rosenthal TC, Majeroni BA, Pretorius R, Malik K. Fatigue: an overview. Am Fam Physician 2008;78:1173–9.
92. Åkerstedt T, Knutsson A, Westerholm P, Theorell T, Alfredsson L, Kecklund G. Mental fatigue, work and sleep. J Psychosom Res 2004;57:427–33.
93. Mense S, Gerwin RD. Muscle pain: understanding the mechanisms. Berlin Heidelberg: Springer-Verlag; 2010:1–317 pp.
94. Tissot Van Patot MC, Bendrick-Peart J, Beckey VE, Serkova N, Zwerdlinger L. Greater vascularity, lowered HIF-1/DNA binding, and elevated GSH as markers of adaptation to in vivo chronic hypoxia. Am J Physiol Lung Cell Mol Physiol 2004;287:31–3.
95. Acosta C, Gloria JM, Lavaque A, García V, Torres E, Agüero C, et al. Relationship of geographic altitude with foveal avascular zone metrics and vascular density values assessed by OCT angiography. Ophthalmol Retina 2020;4:394–402.
96. Walter R, Maggiorini M, Scherrer U, Contesse J, Reinhart WH. Effects of high-altitude exposure on vascular endothelial growth factor levels in man. Eur J Appl Physiol 2001;85:113–7.
97. Zubieta-Calleja G, Zubieta-DeUrioste N, Venkatesh T, Das KK, Soliz J. COVID-19 and pneumolysis simulating extreme high-altitude exposure with altered oxygen transport physiology; multiple diseases, and scarce need of ventilators: Andean Condor's-eye-view. Rev Recent Clin Trials 2020;15:347–59.
98. Zubieta-Calleja G, Zubieta-DeUrioste N. Extended longevity at high altitude: benefits of exposure to chronic hypoxia. BLDE Univ J Health Sci. 2017;2:80–90.
99. Patil SM, Khodnapur JP, Das KK, Podder A. The role of serum erythropoietin (EPO) and vascular endothelial growth factor (VEGF) in pulse wave velocity (PWV) among hypertensive patients: a cross-sectional study. Cureus 2024;16:e62416. [Internet]. Available from:.
100. Zubieta-Castillo G, Zubieta-Calleja G Mal de Montaña Crónico y los Mineros. Cuad la Acad Nac Ciencias Boliv [Internet]. 1985;5:3–8.
101. Zubieta-Castillo G, Zubieta-Calleja GR. Facts that prove that adaptation to life at extreme altitude (8848m) is possible. In: Lukyanova NTL, editor. Adaptation biology and medicine: health potentials [Internet]. New Dehli, India; 2008:347–55 pp. Available from: https://www.researchgate.net/publication/236260003_Facts_that_Prove_that_Adaptation_to_Life_at_Extreme_Altitude_8848m_is_Possible.
102. Grocott MPW, Martin DS, Levett DZH, McMorrow R, Windsor J, Montgomery HE, et al. Arterial blood gases and oxygen content in climbers on Mount Everest. N Engl J Med 2009;360:140–9.
103. Pulm CCM. Guidelines in pulmonary & critical care [Internet]. 2020. Available from: https://pulmccm.org/pulmonary-and-critical-care-guidelines-clinical-practice-recommendations-ats-accp-bts-ers/.
104. Ma J, Ji L, Li Z, Liu H, Zhao C, Xiong H, et al. Downregulation of intrinsic apoptosis pathway in erythroblasts contributes to excessive erythrocytosis of chronic mountain sickness. Blood Cells. Mol Dis 2019;76:25–31.
105. Zubieta-Calleja GR, Zubieta-Castillo G, Paulev PE, Zubieta-Calleja L. Non-invasive measurement of circulation time using pulse oximetry during breath holding in chronic hypoxia. J Physiol Pharmacol 2005;56:251–6.
106. Zubieta-Calleja G, Urioste ND. A unique, intuitive, creative, innovative, bold scientist in endless quest of the truth and a giant in high-altitude medicine: Prof. Dr. Gustavo Zubieta-Castillo, "The Parvatha Guru" (May 20, 1926-September 17, 2015). BLDE Univ J Health Sci 2016;1:73.
107. Zubieta-Calleja GR, Zubieta-Castillo G, Zubieta-Calleja L, Zubieta-Calleja N. Exercise performance in chronic mountain sickness (CMS) patients at 3510m. High Alt Med Biol 2002;3:114–5.
108. Soria R, Egger M, Scherrer U, Bender N, Rimoldi SF. Pulmonary arterial pressure at rest and during exercise in chronic mountain sickness: a meta-analysis. Eur Respir J 2019;53. https://doi.org/10.1183/13993003.02040-2018.
109. Naeije R, Vanderpool R. Pulmonary hypertension and chronic mountain sickness. High Alt Med Biol 2013;14:117–25.
110. Zubieta-Castillo G. Forever: loss of adaptation does not exist [Internet]. Altitudeclinic.com; 2010. Available from: http://altitudeclinic.com/blog/2010/07/forever-loss-of-adaptation-does-not-exist/.
111. Zubieta-Castillo G, Zubieta-Calleja GR, Zubieta-Calleja L, Zubieta-Calleja N. Adaptation to life at the altitude of the summit of Everest. Fiziol Zh; 2003.
112. Zubieta-Calleja G, Zubieta-DeUrioste N. Pneumolysis and "silent hypoxemia" in COVID-19. Indian J Clin Biochem [Internet] 2020;36:112–6. Available from.
113. Zubieta-Castillo G, Zubieta-Calleja G. Enfermedades Pulmonares y Mal de Montaña Crónico. Cuad la Acad Nac Ciencias Boliv [Internet]. 1986;68:3–12.
114. Gassmann M, Mairbäurl H, Livshits L, Seide S, Hackbusch M, Malczyk M, et al. The increase in hemoglobin concentration with altitude varies among human populations. Ann N Y Acad Sci 2019;1450:204–20.

115. Patnaik MM, Tefferi A. The complete evaluation of erythrocytosis: congenital and acquired. Leukemia 2009;23:834–44.
116. Mangin O. High oxygen affinity hemoglobins. Rev Med Interne 2017; 38:106–12.
117. Sime F, Peñaloza D, Ruiz L. Bradycardia, increased cardiac output, and reversal of pulmonary hypertension in altitude natives living at sea level. Br Heart J 1971;33:647–57.
118. Higgins J. Pulmonary oxygen toxicity. Physiotherapy 1990;76:588–92.
119. Beleslin-Cokic BB, Cokic VP, Yu X, Weksler BB, Schechter AN, Noguchi CT. Erythropoietin and hypoxia stimulate erythropoietin receptor and nitric oxide production by endothelial cells. Blood 2004; 104:2073–80.
120. Verges S. Cardiovascular function and chronic mountain sickness in the highest city of the world. In: 7th chronic hypoxia Symposium [Internet]; 2019. Available from: http://zuniv.net/symposium7/Abstracts7CHS.pdf.
121. Zubieta-DeUrioste N. Polyerythrocythemia and cerebro-vascular accidents at different altitudes. Indian J Clin Biochem In: 15th Asia-Pacific federation for clinical biochemistry and laboratory medicine (APFCB) congress, 17–20 November, 2019, Jaipur, India; 2019:42 p.
122. Faeh D, Gutzwiller F, Bopp M, Swiss National Cohort Study Group. Lower mortality from coronary heart disease and stroke at higher altitudes in Switzerland. Circulation 2009;120:495–501.
123. Lazo-Porras M, Bernabe-Ortiz A, Gilman RH, Checkley W, Smeeth L, Miranda JJ. Population-based stroke incidence estimates in Peru: exploratory results from the CRONICAS cohort study. Lancet Reg Heal – Am [Internet]. 2022;5:100083., [cited 2021 Nov 16]. Available from: https://linkinghub.elsevier.com/retrieve/pii/S2667193X2100079X.
124. Hayes DP. Cancer protection related to solar ultraviolet radiation, altitude and vitamin D. Med Hypotheses 2010;75:378–82.
125. Scoditti E, Massaro M, Garbarino S, Toraldo DM. Role of diet in chronic obstructive pulmonary disease prevention and treatment. Nutrients 2019;11. https://doi.org/10.3390/nu11061357.
126. Zubieta-Calleja GR. Ode to the porters of oxygen in the new Millennium. Newsl Int Soc Mt Med [Internet] 2000;10:9–10.
127. Silver RT. Treatment of polycythemia vera. Semin Thromb Hemost 2006;32:437–42.
128. Kryger M, McCullough RE, Collins D, Scoggin CH, Weil JV, Grover RF. Treatment of excessive polycythemia of high altitude with respiratory stimulant drugs. Am Rev Respir Dis 1978;117:455–64.
129. Sharma S, Gralla J, Ordonez JG, Hurtado ME, Swenson ER, Schoene RB, et al. Acetazolamide and N-acetylcysteine in the treatment of chronic mountain sickness (Monge's disease). Respir Physiol Neurobiol 2017; 246:1–8.
130. Paulev PE, Zubieta-Calleja GR. Essentials in the diagnosis of acid-base disorders and their high altitude application. J Physiol Pharmacol 2005;56:155–70.
131. Zubieta-Calleja JG. Extremely high altitude hypoxic conditions during Mount Everest expeditions, residence at South Pole stations, in Tibet and among the Andes: Van Slyke equation modification is crucially important for acid–base measurements. J Biol Phys Chem 2012;12:103–12.
132. Amaru R, Villarroel M, Miguez H, Peñaloza R, Torres G, Barbui T, et al. Hematopoietic progenitor cells from patients with chronic mountain sickness lack the JAK2V617F mutation, show hypersensitivity to erythropoietin and are inhibited by statins. Blood 2009;114:1894.
133. Kurata C. Medical check-up findings characteristic of smokers: aimed at improving smoking cessation interventions by physicians. Intern Med 2006;45:1027–32.
134. Zubieta-Calleja GR, Zubieta-DeUrioste N, de Jesús Montelongo F, Sanchez MGR, Campoverdi AF, Rocco PRM, et al. Morphological and functional findings in COVID-19 lung disease as compared to Pneumonia, ARDS, and high-altitude pulmonary edema. Respir Physiol Neurobiol 2023;309:104000.
135. Viruez-Soto A, López-Dávalos MM, Rada-Barrera G, Merino-Luna A, Molano-Franco D, Tinoco-Solorozano A, et al. Low serum erythropoietin levels are associated with fatal COVID-19 cases at 4,150 m above sea level. Respir Physiol Neurobiol 2021;292:103709., [Internet]. [cited 2021 Jun 23].
136. Zubieta-Calleja G, Merino-Luna A, Zubieta-DeUrioste N, Armijo-Subieta NF, Soliz J, Arias-Reyes C, et al. Re: "Mortality attributed to COVID-19 in high-altitude populations" by Woolcott and Bergman. High Alt Med Biol 2021;22:102–4.
137. Zubieta-Calleja G. The advantages of ultraviolet radiation in controlling the coronavirus at high altitude [Internet]; 2020. [cited 2020 Jul 28]. Available from: http://altitudeclinic.com/blog/2020/04/u_v-radiation-covid-2-at-high-altitude/.
138. Zubieta-Calleja G, Zubieta-DeUrioste N. Sixteen possible scientific explanations in support of lower COVID-19 case fatality rate at high altitudes. [cited 2022 Feb 23]; Available from: https://osf.io/u5nyz/.
139. DeUrioste N, Reyes C, Sanchez L, Subieta N, Luna A, Solarte I, et al. COVID-19 mortality is attenuated at high tropical and subtropical altitude: an observational study of a database covering five Latin American countries. Med Res Arch 2023;11. https://doi.org/10.18103/mra.v11i8.4299, [cited 2024 Jan 14], Available from: https://esmed.org/MRA/mra/article/view/4299.

Supplementary Material: This article contains supplementary material (https://doi.org/10.1515/mr-2024-0036).