December 10, 2008

Evaluation of dissertation for the doctor of medical science (dr. med.) degree by Gustavo Zubieta-Calleja, MD

Title:

Human adaptation to high altitude and to sea level

Acid-base equilibrium, ventilation and circulation in chronic hypoxia

Opponents:

Peter Norsk, professor, dr. med. (formand)
Bengt Saltin, professor, med. dr.
Johan Kofstad, professor, med. dr.

Formalities

The dissertation consists of a compilation of 6 previously published papers (A – F) and an overview devided into 6 chapters (A – F), which each summarizes each of the papers (A – F) followed by a conclusion and a list of 43 references. The work has been conducted at the High Altitude Pathology Institute at the Clinica IPPA in la Paz, Bolivia, in collaboration with the Faculty of Health Sciences at the University of Copenhagen. The first papers (A & C) were published in 2005 and the last (B & F) in 2007. Five of the six papers are published in Journal of Physiology and Pharmacology issued by the Polish Physiological Society with an impact factor of 4.466 (2007) and one in Research in Sports Medicine in 2007.

Gustavo Zubieta-Calleja is the first author of three of the papers and the second author of the rest. There are written declarations from the co-authors that he has contributed extensively to the six papers.

Background and main results

The background for the work of the dissertation is described in the introduction. Close to 2 million people live in the city of La Paz, Bolivia, and usually medicine in the Bolivian Andes region is practised according to sea level environmental conditions. Most physicians base their practise on sea level training, which do not adequately take into consideration the problems encountered at high altitude with considerable lower oxygen tension. In La Paz, the barometric pressure is 490 mm Hg and the oxygen tension 94 mm Hg with a simultaneous arterial partial pressure of 60 mm Hg.

Another problem is the adaptation processes of high altitude residents to sea level conditions, which are broadly overlooked. An example is the difficulties encountered by soccer players from La Paz switching to high oxygen pressures at sea level, which are poorly understood.

Therefore, it was the purpose of the work of the dissertation to address six major questions, which are separately dealt with in each of the publications:

A. Are sea level acid-base charts suitable for diagnosis of disorders and their treatment at high altitude?
B. Is it possible to improve the high altitude diving tables?
C. Is there a difference in circulation time between patients with chronic mountain sickness and normal residents at high altitude?
D. Does Chronic Mountain Sickness (CMS) patients save energy by decreasing ventilation and increasing the number of red cells, thereby achieving the most energy efficient mechanism of oxygen transport in order to sustain life?
E. Can CMS be defined as polyerythrocythemia due to a broad spectrum of medical conditions?
F. What is the explanation for acute, subacute and chronic Mountain Sickness at high altitude? What are the physiological changes of high altitude residents and temporary visitors to high altitude upon return to sea level?

Systematic evaluation of papers A - F

A. Paulev, P E., Zubieta-Calleja. Essentials in the diagnosis of acid-base disorders and their high altitude application. J. Physiol. Pharmacol. 56 (Suppl. 4): 155-170, 2005.

The Astrup/Siggaard-Andersen school using computer strategies and the *Acid-Base Chart* makes the diagnosis of acid-base disorders easy at a glance on the chart, when the data are evaluated in context with the clinical story. Siggaard-Andersen introduced *base excess* (*BE*) in the extracellular fluid (*ECF*), extended to include the red cells (*eECF*), as a measure of metabolic acid-base disturbances. The authors suggest the use of *Titratable Hydrogen Ion Concentration Difference* (*THID*) in the *eECF* instead of *BE*, since the essential variable is not a base and not always an excess. *THID* emphazises that the essential variable is the hydrogen ion titrated as a concentration difference from normal. *THID* is zero in normal persons, positive in primary metabolic acidosis and negative in primary metabolic alkalosis.

Specific charts are developed for altitudes of 2500, 3500, and 4500 m. Altitude correction factors are included in the van Slyke equation. This is important for the growing high altitude populations around the world.

One methodological comment: In the Scandinavian countries the unit mM means mmol/L. M in capital letter is read molar and means mol/L. These units are not used consequently throughout the text.

Conclusion: The new knowledge gained from this report is that a better understanding and a more correct picture is obtained of the acid-base relationship under hypoxic conditions. From a didactic point of view the use of titrable hydrogen ion concentration difference used in this material gives a more direct measure of the metabolic component of the acid-base balance than base excess.

B: Paulev, P. E., Zubieta- Calleja, G. R.. High Altitude Diving Depths. Res. Sports Med. 15:213-23, 2007.

A relatively higher risk of developing decompression sickness (DCS) is present when diving in mountain lakes in contrast to sea diving. A determinant for nitrogen exchange between the body and the surrounding breathing medium is the nitrogen tension in the water vapor-saturated, tracheal air. At any altitude above sea level, the barometric pressure (PB) is below 1 atmosphere absolute pressure (PB<760 Torr). The ratio between the inspired tracheal nitrogen tension at sea level and that at any PB must be (760 - 47)/(PB - 47), since the dry inspired nitrogen fraction in atmospheric air is constant and thus eliminated. This ratio is actually equal to the *Nitrogen tension ratio* for loading as well as for deloading the body for nitrogen at any altitude-PB relative to sea level (760 Torr).

Mountain lakes contain fresh water with a relative density that can be standardized to 1000 kg m^{-3} and sea water can be standardized to a relative density of 1033 kg m^{-3}. Thus, the *Water density ratio* is 1000/1033. The difference in relative density affects the size of the inspired nitrogen pressure.

It must be an acceptable strategy to use an accurate correction factor, so it is possible to convert the *actual lake diving depth* (ALDD) to a *standardized equivalent sea dive depth* (SESD). SESD is defined as the sea depth in meter for a standardized sea dive equivalent to a mountain lake dive at any altitude. Therefore, SESD = ALDD * (760 - 47)/(PB - 47) * (1000/1033) and SESD = ALDD * SESD factor.

The authors have chosen to modify the US Navy dive table running to a maximum for professional divers of 60 m at sea level. At the surface of Lake Titicaca there is a typical PB of 480 Torr. The authors consider an actual dive depth of 38 m and calculate an SESD factor of 1.594. Thus SESD = 38 * 1.594 = 60.6 m seawater, showing that less than 38 m is the absolute limit for compressed air diving in this lake and only for highly trained professional divers.

The present model is a major 5 point improvement of previous models:

1. The effect of the water vapor pressure in the inspired tracheal air has never been included before. This factor increases in importance with increasing altitude.
2. The difference between the density of fresh water and sea water has never been included before. This factor is standardized to 1000/1033.
3. The classical sea decompression stops are corrected for use at altitude by division with the SESD factor.
4. The ascent rate at altitude is corrected. The classical sea ascent rate is divided by the SESD factor hereby providing the *lake ascent rate*.
5. The authors suggest to use an extra stop at the last decompression stage for 1 min also after non-decompression dives, since bubbles have been recorded with ultrasound even after such dives.

The new tables presented here are being tested in cooperation with the High Altitude Naval Diving School at Titicaca in Bolivia. Until now, no complications have been recorded.

Conclusion: The new knowledge gained by the material in this report is that a better understanding is obtained of the difference between diving in sea compared to dives in lakes in the highland. As an example as to how dangerous diving in high altitude lakes is: A 38 meter dive in the lake Titicaca is as dangerous as a 60 meter sea-dive.

C: Zubieta-Calleja, G. R., Zubieta-Castillo, G., Paulev, P. E., Zubieta-Calleja, L. Non-invasive measurement of circulation time using pulse oximetry during breath holding in chronic hypoxia. J. Physiol. Pharmacol. 56 (Suppl. 4):251-56, 2005.

In this chapter the question is whether CMS patients had a longer circulation time than healthy controls. This was measured by pulse oximetry, ie. a deep breath is taken where after the subject holds his/her breath. The SaO_2 is followed continuously and the time point when SaO_2 starts to incline (due to the "extra" O_2 that comes with a deep breath) is taken as the circulatory time. The results are clear-cut. There is no difference between the groups.

The data presentation is poor and leaves the reader with many unanswered questions. Original results from only one healthy subject are presented. The striking thing is that SaO_2 can be normalised with one deep breath although PAO_2 and PaO_2 must be rather low at the altitude at which the measurements were performed. It would have been interesting also to see the responses of CMS patients. This point is raised, as it must be difficult to identify the proper points to use for the estimation of the circulation time. Several other methods to estimate circulation time are mentioned pointing at quite significant differences between methods in the observed circulation time. However, why there are these differences is not discussed and the validity of the methods used in the present study has not been checked.

What is also missing is an explanation or an in depth discussion of why the rather large difference in Hct between groups (and most likely also in blood viscosity) has no effect on the circulation time. This leads over to another question which is whether the observed circulation time with the method used is representative for other regions and tissues of the body. Especially critical is whether finger pulse oximetry primarily measures skin S_aO_2 and then skin circulation. Room temperature can then be critical but if all subjects were studied at the same temperature is not reported.

All in all the presented data are probably true, suggesting no difference in circulation time to the skin of the finger, but the extent to which this finding can be extrapolated to other parts of the body is not answered and no explanation is provided for the lack of difference between healthy young subjects and aged CMS patients.

Conclusion: Although the results appear clear-cut with no difference in circulation time comparing CMS patients with controls, the impact of the results will be very minor. This is due to the use of a questionable method and non-optimal equipment, which is reflected in some values that cannot be correct. Moreover, neither the methods used nor the observations made are discussed in the light of the literature in the area.

D: Zubieta-Calleja, G. R., Paulev, P. E., Zubieta-Calleja, L., Zubieta-Calleja, N., Zubieta-Calleja, G. Hypoventilation in chronic mountain sickness: A mechanism to preserve energy. J. Physiol. Pharmacol. 57 (Suppl. 4):425-30, 2006.

In this section the question raised is whether CMS is accompanied by hypoventilation. In the article only a trend, but no significant difference could be found at rest when comparing a healthy group (n=17) with CMS patients (n=13). The patient exhibited marked symptoms of CMS and they had a Hct of 72% compared with 50 % in the control.

In spite of the non-significant difference in V_E at rest of 0.81 l/min (<10%) it is claimed that this "lower" ventilation is an energy (O_2) saving mechanisms. Unfortunately no VO_2 data are presented in the article (although in the methods section it is stated that the measurement of VO_2 has been performed). In the chapter in the thesis on the subject some VO_2 data are presented for three groups (whether they are the same as the subjects in article D is not clarified). The VO_2 and VCO_2 data can hardly be correct. A VO_2 of 138 ml/min is low especially when the VCO_2 is 255 ml/min, resulting in a RER at rest of 1.88. A RER of 0.82 is also reported, but the corresponding VO_2 and VCO_2 data are not given. The effect of hyperoxia is investigated in a third study. Resting VO_2 is increased with close to a 100% with no change in VCO_2 production and unchanged ventilation.

The concern about accuracy of the measurements of oxygen uptake and carbon dioxide production are underscored by the data presented in article D (and article B). During exercise V_E is reported to be the same in the groups under study (article D, figure 1). The body weight difference is 8.5 kg (>10%) and in the treadmill test fixed speed and inclination are applied which ought to result in a lower oxygen uptake in the lightest group of subjects as well as a high V_E/VO_2 (not presented). The values reported in article B (table 3 and figure 5) are even more of a concern. Studies are performed at rest and during exercise at 3,500 m.a.s.l. and at a simulated altitude of ~5,300 m.a.s.l. and again at this latter altitude in a field laboratory. Both resting and submaximal VO_2 were similar but high to very high in the first two conditions. When repeated in the field only half the VO_2 values were observed although there is no reason for VO_2 to differ in the three settings and especially not comparing simulated and "real" exposure to ~5.300 m.a.s.l. In neither the B or D sections of the thesis these unrealistic observations are commented upon. Moreover, relevant other studies in the field are not cited, not even a very similar study of Aymara natives performed at Plano Alto (~4,100 m.a.s.l.) and at Chacaltaya (~5,300 m.a.s.l.), where the results in many aspects were very different.

With this background it is difficult to trust many of the data presented in section D and the same is true for corresponding data in section B. To this should be added that in section D, the hypothesis was proven wrong (no significant difference in V_E between healthy men and patients with CMS). Nevertheless, the author discusses the findings as if the ventilation was lower in the CMS patients and responsible for a possibly reduced O_2 and energy demand. Claims which have no support in the reported data.

Conclusion: In spite of non-statistically significant findings, it is concluded that there is a "sparing" (evt. economising) effect of energy expenditure in severe hypoxia. The few data mentioned in the section are not coherent and some of them cannot be correct. Nevertheless, they are reported as facts and no word of caution is given, suggesting that the author is unaware of the problem he must have had with his equipment. Some of the data presented under B stem from the same project as reported under D. The fact that they are brought into the evaluations makes the suspicion of erroneous results even more legitimate. Oxygen uptake at a given low submaximal workload is unaffected by altitude at least up to 5.300-5.400 metres above sea level. This is well documented by others who have also studied Aymara natives from El Plano and at Chacaltaya (Bolivia). These latter data are not discussed and no reference is made to these reports. In principle, the situation is the same as in section C, but under D it is unacceptable that the wealth of data on the subject in the field is not included in the discussion neither in the original article, nor in the thesis.

E: Zubieta-Castillo Sr, G., Zubieta-Calleja Jr, G. R., Zubieta-Calleja, L. Chronic mountain sickness: The reaction of physical disorders to chronic hypoxia. J. Physiol. Pharmacol. 57 (Suppl. 4.):431-42, 2006.

1. Chronic mountain sickness (CMS) is present in high altitude residents with hematocrit values increased above the normal level at the actual altitude (>58%). CMS is an adaptative reaction to an underlying malfunction. The hematocrit was measured by centrifugation.
2. The authors have reviewed 240 cases of CMS and no specific symptoms or signs could be quantified.
3. CMS is secondary to one or more anomalities in the cardio-respiratory, hematological or renal systems.

4. CMS is most likely to occur in individuals over 40 years of age, who have a tendency to gain weight. They have a predisposition to respiratory or other disorders that are sensitive to hypoxia.
5. CMS patients may suffer from 3 different causes of hypoxia (the triple hypoxia syndrome) superimposed: high altitude hypoxia, CMS hypoxia, and acute, reversible hypoxia caused by an acute respiratory infection.
6. CMS patients are able to hold their breath twice as long as normals, suggesting that they are well adapted to hypobaric hypoxia.
7. The authors suggest to use the hematocrit levels to judge the degree of CMS. This evaluation is simple and objective in contrast to the questionaire proposed by the consensus group.

Conclusion: The material from the database in La Paz, Bolivia is very useful for our understanding of Chronic Mountain Sickness (CMS). The use of hematocrit in this report to judge the degree of CMS is an objective method in contrast to the subjective method with use of questionnaires used in other investigations by other authors.

F: Zubieta-Calleja, G. R., Paulev, P. E., Zubieta-Calleja, L., Zubieta- Castillo, G. Altitude adaptation through hematocrit changes. J. Physiol. Pharmacol., 58 (Suppl. 5):811-18, 2007.

In this chapter time needed for adaptation to various altitudes are investigated. The analysis is based on measurements of the haemotocrit (Hct) primarily at an altitude of around 3,500 m.a.s.l. in one subject. It is found that it takes some 40 days for the Hct to reach an elevated stable level of 50%. Using the ratio altitude/days an acclimatization time of 11.4 days/1000 m is stated as the adaptation time. It is further proposed that this adaptation time can be applied in general to other altitudes and people. Although the measurement is based on only one subject it may agree quite well with the multitude of studies that exist on this issue. The final value of 50% in Hct is, however, in the low range. Moreover, the rate of rise is also at the slow side. The question arises, but is not brought up, whether the fact that the subject is an altitude resident (3,500 m.a.s.l.) contributes to the observed findings and that the they deviate from the bulk of data in the field.

Results are also presented on the Hct during descent from altitude (n=3). The lowering of the Hct is quite slow. There is a tiny trend for a faster drop during the first days in two subjects, but the reduction is much smaller and slower than what is commonly reported. These fast alterations in Hct do not reflect the real increase or decrease in red cell mass but rather changes in plasma volume. A discussion of the role of plasma volume is lacking. This is surprising not the least in view of recent studies, showing that the variation in the serum erythropoietin level not only regulates the erythropoesis, but also the plasma volume. In general the number of references cited in this chapter is very limited and does not at all reflect the wealth of investigations on the topic.

Conclusion: The findings in chapter F could be looked upon as a pilot study (n = 1 and 3). If the trend for a difference comparing the present results on altitude residents with those in the literature, primarily obtained in studies of s.l. residents could be confirmed in a larger group of subjects and explained, it could have been a worthwhile contribution to the understanding of the adaptive blood volume response to chronic hypoxia. This part of the thesis does not bring about any novel findings as it is based on only Hct measurements in a very limited number of subjects. It has no impact.

Evaluation of the overview

General: The overview is divided into chapters A – F in accordance with each of the submitted sub-publications (A – F). Normally, the purpose of an overview is to 1) present a general hypothesis of the dissertation, 2) summarize the work by dividing it into sub-hypotheses, 3) describe the methodology in a selfcritical fashion with comparisons to other techniques and present results and main conclusions, and 4) discuss the significance of the findings in relation to what has already been presented in the literature.

This overview distinguishes itself from the normal format of an overview as follows:
1) There is no general hypothesis of the thesis. Rather, the whole work concerns six different aspects of high altitude physiology, and it is not clear to the reader, what the connection is between the six publications.
2) The methodologies are not crititcally presented or discussed.
3) The significance of the findings in relation to literature is not discussed and the reference list is very incomplete with only 43 references.

Chapter A: In chapter A, the descriptive data of paper A has been expanded by a table and four figures. The main findings constitute descriptions as to how the normal distribution is in 1,865 patients in La paz of pH, P_aO_2, and P_aCO_2. In addition, the development of the corrected Van Slyke formula is described. The descriptive data of the 1,865 patients and the development of the of three tables based on the Siggaard-Andersen nomogram are interesting and should be applied for clinical purposes but adds very little new scientific knowledge to what is already known.

Chapter B: The Standard Equivalent Sea Depth (SESD) for conversion of the Actual Lake Diving Depth (ALDD) to an equivalent sea dive depth is shortly described and is thus a summary of paper B. In addition, two chapters on exercise and football at high altitude are added with new data on respiratory exchange rate and arterial oxygen saturation in 17 male subejcts performing graded dynamic exercise at three different altitudes corresponding to La Paz (3510 m), Chacaltaya and in the Chacaltaya Glass Pyramid Laboratory (5200 m). A table is presented with VO_2, VCO_2, R, S_aO_2 and pulse rate. The interpretation of the data consists of two and a half line stating: "The accumulative sub-maximal work capacity is essentially the same during the three different conditions at both altitudes in spite of a lower oxygen consumption and carbon dioxide production at high altitude". The purpose and significance of these data are not described and discussed so that it is not understood to the uninformed reader as to why the study was done.

In addition, two groups were tested during the same exercise protocol as above. One group consisted of seven healthy males living at 4,200 m and another consisted of 17 healthy males from La Paz. It was not mentioned at which altitude the exercise was done. During exercise, arterial oxygen saturation, pulse rate and ventilation were monitored. Both groups exhibited similar responses, even though it is claimed that in the La Paz group, oxygen saturation dropped already during the 2nd step of the exercise, which was not the case for the other group. No statistical analysis is mentioned and the purpose and significance of the results not described. It is also shortly mentioned that group of seven played soccer for 40 min at 6,542 m altitude which together with the fact that the Bolivian army had done likewise as well as the President of Bolivia, who had played soccer at an altitude of 6,000 m. However, these observations must be considered anecdotal, since no data are presented.

<u>Chapter C:</u> This chapter concerns 1) breathholding at high altitude and 2) considerations on circulation in relation to gravity. These two parts are in addition to the breathholing data presented in paper C, where breathholding and pulse oximetry were used to measure circulation time. The pulse oximetry pattern during breathholding is described, and it is concluded that the average breathholding time in 14 subjects was 65.2 s with a maximum saturation of 97.1 % and that voluntary hyperventilation in La Paz for 2.5 min extends the breath holding time about twice, and four times when hyperventilating with 90% oxygen. It is not described, why these findings are important, and for what purpose the investigations were done.

The 2nd part on gravity related circulation concerns a total different matter, because the author here describes why the dermal thickness of the forehead swells during a trendelenburg tilting of -6° relative to the thickness of the dermis in the tibia. No data is presented, but it is mentioned that 1) one effect of spaceflight is anemia and 2) the author has modified a dermatology instrument to measure dermal thickness. The instrument is not described and neither is the relavance of the postulated anemia during spaceflight. The explanation for the thickness of the dermal layer in the forehead during an anti-orthostatic maneuver is trivial and adds no new knowledge to the matter.

<u>Chapter D:</u> In addition to what has been presented in paper D, which is shortly summarized in a half page description, it is described why 1) hyperventilation at high altitude increases the arterial PO_2, 2) a deep inspiration increases arterial PO_2 and 3) why the respiratory quotient can change with hypo- and hyperventilation. Regarding the two first items, text book considerations are described with no new knowledge presented. Regarding the 3rd item, the author has conducted tests of his own where in 12 – 15 soldiers oxygen uptake and carbon dioxide production were measured and R calculated accordingly. The effects on these variables of descending 1,000 m from 4,100 m as well as switching to sea level oxygen partial pressure (150 mm Hg) were investigated. It was observed that R decreased from 1.56 to 0.82 and from 1.27 to 0.76 during these two occasions. The decrease was explained by a citation from Paulev and Siggaard-Andersen,

where they state that hypo- and hyperventilation can change the R-value accordingly. Thus, the data presented here by the author adds no new knowledge to the issue.

Chapter E:

In this chapter, the terminology of Chronic Mountain Sickness (CMS) is discussed followed by a brief report on some results on arterial oxygen saturation, pulse rate, ventilation, and breath holding time obtained in the laboratory at La Paz comparing CMS patients with normals. It is concluded that saturation is lower in CMS but compensated for by the higher hematocrit and that CMS-patients exhibit pulmonary insufficiency. This is not new. It is also concluded that breathholding time is much longer in CMS, which is stated as proof for the remarkable adaptation process in chronic hypoxia. The main problem with the experimental data is that the CMS group is 2 – 3 times older than the control group, which renders it difficult to understand as to what the effects are of age and CMS, respectively.

In the terminolgy discussion of CMS, it is essentially stated that being adapted to high altitude renders a hematocrit up to 58 % normal, whereas at sea level, it is termed Polycythemia. A hematocrit >58 % is termed Polyerythrocythemia (CMS) and at sea level Increased Polycythemia. The concept of "excessive polycythemia" in CMS is discarded by the author, because a high hematocrit is a necessity for maintinaing an adequate oxygen transport capacity at high altitude.

Thus, in this chapter, no new knowledge is produced.

Chapter F:

This is a very broad description of how the human organism adapts to changes in the environment with very trivial text book considerations. Much is a repetition of paper F, where the author has reported data on hematocrit in himself when travelling between Copenhagen and La Paz. It is concluded that the adaptation time regarding hematocrit when going from sea level to high altitude is some 40 days and considerable less when going from high to low altitude in three subjects. This description is followed by a presentation of some new data regarding 6 young males, who were born and living in La Paz and brought to sea level. It is reported that their ventilation went from as high as 13.128 ml/min to 2.300. This is interesting, but no statistical analysis is reported and the males were not characterized. This makes it difficult to interpret the data, which, however, seems interesting.

At the end of this chapter, blood letting for space travel is briefly discussed. No new data is presented. During spaceflight, the atmosphere in the space cabin is of same composition and pressure as at sea level on the Earth, so it is very difficult to understand the similarities of being weightless in space and hypoxic at high altitude. The author claims that the anemia observed in space is energy consuming, which could then be counteracted by blood letting before travelling to space. When returning to Earth, blood could be re-infused. These considerations are purely speculative and have in fact nothing at all to do with high altitude medicine.

The author also in the final section of the chapter suggests to reduce the ambient pressure in space cabins to two thirds of an atm. This could stimulate the erythropoesis. The benefit of this for the astronauts is difficult to understand.

Conclusions:

The overview is finalized by a conclusion divided into six separate sections corresponding to each of the chapters and papers. Even though the 6 questions presented in the beginning of the overview are answered in the conclusions, they are not at all discussed in relation to existing literature and the significance and impact of the work is thus difficult to interpret.

Conclusion

Strengths:

The following are strengths and novelties of the dissertation:

- Introduction of THID (Titrable Hydrogen Ion Concentration Difference), which emphazises that the essential variable is the hydrogen ion titrated as a concentration difference from normal. In addition the altitude specific acid-base charts for 2,500, 3,500, and 4,500 m.a.s.l is also novel as well as the altitude correction factors in the van Slyke equation.

- Introduction of nitrogen tension ratio and taking into consideration the water density ratio for calculation of SESD (Standardized Equivalent Sea dive Depth). These new tables are of practical use and are currently being tested at the High Altitude Naval Diving School at Titicaca in Bolivia

- The materials from the Clinica IPPA base (Clinica IPPA base = High Altitude Pathology Institute base) regarding 1,823 patients of which 240 had hematocrits above 0.58. The hematocrit is used for the the diagnosis CMS. This is a simplification of the consensus agreement of the world congress in high altitude medicine in Lhasa (2004). There are two regions in the world with people living permanently at high altitude: The Nepal/Tibet/West-China region and the Andesregion. The database from Clinica IPPA is therefore exclusive in the world.

Weaknesses:

The following are the major weaknesses of the dissertation:

- The overview is not coherent and consists of six independent chapters with no common thread or major hypothesis, and it is unclear as to why the 6 topics were chosen. Also, the presentation of results are not at all related to existing literature and with a list of only 43 references, the significance of the findings have not been evaluated by the author.

- The new findings described in the overview are poorly and inadequately described, the methodology and equipment not presented in a sufficient manner and no statistical analysis performed to argue for several of the postulated new findings.

- The relationship to space travel is awkward and not explained as to why this is relevant to high altitude hypoxia, because in space, the atmosphere of space cabins is similar to that of sea level on Earth. The effects of spaceflight on the erythrocyte volume are caused by weightlessness, which has nothing to do with high altitude medicine. The postulated benefits for astronauts of reducing cabin pressure and/or bleeding them before flight seems totally unfounded and very theoretical.

- In the reported studies, there are several methodological concerns. As examples, studies are performed at rest and during exercise at 3,500 m.a.s.l. and at a simulated altitude of ~5,300 m.a.s.l. and again at this latter altitude in a field laboratory. Both resting and submaximal VO_2 were similar but high to very high in the first two conditions. When repeated in the field only half the VO_2 values were observed, although there is no reason for VO_2 to differ in the three settings and especially not comparing simulated and "real" exposure to ~5,300 m.a.s.l. In neither the B or D sections of the thesis these unrealistic observations are commented upon. Thus, the methodology of measurement of VO_2 is of concern.

- Results on Hct during descent from altitude (n=3) is of concern. There is a tiny trend for a faster drop during the first days in two subjects, but the reduction is much smaller and slower than what is commonly reported. These fast alterations in Hct do not reflect the real increase or decrease in red cell mass but rather changes in plasma volume. A discussion of the role of plasma volume is lacking. This is surprising not the least in view of recent studies showing that the variation in the serum erythropoietin level not only regulates the erythropoesis but also the plasma volume. In general the number of references cited in this chapter is very limited and does not at all reflect the wealth of investigations on the topic.

Conclusion:

With the increasing inhabitants and visitors to the high altitude regions in the world in particular the Andes region in South Amerika and the central part of Asia, this dissertation may have some practical and useful conseqences for many people. There is apparently only little logic between the 6 articles, where the only common feature is

hypobaric hypoxia, but nevertheless, they contain some new data so that the field of high altitude medicine from this material is pushed forward to some degree.

Based, however, on the above major weaknesses that

- the work of this dissertation is not based on a main hypothesis but is merely a conglomerat of several not interrelated minor questions of questionable importance except for those raised in papers A and B,
- the author has not demonstrated the ability to convincingly present the results in relation to existing literature and thus explain the significance and impact of the work,
- the author has not demonstrated thorough knowledge of the literature within the field by only including 43 references in the overview,
- most of the results do not produce new knowledge (C – F + overview),
- there are serious concerns as to the methodology of VE- and VO_2-measurements, and
- several conclusions of the results of the new investigations described in the overview are not based on statistical evaluations and not on information on the characteristics of the subjects and the methodology used,

it cannot be recommended that this dissertation is accepted for defence to obtain the doctor of medical science (dr. med.) degree.

Date:____________ ____________________________
Peter Norsk, professor, dr. med.
(Chairman)

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Date: 11/12/08

Peter Norsk, professor, dr. med.
(Chairman)

Date:__________

Johan Kofstad, professor, dr. med.

Date:__________

Bengt Saltin, professor, med. dr.

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Based, however, on the above major weaknesses that

- the work of this dissertation is not based on a main hypothesis but is merely a conglomerat of several not interrelated minor questions of questionable importance except for those raised in papers A and B,
- the author has not demonstrated the ability to convincingly present the results in relation to existing literature and thus explain the significance and impact of the work,
- the author has not demonstrated thorough knowledge of the literature within the field by only including 43 references in the overview,
- most of the results do not produce new knowledge (C – F + overview),
- there are serious concerns as to the methodology of VE- and VO_2-measurements, and
- several conclusions of the results of the new investigations described in the overview are not based on statistical evaluations and not on information on the characteristics of the subjects and the methodology used,

it cannot be recommended that this dissertation is accepted for defence to obtain the doctor of medical science (dr. med.) degree.

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Peter Norsk, professor, dr. med.
(Chairman)

Date:____________

Johan Kofstad, professor, dr. med.

Date: 11. december 2008

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