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Does chronic mountain sickness (CMS) have perinatal origins?

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Abstract

Chronic mountain sickness (CMS) occurs in ~10% of male high-altitude residents. It is characterized by hypoventilation and hypoxemia but its underlying cause remains unknown. We hypothesized that CMS' origins reside in exaggerated perinatal hypoxia that serves, in turn, to impair the development of pulmonary structure and/or respiratory control. As a preliminary test, we asked if birth weights were low and other signs of perinatal hypoxia were present in 12 young men with excessive erythrocytosis (EE, Hb ≥ 18.3 g/dL), a condition thought to be a preclinical phase of CMS. Their birth weights were uniformly low (2571 ± 243 g) and all but one demonstrated perinatal hypoxia as manifested either by being small for their gestational age (SGA, 8%), preterm (67%), born to a preeclamptic (PE) mother (50%), or diagnosed with neonatal hypoxia (83%). Impaired growth *in utero* has been shown to raise susceptibility to adult disease; these are the first data to demonstrate a possible influence of reduced fetal growth and/or exaggerated perinatal hypoxia on increasing the susceptibility to CMS. Future studies, with more detailed testing in larger samples of control as well as EE subjects, with longitudinal follow-up, are required to determine the role of perinatal hypoxia in the development of CMS.

Keywords: Birth weight; Hypoxia; High altitude; IUGR; SGA; Preeclampsia

1. Introduction

There is perhaps no one in the field of high-altitude physiology with a more distinguished genealogy than Carlos Monge Cassinelli, or "Choclo" as his many friends knew him. The name "Monge" is literally synonymous with chronic mountain sickness (CMS), the topic considered here, since his father Carlos Monge Medrano[1] was the first to describe this condition (Monge, 1925). Even today CMS is often referred to as "Monge Disease" (Medical Dictionary, 2004). Noteworthy is that it was a joint publication by Carlos Monge M. and Carlos Monge C. that helped spark the current generation's scientific interest in this still poorly-understood condition (Monge and Monge, 1966).

Choclo's scientific career was broad ranging. He addressed normal as well as abnormal ventilatory, hematological and metabolic responses to high altitude and also had an active interest in comparative physiology, publishing multiple papers on oxygen transport responses in Andean amphibians, rodents and birds. Fortunately, these contributions have been well reviewed elsewhere (Winslow and Monge, 1987; Hochachka, 1995; West, 2006).

Here, we review the physiological and clinical criteria for defining CMS. Next, we consider what is known regarding the trigger(s) for developing this disease and describe a new approach for understanding this still-enigmatic condition. Specifically, we ask if the origins of CMS arise from impaired development of pulmonary structure and/or respiratory control during perinatal life. Background information is provided concerning the importance of the fetal and neonatal/infant periods for diseases that become manifest later in life, or what has become known as "fetal programming" or the field of "developmental origins of adult disease" (Barker, 2001). We then present preliminary data suggesting that this new approach may be useful for understanding the origins of CMS. While the information available is necessarily preliminary, we think Choclo would

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[1] In Latin America, women do not commonly change their name with marriage and the infant commonly receives surnames from both parents, with the paternal surname being listed first. Usually, only the paternal surname is used, but sometimes the maternal surname follows or is abbreviated by its first letter.

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be pleased to know that new ideas are being applied in order to improve our understanding of CMS, the "Monge-family" disease.

2. Definition of CMS, "normal" and "optimal" hemoglobin

A recent consensus statement defines CMS as a clinical syndrome that occurs among lifelong or long-term residents of high altitude (≥2500 m or 8000 ft) "characterized by excessive erythrocytosis (hemoglobin [Hb] Hb ≥ 19 g/dL in females and Hb ≥ 21 g/dL males), severe hypoxemia, and in some cases moderate or severe pulmonary hypertension, which may evolve to cor pulmonale, leading to congestive right heart failure" (León-Velarde et al., 2005). According to this view, the principal diagnostic feature of CMS is a hemoglobin concentration above normal for a specified altitude. But diagnosis of "mild" CMS requires the presence of more than elevated hemoglobin; at least three of the following seven signs or symptoms must also be present—breathlessness and/or palpitations, sleep disturbance, cyanosis, dilation of veins, paresthesia ("pins and needles" sensation in the digits), headache, and tinnitus ("ringing in the ears"). More or more severe symptoms constitute "moderate" or "severe" disease respectively. Additional symptoms and signs can also occur (*e.g.*, dizziness, excessive physical and mental fatigue, lack of appetite, inability to concentrate and/or impaired memory, clubbing of the digits ["drumstick fingers"], mental confusion, depressive mental states and personality changes). As emphasized in the consensus statement, a diagnosis of CMS should be reserved for persons without chronic pulmonary diseases such as emphysema, chronic bronchitis, cystic fibrosis, or other conditions causing hypoxemia. The arterial hypoxemia, hypercapnia and other symptoms usually worsen with time, leading to pulmonary arterial hypertension and, together with higher blood viscosity, coalescing into *cor pulmonale* or congestive right heart failure. The clinical signs and symptoms of CMS disappear after descent to low altitude, but reoccur upon return (León-Velarde et al., 2005).

CMS is a significant public health problem worldwide but especially in the Andean countries of South America where more than 35 million people live above 2500 m (Niermeyer et al., 2001). It extracts a heavy toll, not just in terms of mortality but also morbidity because its symptoms are sufficiently debilitating that most persons with the disease cannot work or lead productive lives. Not everyone is equally susceptible; its incidence rises with age, with a prevalence in 60–69-year-old men approaching 34% (Monge-C et al., 1989). Although unknown in childhood, CMS can occur in adults as young as 17 years (E. Vargas, personal communication). Women are protected relative to men but this protection largely disappears after the menopause (León-Velarde et al., 1997), perhaps due to effects of female hormones on ventilation and/or erythropoiesis (Asmus et al., 1999). CMS has been described in South America, North America (Kryger et al., 1978b) and Asia (Wu et al., 1998), but its occurrence is uncertain in the high-altitude regions of Africa or the Middle East. The frequency of CMS appears to vary in relation to probable differences in duration of high-altitude exposure (Moore et al., 1998) but more rigorous study with suitable low-altitude controls is required in order to document such population differences and their interactions with known risk factors (*e.g.*, age and gender).

Defining CMS requires establishing what is the "normal" hemoglobin level at a given altitude. The approach for doing this has generally been to examine the distribution of values obtained in healthy persons to assure that they are distributed normally, and then to establish the upper limit of normal as ≥2 standard deviations above the mean. An example of a particularly careful study using this approach is that of Tufts and co-workers who studied 526 healthy male residents of La Paz-El Alto, Bolivia (3600–4000 m) judged iron-sufficient by having transferrin saturation ≥16% (Tufts et al., 1985) (Table 1). Values were plotted as cumulative frequencies using a Gaussian distribution, the extreme high and low segments excluded, and the resultant mean (18.8 ± 1.4 g/dL) plus or minus two standard deviations considered "normal" (15.2–22.8 g/dL). Similar results have been seen in other studies (Table 1) with cutoff values averaging ~21 g/dL or that proposed in the recent consensus statement (León-Velarde et al., 2005).

Related to the definition of "normal" hemoglobin is the question of what constitutes the "optimal" value. Choclo coauthored a landmark article in which he defined "optimal" as the hemoglobin value that permitted the maintenance of mixed (mean) venous Pv_{O_2}, arriving at a value of 14.7 g/dL for high-altitude males (Villafuerte et al., 2004). Because these calculations involved making assumptions that constrained cardiac output, the late Jack Reeves together with Fabiola León-Velarde revisited this subject using previously published data in 206 long-term high-altitude residents that had been studied at rest.

Table 1
Some cut-off values used for defining chronic mountain sickness (CMS)

Reference	Country	Altitude (m)	Ages (years)	Gender	Cut-off (g/dL)
Tufts et al. (1985)	Bolivia	3600–4000	18–60	Males	≥22.8
Wu et al. (1998)	China	2260–5226	>15	Males	≥20
León-Velarde et al. (1993)	Peru	4300	20–69	Males	≥21.3
			15–29	Males	≥21
Vásquez and Villena (2001)	Bolivia	4100		Females	≥19
				Males	≥21
León-Velarde et al. (2005)	World	>2500		Females	≥19

They also used a somewhat different standard for defining "optimal" (Reeves and León-Velarde, 2004); specifically, the hemoglobin concentration that maintained the difference in arterial–venous oxygen content ($Ca_{O_2} - Cv_{O_2}$) close to sea-level values. Two-thirds of the high-altitude residents' resting $Ca_{O_2} - Cv_{O_2}$ values fell in the low-altitude range, with values being related to their level of arterial O_2 saturation (Sa_{O_2}). When Sa_{O_2} was in the range of 85–90% and hemoglobin levels were at or below 17.5 g/dL, hemoglobin had a cardiac output-sparing effect. These authors therefore concluded,

> "If the function of a higher hemoglobin concentration is to relieve the requirement for increased blood flow, then the maximal effectiveness in the cohort examined appeared to be at a hemoglobin concentration of 17.5 g/100 ml and a Sa_{O_2} of approximately 87%" (Reeves and León-Velarde, 2004).

As noted below, this 17.5 g/dL hemoglobin value corresponds to the average seen in healthy male residents of 3600–4000 m in Bolivia.

Thus, work built on the pioneering studies carried out by Choclo and his father has led to broad-scale recognition in recent years of the importance of CMS as a public-health problem. Consensus has been achieved for defining what is "normal" for hemoglobin levels, the cutoff values for and the signs and symptoms of CMS.

3. What is the trigger for developing CMS?

While considerable progress has been realized in studying CMS, the fundamental challenge remains; namely, to know the events responsible for the hypoxemia and hence erythropoietic stimulus underlying this condition. Hypoventilation is clearly a major contributor, with the level of ventilation correlating closely but inversely with the hemoglobin level present (Vargas and Spielvogel, 2006). One idea is that the trigger was a relatively blunted hypoxic ventilatory response (HVR) (Kryger et al., 1978b; León-Velarde and Richalet, 2006). But since healthy lifelong high-altitude residents also have low HVRs (LeFrancois et al., 1966; Severinghaus et al., 1966; Weil et al., 1971), a blunted HVR may be necessary but it is not a sufficient cause of the hypoventilation observed. The contribution of an abnormal erythropoietic response has also been evaluated, but this too seems insufficient to account for the higher hemoglobins observed (Winslow and Monge, 1987). Another candidate is sleep-disordered breathing. CMS patients have an increased frequency of apneas, hypopneas, and prolonged episodes of hypoventilation (Kryger et al., 1978a; Sun et al., 1996; Richalet et al., 2005). At sea level, obesity and/or neuromuscular disease are often responsible for sleep-disordered breathing but these characteristics are not found generally in persons with CMS. We suggested some years ago that poor regulation of brain blood flow during sleep might be involved (Sun et al., 1996). In studies carried out in persons of principally Chinese ancestry living in Lhasa, Tibet (PRC) at 3600 m, we observed that CMS patients *versus* healthy, age-matched controls had more and more severe episodes of sleep-disordered breathing, spending three times as long and therefore being severe hypoxemic ($Sa_{O_2} < 70\%$) for a much greater portion of the night (49% *versus* 5% respectively, $p < 0.01$) (Sun et al., 1996). Additionally, whereas the exaggerated hypoxia and hypercapnia occurring during episodes of sleep-disordered breathing raised internal carotid artery blood flow velocity in healthy controls, flow velocity did not change in persons with CMS despite the greater severity of the hypoxia and hypercapnia present. This suggested to us that autoregulation of brain blood flow was impaired in CMS. If so, poor regulation of brain blood flow and reduced brain O_2 delivery could contribute to a vicious cycle that further disordered breathing and exaggerated hypoxia during sleep. Additional studies on the factors responsible for and consequences of sleep-disordered breathing in CMS are clearly needed.

Also important will be studies for establishing the time course of the disease since such information is required to move beyond simple associations to cause and effect relationships. One problem for doing so is that the age-associated rise in the incidence of CMS makes it difficult to disassociate the cause of CMS from factors related to aging (Monge-C et al., 1989). Another difficulty is that it is hard to exclude persons with chronic lung diseases such as emphysema and chronic bronchitis, since these conditions cannot be easily detected in their early, preclinical phase. In addition, time course studies are challenging to conduct under any circumstances and especially those present in developing countries where the majority of high-altitude residents live.

Investigators at the Bolivian High-Altitude Biology Institute (Instituto Boliviano de Biología de Altura, IBBA) have an advantage for the conduct of longitudinal studies since Bolivia's population is concentrated at high altitude. Further, IBBA is located within Bolivia's largest public-hospital complex where persons are seen routinely for medical care. Thus, over the past decades, nearly 20,000 adult residents of 3200–4100 m have been seen clinically for reasons ranging from evaluation for heart, lung or blood disorders to providing work- or school-related physicals.

IBBA's clinical experience has led its investigators to hypothesize that an early, preclinical form of CMS exists in 20–30-year-old young men that is characterized by modestly, but not necessarily sufficiently elevated hemoglobin levels to result in diagnosis of the disease (Vargas and Spielvogel, 2006). Illustrating this trajectory are the data in Fig. 1 from one of these ~20 young men over a period of 4 years. Of note, the uniformly high Pa_{CO_2} values began to rise further and Pa_{O_2} tensions to decline slightly *before* the rise in hemoglobin became pronounced. Clinical signs and symptoms of cyanosis and severe headaches also became progressively worse.

IBBA investigators have also employed a second, cross-sectional approach. To do this, they first used their ~8200 person database (6200 healthy adult residents of La Paz-El Alto plus 2158 persons participating in a community health survey in Chorolque [4850 m] and Viacha [4100 m] (IBBA, 1978)) to determine the mean hemoglobin value for healthy males living at high altitude. This value was 17.5 ± 0.4 g/dL (S.D.), coincidentally the same as the "optimal" resting hemoglobin value calculated by Reeves and León-Velarde (2004). Excessive erythrocytosis (EE) was then defined as two or more standard

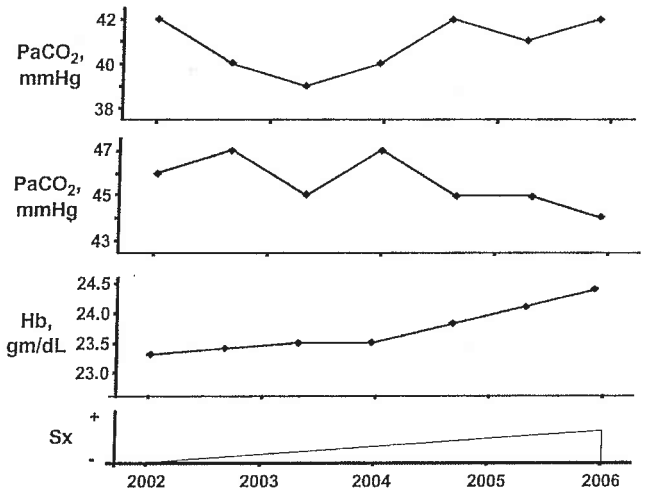

Fig. 1. Arterial CO_2 tensions (Pa_{CO_2}), arterial O_2 tensions (Pa_{O_2}) and hemoglobin (Hb) values are shown for one young man with elevated hemoglobin levels who was seen clinically at IBBA over a period of four years. While Pa_{CO_2} levels were uniformly high, indicating severe hypoventilation, they began to rise further and in parallel with gradually deteriorating Pa_{O_2} and increasing hemoglobin concentrations. Signs and symptoms (Sx) of CMS noted clinically were cyanosis and severe headaches, both of which increased gradually in severity and/or frequency over this 4-year period.

deviations above the mean or ≥18.3 g/dL. Applying this criteria to their study population yielded an estimated prevalence for EE of 7.5% in males <30 years of age, which agreed well with a previous Bolivian value of 8% (Tufts et al., 1985). Next, younger (<30 years) *versus* older (≥30 years) men with and without EE were compared to address whether EE is a preclinical form of CMS (Vargas and Spielvogel, 2006). The younger as well as the older men with EE hypoventilated and were more hypoxemic than controls (Table 2), similar to what has been observed previously in persons with CMS (Kryger et al., 1978b; Sun et al., 1996; León-Velarde et al., 1997; Wu et al., 1998). The younger aged men were especially interesting as they showed clear reductions in Pa_{O_2} even though their pulmonary function tests (forced expiratory volume in 1-s/forced vital capacity, FEV_1/FVC) were in the normal range. However, even though normal, their forced expiratory flows at 75% of FVC ($FEF_{75\%}$) and diffusing capacity for carbon monoxide (DLCO) differed from results obtained in healthy young men, indicating possible abnormalities in pulmonary structure or function. The ventilatory parameters worsened with age, with virtually all differing in the younger *versus* older EE groups. CMS signs also became more frequent and symptoms of more severe with advancing age (Table 3). Specifically, cyanosis, excessive fatigue and inability to concentrate were the most common symptoms in the younger aged men, with older-aged subjects exhibiting marked increases in the frequency of shortness of breath, excessive fatigue, sleep-related problems (somnolence, insomnia), mental confusion, and depression or personality changes.

Table 3
Frequency of CMS signs and symptoms in young (<30 years, Yng) *vs.* older (>30 years, Old) males with EE

Variable	Young EE	Old EE
Sample size	30	28
Frequent, severe headaches (%)	60	90
Cyanosis, central/peripheral (%)	60/100	90/100
Dizziness (%)	10	40
Short of breath (%)	30	70
Palpitations (%)	5	20
Excessive fatigue (%)	40	80
Inability to concentrate (%)	70	90
Somnolence (%)	10	70
Insomnia (%)	5	40
Clubbing of digits (%)	10	70
Mental confusion (%)	20	70
Depression, personality change (%)	50	90

In sum, although the "trigger" for developing CMS remains elusive, recent studies suggest that control of breathing and regulation of brain blood flow during sleep may be especially important. Longitudinal or cross-sectional studies designed to determine whether EE is an early, preclinical phase of CMS are likely to be especially informative for unraveling the many "chicken and egg" aspects of this disease.

4. Developmental origins of adult disease

Given our longstanding interest in the causes and consequences of the reduction in birth weight seen at high altitudes (Niermeyer et al., 2001; Moore, 2003), we were particularly interested in the important work begun nearly two decades ago

Table 2
Ventilatory characteristics of young (<30 years, Young) *vs.* older (>30 years, Old) males with and without EE (Vargas and Spielvogel, 2006)

Variable	Young controls	Young EE	Controls *vs.* EE, *p*-value	Old controls	Old EE	Controls *vs.* EE, *p*-value	Young *vs.* old EE, *p*-value
Sample size	30	30	–	27	28	–	–
Age (years)	22 ± 2	22 ± 4	NS	43 ± 3	36 ± 9	NS	$p < 0.05$
Hemoglobin (g/dL)	16.8 ± 0.6	19.5 ± 0.7	$p < 0.05$	17.2 ± 0.4	21.7 ± 0.6	$p < 0.05$	$p < 0.05$
Body mass index	23.8 ± 0.5	25.4 ± 1.2	NS	27.2 ± 0.9	27.4 ± 1.0	NS	$p < 0.05$
Pa_{O_2} (mmHg)	60 ± 1	53 ± 4	$p < 0.05$	59 ± 1	49 ± 6	$p < 0.05$	$p < 0.05$
Pa_{CO_2} (mmHg)	31 ± 2	34 ± 4	NS	31 ± 2	36 ± 7	NS	$p < 0.05$
Alveolar ventilation (L/min)	6.1 ± 0.7	4.3 ± 0.8	$p < 0.05$	5.8 ± 0.7	4.1 ± 0.8	$p < 0.05$	$p < 0.05$
FEV_1/FVC	86 ± 2	82 ± 2	$p < 0.0001$	84 ± 1	75 ± 2	$p < 0.01$	$p < 0.05$
$FEF_{75\%}$	98 ± 2	76 ± 3	$p < 0.01$	90 ± 5	70 ± 4	$p < 0.001$	NS
DLCO	38 ± 1	29 ± 1	$p < 0.001$	35 ± 1	24 ± 1	$p < 0.0001$	$p < 0.05$
HVR, Dejour test	1.8	0.8	$p < 0.0001$	1.3	0.6	$p < 0.01$	NS

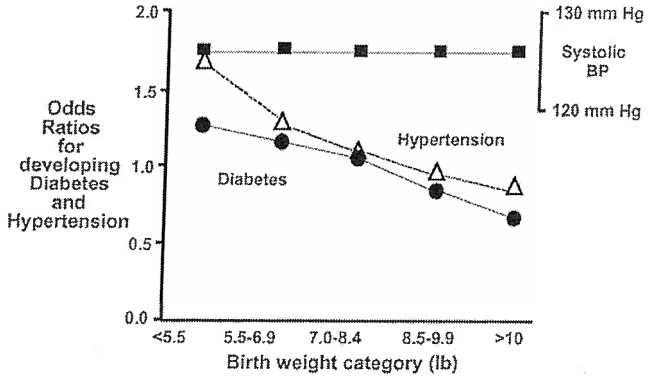

Fig. 2. The risk of developing hypertension and diabetes is greater in persons with lower compared with normal birth weights. Shown are the odds ratios (a measure of association in which "1.0" indicates no relationship and values less than or greater than 1.0 indicate negative or positive associations respectively) for becoming hypertensive or diabetic later in life. Also shown are systolic blood pressure values; these are unrelated to birth weight, indicating that the birth weight associated rise in frequency of hypertension is due to higher diastolic pressures. Figure adapted from (Gluckman and Hanson, 2004).

by David J.P. Barker and colleagues concerning the influences of birth weight on the risk of developing cardiovascular disease later in life, first termed "fetal programming" but now "developmental origins of adult disease". This field of study began with David Barker's seminal observations in the 1960s and 1970s that the districts in England with the highest mortality from cardiovascular disease in 55–74-year olds were also those with the highest neonatal mortality 55–74 years ago (Barker and Osmond, 1986). Reasoning that the high neonatal mortality rates were likely due largely to lower birth weights and considering that the same factor(s) might underlie both phenomena, he undertook epidemiologic studies to determine whether poor growth *in utero* predisposed persons to developing cardiovascular and other illness later in life.

Numerous reviews and countless articles have since appeared (DOHaD,.2007). Using large-scale surveys conducted in England (Hertfordshire, Sheffield), Sweden, Finland, Wales, USA and more recently India, mortality rates from coronary heart disease nearly doubled from low (<5.5 lb or 2500 g) to normal birth weights, with a slight upward trend reappearing at above-normal values (>9.5 lb or 4300 g) (Burke et al., 2004; Gluckman and Hanson, 2004). Since such relationships remained after controlling for a range of lifestyle factors (smoking, exercise, employment, and alcohol consumption), these authors suggested that impaired growth *in utero* contributed to the mortality rise observed (Barker, 2001). Subsequent studies using both human and experimental animal preparations have shown that poor growth *in utero* not only affects the organ systems involved in increasing susceptibility to heart disease but also the risk of developing hypertension and diabetes (Fig. 2). As shown in Fig. 2, the effects of birth weight are specific for the particular disease outcome with, for example, the risk of hypertension but not the actual systolic blood pressures being related to birth weight (Gluckman and Hanson, 2004). Lower birth weight has been shown to predispose persons to other disorders including obesity, osteoporosis, schizophrenia, depression, cancers of the breast and ovary, and polycystic ovary syndrome (Barker, 2001).

While most of the studies done by the Barker group have addressed the consequences of lower birth weight due to poor maternal nutrition, similar relationships have been observed when the birth weight reduction was due to other causes. Lower birth weights have been commonly observed at high altitudes (Lichty et al., 1957; Jensen and Moore, 1997; Lopez Camelo et al., 2006) but no study, to the best of our knowledge, has directly addressed their consequences for susceptibility to later in life diseases. Previous studies provide evidence in support of as well as opposed to the existence of such consequences.

In support of such a relationship, Ingrid Asmus observed that male residents of Leadville, Colorado (3100 m) with CMS had lower birth weights than age-matched healthy controls (I. Asmus, personal communication). Additionally, both the lower birth weights seen in studies of fetal programming and those at high altitude appear due to reductions *in utero* placental blood flow, which may result, in turn, from effects of hypoxia that interfere with the normal vascular changes required to raise uterine blood flow during pregnancy (Myatt, 2005). The lower birth weights observed at high altitudes are associated with an increased mortality risk, especially in Bolivia (Gadow et al., 1991; República de Bolivia, 1998; Lopez Camelo et al., 2006). We have shown that the pregnancy-associated increase in uterine artery blood flow is curtailed at high compared with low altitude in Colorado (Zamudio et al., 1995). UA blood flow during pregnancy is also greater in Andean compared with European high-altitude residents (Wilson et al., in press), consistent with the protection from altitude-associated reductions in birth weight seen in Andean compared with shorter term high-altitude residents (Haas et al., 1980; Zamudio et al., 1993; Moore et al., 2001; Julian et al., 2007). Thus, even though genetic or other population-specific factors may help maintain normal levels of uteroplacental blood flow and protect against hypoxia-associated reductions in fetal growth in multigenerational groups, it is likely that considerable numbers of babies were and continue to be born at high altitude in Bolivia who have been subjected to impaired fetal growth.

Against the likelihood that altitude-associated reductions in birth weight raise cardiovascular disease risk during adulthood are older observations showing that blood pressures falls with years residence at high altitude (Marticorena et al., 1969). Additional data from New Mexico also show a decline in mortality from heart disease with increasing altitude (Buechley et al., 1979). The extremely limited nature of these data and inability, for example, to control for variation in other altitude-related risk factors for cardiovascular disease (*e.g.*, smoking) recommends further exploration of an association between reduced birth weights and increased risk of coronary heart disease, hypertension, diabetes and other such "fetally-programmed" diseases. Fortunately such studies are presently underway in Bolivia (D. Giussani, personal communication).

One possibility is that the consequences of reduced birth weight at high altitude are more important for the right side of the circulation than for the left-side, which is where virtually all "fetal programming" studies to date have been performed.

We reasoned that such "right-side" effects could influence the development of the lung and its circulation at the levels of the airways, vasculature and/or respiratory control. Previous studies have shown that chronic hypoxia affects airway structure; specifically, rat pups whose mothers were exposed to 10% FI_{O_2} for 9 h on the last day of gestation and for 1–2 h after birth had a delayed increase in lung volume, impaired septation of gas exchange saccules, blunted expansion of gas exchange surface area, and accelerated thinning of the alveolar walls (Massaro et al., 1989). Since rats are born in a comparatively premature state, the relevance of these observations to the human condition may be questioned. But consistent with chronic hypoxia affecting lung structure in humans are the observations of Mortola and co-workers who showed that healthy newborns in La Paz (3600 m) had 33–37% greater pulmonary compliance, absolutely or on per kg, than babies born at low altitude (300 m) (Mortola et al., 1990). In relation to respiratory control, chronic perinatal hypoxia delays the onset and decreases the ventilatory sensitivity to hypoxia at maturity (Eden and Hanson, 1987; Okubo and Mortola, 1990; Joseph et al., 2000). Maturation of the chemoreceptor pathway also differs by gender, with prepubertal female rats having higher HVRs than males (Mortola and Saiki, 1996). Sex hormones may be involved since progesterone enhances HVR and reduces the occurrence of apneas in rat pups, and prenatal estradiol blockade blunts HVR during the neonatal period (Doan et al., 2004). These latter observations clearly have implications for explaining the blunted HVR and the male preponderance seen in CMS.

In summary, recognition of the developmental origins of adult diseases has stimulated a number of studies on the later-in-life influences of impaired fetal growth. Since birth weight is clearly reduced at high altitude and impaired intrauterine development affects the maturation of organ systems involved in oxygen transport, we hypothesized that susceptibility to CMS was developmentally programmed. But lacking were data with which such a hypothesis could be preliminarily tested.

5. Is CMS fetally programmed? A pilot study

While many studies have been conducted concerning the developmental origins of adult disease, only two have investigated the effects of reduced birth weight on the respiratory or pulmonary-related systems likely to be involved in CMS. One, from the Barker group, showed that lower birth weight was associated with lower FEV_1 and increased mortality from chronic bronchitis (Barker, 2001). The other was by Sartori and colleagues who found that young adults who had experienced severe hypoxia during neonatal life had much greater elevations in pulmonary arterial pressures after ascent to high altitudes when compared with normal, age-matched controls (Sartori et al., 1999). Since, as reviewed above, exaggerated intrauterine or neonatal hypoxia alters the maturation of lung structure, we reasoned that such the lower $FEF_{75\%}$ and DL_{CO} values seen previously in EE and/or CMS (Vargas and Spielvogel, 2006) could have been due to such alterations in lung structure, manifesting as air-trapping and impaired diffusion. Impaired development of respiratory control could be contributing not only to the blunted HVRs but also to an increased frequency of sleep-disordered breathing during adulthood and perhaps at earlier ages as well. We therefore hypothesized that perinatal events "program" CMS by influencing the maturation of lung alveolarization, the pulmonary circulation and/or control of breathing (Fig. 3).

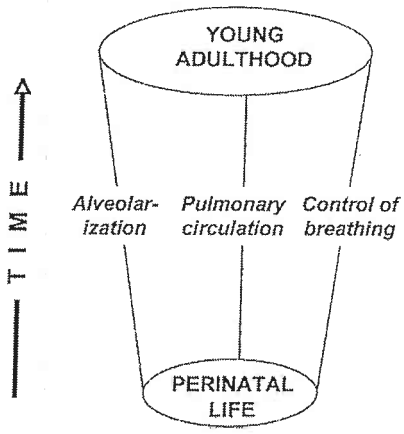

Fig. 3. An hypothesized schema for how reduced birth weight and/or exaggerated hypoxia during perinatal life could influence the development of respiratory- and pulmonary circulation-related systems so as to increase susceptibility to CMS during adulthood.

As a preliminary test of this hypothesis, we contacted 12 of the 15–35-year-old males identified previously as having EE. Young men were chosen in order to avoid the confounding effects of aging or chronic lung disease on the development of CMS and to increase the likelihood of being able to find birth-related information, since their births would have occurred more recently[2]. We were able to locate 12 such persons living in La Paz-El Alto and available for study. Subject consent, demographic, respiratory and cardiovascular characteristics were measured at IBBA as previously described (Vargas and Spielvogel, 2006). Briefly, weight, height and other subject demographic characteristics were obtained by physical exam or interview. Arterial samples were withdrawn for determination of blood gases and ventilation measured by pneumotachograph. Flow-volume loops were obtained by whole body plethysmography, and EKGs and echocardiography were used to assess right ventricular hypertrophy and pulmonary hypertension. Birth weights were obtained from their mothers, as women in Bolivia commonly retain their infant's medical records ("carnet"), and verified with reference to records obtained from the hospitals where the young men had been born. Preterm was defined as < 37 weeks and small for gestational age (SGA) as < 10th percentile for gestational age and sex using sea-level norms (Williams et al., 1982). There is an ongoing debate concerning how best to judge infant size at birth (Hemming et al., 2006). Since a primary purpose for such classifications is prediction of mortality risk, the standard chosen here was one in which the birth weight cutoffs had been verified with mortality criteria. Moreover, the use of "customized" standards (in which the influences of other

[2] There are no centrally collected vital statistics in Bolivia.

Table 4
Demographic and respiratory characteristics of 12 young, male La Paz residents with EE

ID #	Age (years)	Wt (kg)	Ht (cm)	BMI (cm/kg^2)	Hb (g/dL)	Sa_{O_2} (%)	Pa_{O_2} (mmHg)	Pa_{CO_2} (mmHg)	pHa units	V_A (l_{BTPS}/min)	ΔV_A (l_{BTPS}/min)	FEV_1/FVC	$FEV_{75\%}$
1	26	74.0	173	24.7	19.4	88.0	57.0	33.1	7.39	3.7	0.5	71	68
2	19	59.0	168	20.9	18.0	86.9	50.9	34.5	7.42	4.2	0.5	69	54
3	20	54.0	162	20.5	19.0	89.0	58.4	29.0	7.45	3.8	0.5	66	58
4	25	62.4	159	24.7	19.0	88.0	56.7	32.3	7.40	3.9	0.7	89	69
5	24	76.9	165	28.2	19.0	90.0	60.0	30.7	7.43	4.1	1.2	71	62
6	23	72.0	178	22.7	20.0	90.0	57.9	33.0	7.43	4.2	0.7	96	74
7	24	61.0	170	21.1	23.0	87.0	55.0	34.0	7.40	4.2	-0.4	84	76
8	26	73.2	169	25.6	23.0	86.5	47.8	37.7	7.41	2.9	0.5	49	45
9	32	79.0	169	27.6	19.0	89.7	56.6	34.9	7.42	3.4	0.3	85	61
10	17	86.0	174	28.4	18.6	89.6	55.2	33.7	7.44	3.3	0.6	82	69
11	20	76.8	184	22.7	23.4	87.3	52.6	38.1	7.39	4.4	0.7	94	87
12	28	64.1	161	24.7	25.0	77.5	44.1	44.7	7.38	3.1	0.5	72	80
X	23.7	69.9	169.3	24.3	20.5	87.5	54.4	34.6	7.4	3.8	0.5	77.3	66.9
S.E.M.	1.3	2.9	2.2	0.8	0.7	1.0	1.4	1.2	0.0	0.1	0.1	0.1	0.1

Abbreviations: Wt = weight, Ht = height, BMI = body mass index, V_A = alveolar ventilation.

factors such as maternal height, parity or maternal age are taken into account) has recently been questioned on the grounds that they overestimate mortality risk (Zhang et al., 2007). Neonatal hypoxia was judged if any of the following were noted: oxygen treatment, respiratory distress, apnea, respiratory depression, pulmonary hypertension, hyaline membrane disease, or newborn hypoxia as a discharge diagnosis. Preeclampsia was defined as two or more blood pressures ≥140/90 mmHg at least 6 h apart in a woman who was normotensive when nonpregnant, plus significant proteinuria. Women with blood pressures ≥160/110 mmHg were considered to have severe and all other mild disease.

5.1. Demographic, respiratory, and cardiovascular characteristics

All 12 subjects were normal in terms of body weight, height and BMI (Table 4), and all had resided at high altitude since childhood (Tables 4 and 6). Most were cyanotic and presented only a few other signs and symptoms of CMS, whereas others had more and more-severe symptoms such as frequent severe headaches and sleep disturbances.

The EE subjects hypoventilated (higher Pa_{CO_2} tensions and lower levels of alveolar ventilation) and had lower Sa_{O_2} than healthy subjects studied previously at IBBA (Tables 2 and 4). The rise in alveolar ventilation following three breaths of N_2 was also low, indicating a blunted HVR (Table 4). FVC, FEV_1 and FEV_1/FVC were all in the normal range but $FEF_{75\%}$ values were modestly reduced. Previous studies have found lower pulmonary compliance in younger and especially older aged EE subjects when compared with healthy high-altitude residents (LeFrancois et al., 1966; Vargas and Spielvogel, 2006). The diminished $FEF_{75\%}$ together with prior evidence of reduced compliance suggested to us that abnormalities in lung structure leading to air trapping might be present. All subjects had normal blood pressures and heart rates (Table 5). Most demonstrated pulmonary hypertension and electrocardiographic evidence of right ventricular hypertrophy.

5.2. Perinatal characteristics

All but one of the 12 young men had been born at high altitude (Table 6). Birth weights were remarkably low, averaging ~2500 g (5.5 lb). A high frequency of preterm deliveries (67%) contributed to these lower birth weights. Two were twins (#2 and #3). The overwhelming majority (83%) were hypoxic during neonatal life, demonstrating that hypoxic exposure continued after birth (Table 6).

The young men's mothers had been of normal age and in good health at the time of their pregnancies (Table 6). None were experiencing their first pregnancy. Remarkably, half developed preeclampsia, more than twice the frequency reported previously at high altitude in Colorado or Bolivia (Palmer et al., 1999; Keyes et al., 2003) and upwards of 10× greater than the 5–7% frequency seen at or near sea level (Dekker and Sibai, 2001). Four women had mild and two severe disease. Consistent with the high frequency of preeclampsia were their elevated late-pregnancy blood pressures, averaging ~140/90 mmHg, and uniform presence of substantial proteinuria in all women, including those who remained normotensive (Table 6).

Table 5
Cardiovascular data of 12 young, male La Paz residents with EE

ID #	Age years	BP (mmHg)	HR (bpm)	EKG	P_{PA} (mmHg)
13	20	110/70	60	RVH	PH
14	20	110/60	50	RVH	PH
15	25	120/84	60	NL	NL
16	23	110/60	60	RVH	PH
17	23	100/70	60	RVH	PH
7	24	12070	75	RVH	PH
18	26	92/70	75	RVH	PH
19	17	120/80	72	NL	NL
20	20	110/80	60	RVH	PH
21	27	120/80	60	RVH	PH
X	22.5	111/72	63.2	80% with	80% with
S.E.M.	1.0	3/3	2.6	RVH	PH

Abbreviations: RVH = rt ventricular hypertrophy, NL = normal, PH = hi-alt pulmonary htn.

Table 6
Birth-related data in 12 young, male La Paz residents with EE

ID #	Birth alt (m)	Childhd. alt (m)	Birth wt (g)	Gest age (week)	Fetal comps	Neonatal dx	Mat age	Mat comps	Mat BP (mmHg)	Proteinuria
1	3800	3700	2400	35	SGA prem	Hypoxia	28	None	130/85	na
2	3600	3700	1200	28	Prem	Hypoxia	33	PE	140/90	2+
3	3600	3700	1350	28	Prem	Hypoxia	33	PE	140/90	2+
4	3902	3700	2800	35	Prem	Normal	30	None	120/80	2+
5	3300	3600	2700	34	Prem	Hypoxia	29	None	130/90	2+
6	3800	2450	3000	38	None	Normal	31	None	135/85	2+
7	3800	4100	2800	34	Prem	Hypoxia	32	PE	140/90	2+
8	4300	4100	3100	32	Prem	Hypoxia	33	PE	160/100	2+
9	3902	3400	2800	36	None	Hypoxia	34	None	120/85	3+
10	0	3970	3200	38	None	Hypoxia	23	None	130/85	3+
11	3970	4100	3900	36	None	Hypoxia	35	PE	140/90	2+
12	3950	3700	1600	33	Prem	Hypoxia	23	PE	150/90	3+
X	3493.7	3685.0	2570.8	33.9	8% SGA,	83%	30.3	50% w/	136/88	All
S.E.M.	340.4	135.5	243.4	1.0	67% prem	Hypoxic	1.2	PE	4/2	

In summary, these data were supportive of our hypothesis in three respects. First and as hypothesized, these young men with EE had lower birth weights. Second, exaggerated hypoxia continued during neonatal life, a period during which fetal-programming effects can also occur (Bagby, 2007). Third, while the young men did not manifest the magnitude of rise in hemoglobin or presence of additional signs and symptoms required for the diagnosis of CMS, the cross-sectional and serial data reviewed above supported the likelihood that they were likely to develop CMS with time. However, the preliminary nature of these data and other limitations need to be underscored as well. The number of subjects was very small ($n = 12$); clearly, perinatal data from a larger number of persons with EE or CMS are needed. The data were also acquired from a non-random convenience sample, which may in turn have introduced recall or other kinds of sampling bias. Finally, a suitable direct comparison group was lacking since no data were acquired in healthy controls.

6. Conclusions

Interest in CMS is renewed and growing. The recent consensus statement (León-Velarde et al., 2005) has yielded a common definition for this disorder, permitting clearer recognition of its existence and a common means for scaling its severity. While the elusive trigger for deciding what causes some persons to become excessively polycythemic remains unclear, valuable observations have been made that are likely to guide the search. Better definition of the time course of this disease will be facilitated by opportunities for performing cross-sectional as well as prospective studies in subjects with EE. Further, the new approach described here extends the time frame by asking whether CMS begins *in utero* with impaired growth and/or development of the pulmonary and respiratory-related systems required for successful, prolonged acclimatization to high altitude. Linking CMS with the hypothesis of developmental origins of adult disease is novel, but supported by the preliminary data presented here. Future studies are required to extend these observations to larger numbers of subjects and expand the study design to include controls. More detailed physiological studies as well as longitudinal assessments are also needed in order to determine the consequences of perinatal hypoxia on the maturation of the organ systems likely to be playing central roles in CMS. Hopefully, these as well as other approaches will yield continued progress for improving our understanding of, ability to treat and ultimately prevent this disorder.

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References

Asmus, I., Zamudio, S., Moore, L.G., 1999. Preliminary data: menstrual status, hormone replacement therapy and hemoglobin concentrations in women residing at 3100 m. In: Roach, R.C., Wagner, P.D., Hackett, P.H. (Eds.), Hypoxia: Into the Next Millennium,. Kluwer Academic/Plenum Publishers, New York City, USA.

Bagby, S., 2007. Maternal nutrition, low nephron number, and hypertension in later life: pathways of nutritional programming. J. Nutr. 137, 1066–1072.

Barker, D., 2001. Fetal origins of cardiovascular and lung disease. In: Lenfant, C. (Ed.), Lung Biology in Health and Disease,. Marcel Dekker, New York, p. 432.

Barker, D., Osmond, C., 1986. Infant mortality, childhood nutrition and ischaemic heart disease in England and Wales. BMJ 1, 1077–1081.

Buechley, R., Kay, C., Morris, D., Morton, W., Morgan, M., 1979. Altitude and ischemic heart disease in tricultural New Mexico: an example of confounding. Am. J. Epidemiol. 109, 663–666.

Burke, J., Forsgren, J., Palumbo, P., Bailey, K., Desai, J., Devlin, H., Leibson, C., 2004. Association of birth weight and type 2 diabetes in Rochester, Minnesota. Diab. Care 27, 2512–2513.

Dekker, G., Sibai, B., 2001. Primary, secondary and tertiary prevention of pre-eclampsia. The Lancet 357, 209–215.

Doan, V.D., Gagnon, S., Joseph, V., 2004. Prenatal blockade of estradiol synthesis impairs respiratory and metabolic responses to hypoxia in newborn and adult rats. Am. J. Physiol. Regul. Integr. Comp. Physiol. 287, R612–R618.

DOHaD, 2007. DOHaD stands for Developmental Origins of Health and Disease (http://www.som.soton.ac.uk/research/dohad/centre/whatis/default.htm).

Eden, G.J., Hanson, M.A., 1987. Effects of chronic hypoxia from birth on the ventilatory response to acute hypoxia in the newborn rat. J. Physiol. Lond. 392, 11–19.

Gadow, E., Castilla, E., Lopez Camelo, J., Queenan, J., 1991. Stillbirth rate and associated risk factors among 869 750 Latin American hospital births 1982–1986. Int. J. Gynaecol. Obstet. 35, 209–214.

Gluckman, P., Hanson, M., 2004. Living with the past: evolution, development, and patterns of disease. Science 305, 1733–1736.

Haas, J.D., Frongillo, E.J., Stepcik, C., Beard, J., Hurtado, L., 1980. Altitude, ethnic and sex differences in birth weight and length in Bolivia. Hum. Biol. 52, 459–477.

Hemming, K., Hutton, J., Glinianaia, S., Jarvis, S., Platt, M., 2006. Differences between European birthweight standards: impact on classification of 'small for gestational age'. Dev. Med. Child. Neurol. 48, 906–912.

Hochachka, P., 1995. Carlos Monge Cassinelli—a person view of the setting and signficance of his work. In: Sutton, J., Houston, C., Coates, G. (Eds.), Hypoxia and the Brain,. Queen City Printers, Lake Louise, Canada, pp. ix-ix10.

IBBA, 1978. Informe Encuesta en la Población de Chorolque. In: UMSA, La Paz, Bolivia, p. 102.

Jensen, G.M., Moore, L.G., 1997. The effect of high altitude and other risk factors on birthweight: independent or interactive effects? Am. J. Public Health 87, 1003–1007.

Joseph, V., Soliz, J., Pequignot, J., Sempore, B., Cottet-Emard, J.M., Dalmaz, Y., Favier, R., Spielvogel, H., Pequignot, J.M., 2000. Gender differentiation of the chemoreflex during growth at high altitude: functional and neurochemical studies. Am. J. Physiol. Regul. Integr. Comp. Biol. 278, R806–R816.

Julian, C.G., Vargas, E., Armaza, J.F., Wilson, M., Niermeyer, S., Moore, L.G., 2007. High-altitude ancestry protects against hypoxia-associated reductions in fetal growth. Arch. Dis. Child. Fetal Neonatal. Ed. Feb 28; [Epub ahead of print].

Keyes, L.E., Armaza, J.F., Niermeyer, S., Vargas, E., Young, D.A., Moore, L.G., 2003. Intrauterine growth restriction, preeclampsia and intrauterine mortality at high altitude in Bolivia. Pediatr. Res. 54, 20–25.

Kryger, M., Glas, R., Jackson, D., McCullough, R.E., Scoggin, C., Grover, R.F., Weil, J.V., 1978a. Impaired oxygenation during sleep in excessive polycythemia of high altitude: improvement with respiratory stimulation. Sleep 1, 3–17.

Kryger, M., McCullough, R., Doekel, R., Collins, D., Weil, J.V., Grover, R.F., 1978b. Excessive polycythemia of high altitude: Role of ventilatory drive and lung disease. Am. Rev. Resp. Dis. 118, 659–666.

LeFrancois, R., Gautier, H., Pasquis, P., Leroy, J., 1966. Comparison entre les responses ventilatoires au stimulus oxygene au cours des hypoxies aigue et chronique. J. Physiol. Paris 58, 310–322.

León-Velarde, F., Arregui, A., Monge, C.C., Ruiz, H., 1993. Ageing at high altitude and the risk of chronic mountain sickness. J. Wilderness Med. 4, 183–188.

León-Velarde, F., Maggiorini, M., Reeves, J.T., Aldashev, A., Asmus, I., Bernardi, L., Ri-Li, G., Hackett, P., Kobayashi, T., Moore, L.G., Penaloza, D., Richalet, J.-P., Roach, R.C., Wu, T.Y., Vargas, E., Zubieta-Castillo, G., Zubieta-Calleja, G., 2005. Consensus statement on chronic and subacute high altitude diseases. High Alt. Med. Biol. 6, 147–157.

León-Velarde, F., Ramos, M.A., Hernandez, J.A., Deidiaquez, D., Munoz, L.S., Gaffo, A., Cordova, S., Durand, D., Monge, C., 1997. The role of menopause in the development of chronic mountain sickness. Am. J. Physiol. 41, R90–R94.

León-Velarde, F., Richalet, J.-P., 2006. Respiratory control in residents at high altitude: physiology and pathophysiology. High Alt. Med. Biol. 7, 125–137.

Lichty, J.A., Ting, R.Y., Bruns, P.D., Dyar, E., 1957. Studies of babies born at high altitude. I. Relation of altitude to birth weight. Am. Med. Assoc. J. Dis. Child. 93, 666–669.

Lopez Camelo, J., Campana, H., Santos, R., Poletta, F., 2006. Effect of the interaction between high altitude and socioeconomic factors on birth weight in a large sample from South America. Am J Phys Anthropol. 129, 305–310.

Marticorena, E., Ruiz, L., Severino, J., Galvez, J., Penaloza, D., 1969. Systemic blood pressure in white men born at sea level: changes after long residence at high altitudes. Am. J. Cardiol. 23, 364–368.

Massaro, G.D., Olivier, J., Massaro, D., 1989. Short-term perinatal 10% O_2 alters postnatal development of lung alveoli. Am. J. Physiol. 257, L221–L225.

Medical Dictionary, S.S., 2004. Entry for "Chronic Mountain Sickness". Houghton Mifflin Company, New York.

Monge, C., 1925. Sobre un caso de enfermedad de Vaquez (sindrome eritrémico de altura), p. 7.

Monge, M.C, Monge, C.C., 1966. High-Altitude Diseases: Mechanism and Management. Charles C. Thomas, Springfield, IL.

Monge-C, C., León-Velarde, F., Arregui, A., 1989. Increasing prevalence of excessive erythrocytosis with age among healthy high-altitude miners (letter). N. Engl. J. Med. 321, 1271.

Moore, L.G., 2003. Fetal growth restriction and maternal oxygen transport during high-altitude pregnancy. High Alt. Med. Biol. 4, 141–156.

Moore, L.G., Asmus, I., Curran, L., 1998. Chronic mountain sickness: gender and geographic variation. In: Progress in Mountain Medicine and High Altitude Physiology, 3rd World Congress on Mountain Medicine and High Altitude Physiology, pp. 114–119.

Moore, L.G., Young, D., McCullough, R.E., Droma, T.S., Zamudio, S., 2001. Tibetan protection from intrauterine growth restriction at high altitude. Am. J. Hum. Biol..

Mortola, J.P., Rezzonico, R., Fisher, J.T., Villena-Cabrera, N., Vargas, E., Gonzáles, R., Peña, F., 1990. Compliance of the respiratory system in infants born at high altitude. Am. Rev. Respir. Dis. 142, 43–48.

Mortola, J.P., Saiki, C., 1996. Ventilatory response to hypoxia in rats: gender differences. Respir. Physiol. 106, 21–34.

Myatt, L., 2005. Placental adaptive response and fetal programming. J. Physiol. (Lond.) 572, 25–30.

Niermeyer, S., Zamudio, S., Moore, L.G., 2001. The people. In: Hornbein, T., Schoene, R. (Eds.), Lung Biology in Health and Disease, vol. 161. Marcel Dekker, New York, pp. 43–100.

Okubo, S., Mortola, J.P., 1990. Control of ventilation in adult rats hypoxic in the neonatal period. J. Appl. Physiol. 259, R836–R841.

Palmer, S.K., Moore, L.G., Young, D.A., Cregger, B., Berman, J.C., Zamudio, S., 1999. Altered blood pressure course during normal pregnancy and increased preeclampsia at high altitude (3100 m) in Colorado. Am. J. Obstet. Gynecol. 180, 1161–1168.

Reeves, J.T., León-Velarde, F., 2004. Chronic mountain sickness: recent studies of the relationship between hemoglobin concentration and oxygen transport. High Alt. Med. Biol. 5, 147–155.

República de Bolivia, 1998. Encuesta Nacional de Demografía y Salud. Macro International, Calverton, MD, USA.

Richalet, J., Rivera, M., Bouchet, P., Chirinos, E., Onnen, I., Petitjean, O., Lasne, F., Mutereau, S., León-Velarede, F., 2005. Acetazolamide: treatment for chronic mountain sickness. Am. J. Respir. Crit. Care Med. 172, 1427–1433.

Sartori, C., Allemann, Y., Trueb, L., 1999. Augmented vasoreactivity in adult life associated with perinatal vascular insult. The Lancet 353, 2205–2207.

Severinghaus, J.W., Bainton, C.R., Carcelen, A., 1966. Respiratory insensitivity to hypoxia in chronically hypoxic man. Respir. Physiol. 1, 308–334.

Sun, S., Oliver-Pickett, C., Ping, Y., Micco, A.J., Droma, T., Zamudio, S., Zhuang, J., Huang, S.Y., McCullough, R.G., Cymerman, A., Moore, L.G., 1996. Breathing and brain blood flow during sleep in patients with chronic mountain sickness. J. Appl. Physiol. 81, 611–618.

Tufts, D.A., Haas, J.D., Beard, J.L., Spielvogel, H., 1985. Distribution of hemoglobin and functional consequences of anemia in adult males at high altitude. Am. J. Clin. Nutr. 42, 1–11.

Vargas, P.E., Spielvogel, H., 2006. Chronic mountain sickness, optimal hemoglobin, and heart disease. High Alt. Med. Biol. 7, 138–149.

Villafuerte, F., Cárdenas, R., Monge, C., 2004. Optimal hemoglobin concentration and high altitude: a theoretical approach for Andean men at rest. J. Appl. Physiol. 96, 1581–1588.

Vásquez, R., Villena, M., 2001. Normal hematological values for healthy persons living at 4000 meters in Bolivia. High Alt. Med. Biol., 2.

Weil, J.V., Byrne-Quinn, E., Sodal, I.E., Filley, G.F., Grover, R.F., 1971. Acquired attenuation of chemoreceptor function in chronically hypoxic man at high altitude. J. Clin. Invest. 50, 186–195.

West, J., 2006. In memorian: Carlos Monge C. High Alt. Med. Biol. 7, 180–181.

Williams, R.L., Creasy, R.K., Cunningham, G.C., Hawes, W.E., Norris, F.D., Tashiro, M., 1982. Fetal growth and perinatal viability in California. Obstetrics and Gynecology 59, 624–632.

Wilson, M.J., Lopez, M., Vargas, M., Armaza, J.F., Tellez, W., Rodriquez, A., Julian, C.G., Bigham, A., Shriver, M., Niermeyer, S., Vargas, E., Moore, L.G. Greater uterine artery blood flow during high-altitude pregnancy in indigenous (Andean) than Foreign (European) women. Am J Physiol: Regul., Integr. Comp. Physiol., in press.

Winslow, R.M., Monge, C.C., 1987. Hypoxia, Polycythemia and Chronic Mountain Sickness. The Johns Hopkins University Press, Baltimore.

Wu, T.Y., Li, W., Li, Y., Ge, R.L., Cheng, Q., Wang, S., Zhao, G., Wei, L., Jin, Y., Ge-Don, 1998. Epidemiology of chronic mountain sickness: 10 years' study in Qinghai, Tibet. In: Ohno, H., Kobayashi, T., Masuyama, S., Nakashima, M. (Eds.), Progress in M2ountain Medicine and High Altitude Physiology, Press Committee of the 3rd World Congress on Mountain Medicine and High Altitude Physiology. Matsumoto, Japan, pp. 120–125.

Zamudio, S., Droma, T., Norkyel, K.Y., Acharya, G., Zamudio, J.A., Niermeyer, S.N., Moore, L.G., 1993. Protection from intrauterine growth retardation in Tibetans at high altitude. Am. J. Phys. Anthropol. 91, 215–224.

Zamudio, S., Palmer, S.K., Stamm, E., Coffin, C., Moore, L.G., 1995. Uterine blood flow at high altitude. In: Sutton, J.R., Houston, C.S. (Eds.), Hypoxia and the Brain. Queen City Press, Burlington, VT, USA, pp. 112–124.

Zhang, X., Platt, R., Cnattingius, S., Joseph, K., Kramer, M., 2007. The use of customised *versus* population-based birthweight standards in predicting perinatal mortality. BJOG 114, 474–477.