BIOMEDICINE PROBLEMS OF HIGH TERRESTRIAL ELEVATIONS

Proceedings of a Symposium
Held October, 1967

U. S. Army Research Institute of Environmental Medicine
Natick, Mass.

U. S Army Medical Research and Development Command
Washington, D.C.

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BIOMEDICINE OF HIGH TERRESTRIAL ELEVATIONS

Proceedings of a symposium held at
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Edited by
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PREFACE

The impact upon unacclimatized personnel of exposure to high terrestrial elevations may justly be described as overwhelming. The hostile environmental factors include low barometric (and consequent oxygen) tensions, temperature extremes with rapid fluctuations, high wind velocities, intense solar radiations, rugged terrain features, and limited water supplies. These several factors, alone or in combination, affect performance and produce illness.

This Institute is concerned with (a) the effects of climatic extremes upon the human subject and his performance, (b) mechanisms of acclimatization, and (c) providing the information required for the development of means for protection with minimal decrement of performance. This symposium was therefore organized to present extant knowledge of the biomedical problems engendered by the hypoxia of high terrestrial altitudes. Central to the purpose was the thought that by means of such presentation and discussion, not only would the present "state of the art" be summarized, but also that the gaps in present knowledge would appear in bolder relief, thus revealing the most promising and profitable directions for future research.

May I extend my appreciation to the contributors and participants and especially to Dr. Albert H. Hegnauer, the organizer, chairman, and editor.

JAMES E. HANSEN
Colonel, MC
Commanding

ACKNOWLEDGEMENTS

Obviously, many hands and heads (technical, clerical, scientific advisory, and other) were involved in the development and conduct of the Symposium and subsequently in the compilation of the Proceedings. It is a truism to suggest that the symposium could not otherwise have transpired. It must also be acknowledged that any shortcomings and imperfections are the responsibility solely of the chairman and editor, occasioned by failure to make optimum use of available expertise. Acknowledgement of each and every source of assistance would inevitably degenerate into the platitudinous, and will not be attempted beyond the expression of gratitude to the many for willing and gracious advice and assistance.

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INTRODUCTION

DR. HURTADO:

It is a pleasant duty to express our most sincere appreciation for the honor of having been designated Honorary Chairman of this Symposium, in which many distinguished investigators will present their opinions and experiences concerning the influence of a low ambient pressure. My Peruvian colleagues have requested me to convey also their gratitude for the kind invitation to attend this meeting.

It seems appropriate, at this time, to attempt a brief retrospective consideration of some of the contributions and orientations which have mainly characterized medical research in this field during recent decades and to conclude with a few comments on the present situation and the many possibilities. It was forty years ago, in 1927, when Professor Carlos Monge of Peru initiated a series of systematic studies in an effort to understand how a man born, raised and living at high altitudes was able to tolerate a decrease in the partial pressure of oxygen in the inspired air. Perhaps one of the immediate incentives to carry out this scientific inquiry was the then recent opinion expressed by Barcroft and his collaborators who, after observations made in Cerro de Pasco, at 4,200 meters of altitude, concluded that at that level man is not capable of developing a full acclimatization to the environmental factors. This conclusion, similar to the one previously expressed by Jourdanet from his investigations in Mexico was, in reality, a sort of a challenge to our national pride because, in Peru, several millions of people live permanently in the high Andean region. It was difficult to accept that, mentally and physically, they were below physiological standards, and hard to reconcile such a fact

with the outstanding cultural and technical development reached in past centuries.

It would be impossible briefly to summarize all the observations, made by a great number of investigators, which justified our belief that the native Indians of the highlands exhibit a very definite and effective degree of what has been called "natural acclimatization", in contrast to the "acquired acclimatization", which newcomers to high altitudes may eventually acquire. Perhaps just a few references will demonstrate the validity of this opinion. Historically, there are important facts. Cardich, a Peruvian anthropologist, found some years ago, human skeletons in Lauricocha, at 4,200 meters, and these proved to have an approximate age of 9,000 years when subjected to studies of their radioactive carbon. Very recently, Engel, also in Peru, has reported a similar finding in investigations carried out in Chilca, at 4,000 meters.

Experimentally, there is also significant support of the effectiveness of natural acclimatization. During physical activity, in spite of the accentuation in the degree of arterial blood oxygen unsaturation, and the increased demands in oxygen transport and delivery, we have demonstrated that the high altitude native is able to tolerate very severe stresses and, in some aspects, his efficiency is even higher than that observed in sea level residents under comparative conditions. It has also been found by Velasquez, that when this man is exposed in low pressure chambers to extreme simulated altitudes, the average conscious time largely exceeds the one corresponding to subjects who had been living at sea level.

We have grouped the adaptative processes, which are mainly responsible for natural acclimatization, in two categories. Some of them act along the PO_2 gradient, from inspired air to tissue level, introducing a marked economy in its drop, thus maintaining in the capillaries an oxygen content and tension compatible with diffusion of this gas and its later utilization by the metabolically active cells. Hyperventilation; decreased alveolar-arterial gradient; polycythemia; changes in the affinity of hemoglobin for oxygen, together with modifications in the acid-base balance, fall into this first category. Some of these processes are not yet entirely understood in regard to their pathogenesis. The degree of sensitivity of the respiratory center to the known chemical stimuli still awaits a final answer to some controversial findings. The interaction between hypoxia and erythropoietin, in the regulation of the red cells and hemoglobin volumes in the circulating blood, has recently been the subject of observations of considerable interest. Although there is not a general agreement concerning changes in the affinity of hemoglobin for oxygen, we have some evidence in

favour of this occurrence, but no adequate explanation is available to explain the responsible factors. In the matter of acid-base balance, studies are being carried out in relation to the characteristics of the blood and cerebrospinal fluid, and their relative role in the control of ventilation.

The second category of adaptative processes, which contribute to the efficiency of natural acclimatization, have a high degree of interest. They operate at tissue level and their knowledge has been a consequence of observations carried out in men and some animal species living permanently at high altitudes. An indirect evidence of their existence, and significance, was first derived from the repeatedly confirmed finding that lactate production in physical activity is markedly lower than at sea level, in spite of the hypoxic condition. This may be considered as a protective mechanism, if we think of the reduced buffer protection in the blood of residents at high altitudes.

It has been demonstrated that the capillary vascular bed is quantitatively greater in the tissues of high altitude animals, including man. This fact favours the diffusion of oxygen to the adjacent cells. In addition to this anatomical characteristic, there is already considerable support for believing that important chemical and enzymatic processes at tissue level contribute to the tolerance to a low oxygen tension. Myoglobin is increased and it appears certain that there are modifications in the mechanisms related to an adequate oxygen utilization and energy production. Tissue chemistry and cell morphology, as it may be specially revealed by electron-microscopy, offer very promising fields of investigation which may lead to a more complete understanding of how the body may successfully adapt itself to oxygen limitations. It is not unlikely that the efficiency of natural acclimatization is based, fundamentally, on tissue adaptative factors.

In discussing the subject of acclimatization it is worthwhile mentioning that, very frequently, related studies do not take into due account two fundamental aspects: level of simulated or actual altitude, and length of exposure. In connection with the first one it must be considered that human and other animal organisms have, without doubt, a limit to possible compensatory adjustments. Some of the experimental work carried out, of evident interest, cannot however, be interpreted as representing adaptation in view of the extreme stresses involved. They rather correspond to deterioration. From the point of view of the length of exposure, it must be recognized that a full and effective development of adaptative mechanisms takes a long time, perhaps a life time. In consequence, we are inclined to think that the term acclima-

tization in its true significance should be used as a more restricted criterion. Its correct concept requires the consideration of an integrated physiology and a condition of steady state, characteristics certainly not applicable to newcomers and those temporarily exposed. We may add that it seems more logical to rate the degree of acclimatization in terms of an approach to what is found in natural acclimatization, rather than from the point of view of deviations from what is known to be normal at sea level, as it is commonly estimated.

High altitude research has already gone beyond the strict limits of a physiological framework. Up to a relatively short time ago, acute mountain sickness appeared to be the only defined pathological condition. But we have learned to know that a low pressure environment, per se, may be responsible for the development of some given pathological processes and, in addition, may influence the incidence, evolution and degree of disability of clinical conditions which, so far, have been almost exclusively known by their characteristics at sea level. A few comments will justify this opinion, although it must be pointed out that our knowledge in this field is still very limited. In 1927, Monge indicated that native residents at high altitudes, regardless of age and sex, may eventually lose their acclimatization and develop signs and symptoms which have been grouped under the name of chronic mountain sickness or Monge's disease. The typical case is characterized by a considerable accentuation in the degree of hypoxia and the level of polycythemia, respiratory acidosis, marked right ventricular hypertrophy and severe pulmonary hypertension and frequently shows functional alterations in the central and peripheral nervous system. From observations we have had the opportunity to carry out, we are of the opinion that, in most cases, the loss of acclimatization is explained by the presence of a hypoventilation process. However, it is not known why the respiratory center may lose, at high altitudes, the increased sensitivity to chemical respiratory stimuli present in healthy residents.

In 1937, we observed the occurrence of pulmonary edema during the first few hours of exposure to an altitude environment. Since that time, a large number of cases have been described, and we feel certain that important aspects of this condition will be revealed in the reports to be presented in this meeting. In our experience, and also in the experience of most Peruvian investigators, most cases develop in subjects returning to altitude after

a brief visit to sea level, with no previous history of cardiac symptomatology.

Some information is also available, although in a much more limited degree, in regard to some other clinical conditions. These may be briefly mentioned. The incidence of patent ductus arteriosus, a congenital heart abnormality, is definitely greater in the highland areas. Certain interesting peculiarities have been described in relation to the location and frequency of peptic ulcer; the occurrence of volvulus as a post operative abdominal complication; and gastric secretion changes, with a possibility of an early tendency to develop atrophic gastritis. Attention has also been called to the frequency of liver and gall bladder pathology. An interesting problem for study concerns the incidence of diabetes at high altitudes, if it is defined as the moderate hypoglycemia observed in high altitude natives and some modifications in the carbohydrate metabolism and insulin action.

Cardiovascular diseases offer also important questions to be elucidated, and these have a very special interest on account of the demonstration, made originally in Peru about ten years ago, that all permanent and long time residents at high altitudes have a moderate degree of pulmonary hypertension. We have been impressed with the apparently low incidence of coronary episodes and systemic hypertension in the Andean population, a fact associated with a lower level, throughout life, of peripheral blood pressure. In this respect it may be indicated that at the present time an intensive investigation is being carried out, by Peruvian pathologists, on autopsy material collected at high altitudes, and special attention is being given to a quantitative estimation of sclerotic degenerative lesions of arterial walls in relation to age.

The field of immunology and infectious diseases has also interesting possibilities. A rather superficial impression, based only on general clinical data and morbidity rates, is enticing in this respect. Blood levels of uric acid are elevated in permanent residents of high places, but no relationship has yet been established with the frequency of gout and other arthritic processes.

As a matter of information, and possible interest to this audience, we like to point out that studies are now being made in Peru, by several groups of investigators, on experimental cancer production: the endocrine factors in acclimatization and the modifications, if any, in the fertility rate and pregnancy evolution, including the anatomical characteristics of the placenta. Fetal life has a particular attraction, because it concerns the provision of oxygen to an organism whose growth and development is dependent on another which is hypoxic.

To conclude, allow me to express a conviction which I hope is also yours. High altitude research is no longer an isolated field of work, a sort of a physiologist's hobby, as it has been regarded in the past. It has deep implications in general biology, because a low pressure environment is capable of modifying the characteristics – morphological, functional, chemical, and even psychic – of the animal organisms subjected to its influence, and these may be estimated as many millions in the world. The expansion and intensification of this research would help to widen the concepts of normality and homeostasis, avoiding the erroneous opinion, not infrequently held, that life at high altitudes necessarily represents an abnormal condition.

It has also a definite clinical significance. Such an environmental factor influences the incidence and evolution of disease. Moreover, in many pathological processes at sea level, there are difficulties in the acquisition, transport and utilization of oxygen, and signs, symptoms and disability may have a close dependent relationship. It is then of interest to the clinician to know how the body may best compensate for, or tolerate these deficiencies, and valuable information may be found in the altitude native resident.

Finally, man is now leaving the terrestrial environment in an intense effort to conquer space. Oxygen deficiency, or lack, is one of the many barriers for the successful accomplishment of this objective, so high altitude research may help, at least partially, to achieve this scientific endeavor.

PANEL

ACUTE MOUNTAIN SICKNESS

Chairman: Sujoy Roy

OPENING REMARKS

DR. ROY:

First, I wish to thank you for giving me the honour of chairing the first session on acute mountain sickness. When I see here so many august personalities, led by Dr. Hurtado, I really feel very humble, because my experience in high altitude is very limited. We have been involved in high altitude problems only since 1962.

In the history of mankind, wars have always been waged between nations every few years but never before have battles been fought at altitudes of 18,000 feet. This is what gave us the background and necessity for high altitude study. What we lack in experience in terms of time we have, perhaps, made up by experience in terms of numbers of men.

May I be permitted to pay my homage to the brave Indian soldiers who, under most trying conditions, have been very cheerful and co-operative subjects for medical investigations? I also wish to take this opportunity to convey the regards and felicitations of General A. K. Dev, Director General of Armed Forces Medical Services in India, who was invited to attend this conference but could not come due to a previous commitment.

Before we proceed any further, let us ask ourselves what the justification is for holding this symposium. I can do no better than to quote Sir William Osler who, in 1885, said, "It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease to see exactly where we stand in regard to it, to inquire to what conclusion the accumulated facts seem to point and to ascertain in what direction we may look for fruitful investigations in the future."

Perhaps at the end of this two-day symposium we shall be in a better position to ascertain where we stand.

PATHOPHYSIOLOGY OF ACUTE MOUNTAIN SICKNESS

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Living organisms when placed in unusual environments must undergo physiological and/or behavioral alterations in order to render themselves more fit for survival. The symptomatology coincident with arrival of humans at high terrestrial locations signals some of the early responses to the stress of hypoxia. This set of symptoms or syndrome is known as acute mountain sickness.

The Army's interest in mountain sickness stems from the knowledge that initial combat effectiveness is significantly reduced at high altitudes. It is important from a basic medical point of view to gain insight into the illness encountered on mountains and attempt to prevent or cure it. But it is even more important, from a military point of view, to identify the types of performance decrement and the degree to which that decrement will reduce combat effectiveness. A good definition of mountain sickness would be, "the combination of subjective symptomatology experienced and the degree of functional capability lost while living at high elevations."

The intent of this presentation is to review a few pertinent physiologic and biochemical alterations occurring upon arrival at 14,110 feet on Pikes Peak, Colorado. These data were obtained through the combined efforts of several investigators of the Physiology Division, U.S. Army Medical Research and Nutrition Laboratory. Time does not permit a complete discussion of interacting variables, nor does the current state of knowledge.

Temporal Considerations of Symptomatology

Common subjective symptoms encountered by men during the first few days at altitudes in excess of 10,000 feet are headache, nausea, vomiting, anorexia, insomnia, somnolence, dyspnea, occa-

sionally palpitations, depression, impaired judgment and irritability. Headache, nausea, vomiting and marked fatigue seem to be the most debilitating. The identification and measurement of these symptoms have been reported recently by Evans (1). Not all of the symptoms show the same onset and duration and there is considerable individual variation in the time of maximum severity. For these reasons, one should be cautious in adding individual symptom incidence and severity and calling that "sickness." However, if symptom incidence is considered as a whole, a pertinent finding is observed. Figure 1 illustrates previously reported data taken on college-age females (2). They are presented here to establish roughly the temporal relationship of symptomatology and altitude exposure. Data on men (1) show essentially the same time course with maximum severity occurring after 30 - 40 hours' exposure to 11,000 and 15,000 feet. One can observe from these results a rapid onset reaching maximum in the first or second day, with a decline in severity and incidence such that subjects are essentially asymptomatic by the 5th day of exposure. If one is looking for a physiological or biochemical correlate to symptoms, it is necessary to keep these temporal relationships in mind.

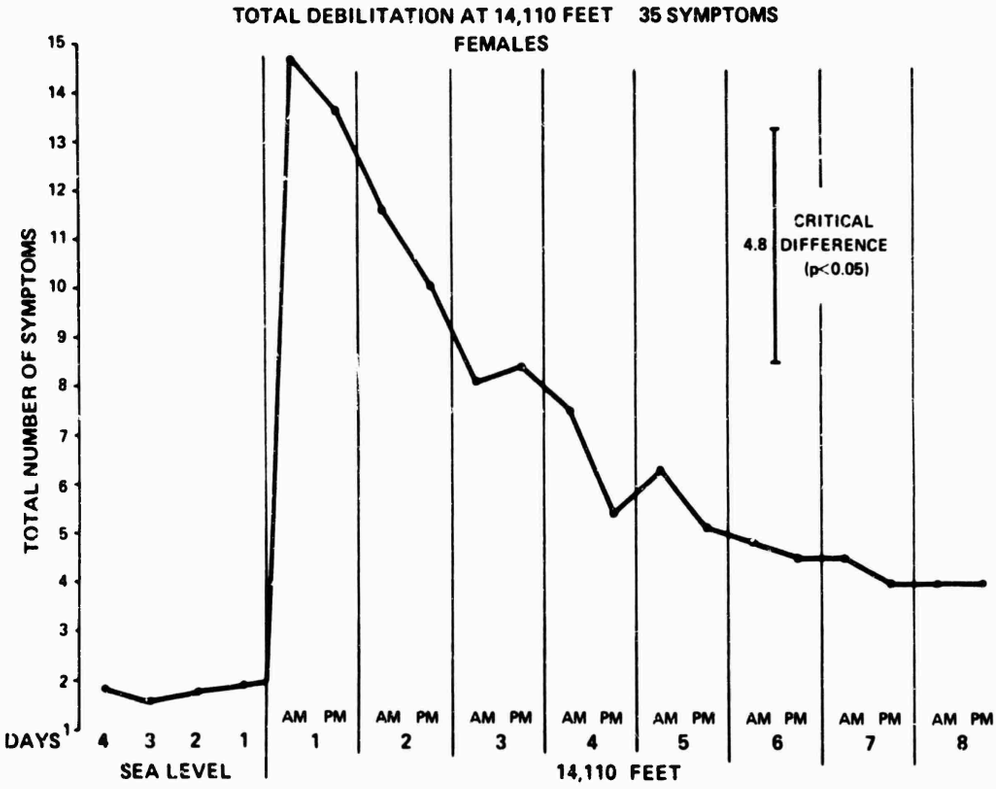

Figure 1. Illness incidence as determined by individual questionnaires – mean values. Statistical significance determined by analysis of variance. From Harris, Shields and Hannon (2).

Changes in Resting Ventilation

Figure 2 summarizes findings in nine men (age 19 - 25 years) of resting ventilation, tidal volume and respiratory rate at sea level, and 2, 5 and 14 days at altitude exposure. Similar results have been reported by others (3). Ventilation rose rapidly in the first two days from a sea level mean of 8.3 L./min (BTPS) and stabilized by day 5 at approximately 12 L./min (BTPS). Tidal volume paralleled ventilation rather closely and was accompanied by marked increases in coefficient of variability which signifies quantitative differences in responses of individuals on this parameter of acclimatization. Breathing rates showed a tendency to increase at two days, then to return toward sea-level values. The deeper breathing at normal rates after five days on the mountain suggests a restructuring of neuronal discharge patterns responding to medullary stimulation through Hering-Breuer pathways. It is apparent that changes in ventilation patterns are most profound early in altitude exposure during the time of most severe symptomatologic response.

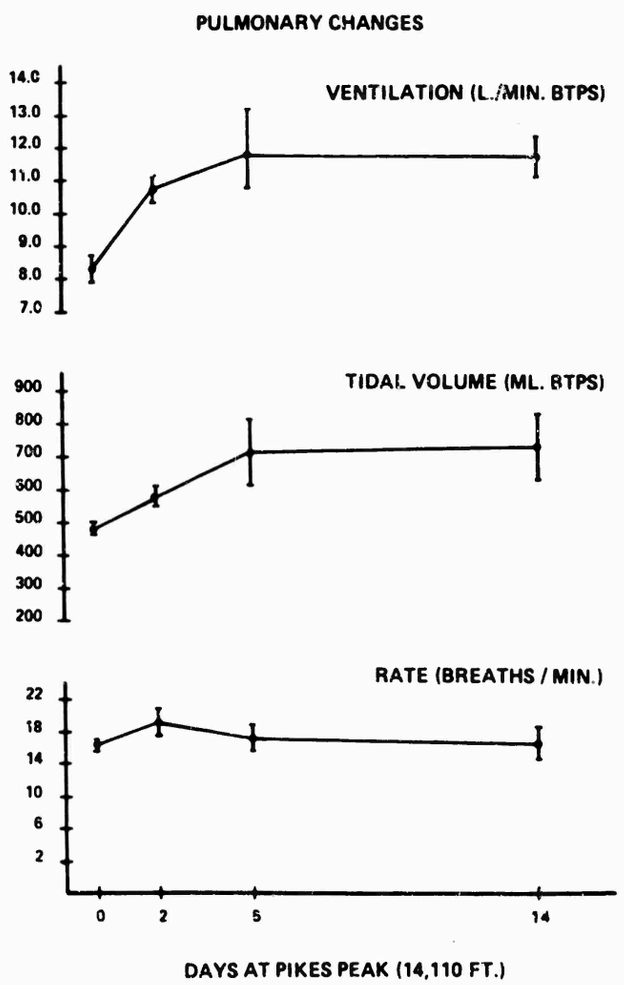

Figure 2. Values plotted are as mean ± S. E. M.

Arterial Blood Gases and pH Adjustments

Figure 3 illustrates alterations in blood gases and pH found in arterial blood in the same subject population for which ventilation data are described. Arterial oxygen tension (PO_2) rapidly declines on ascent to altitude reaching a minimum value of about 40 mm Hg. after two days. On the third day, however, there is some recovery (about 9 mm Hg.) and thereafter steady state value of about 50 mm Hg. is usually seen. Oxygen saturation parallels the fall in PO_2 but appears to reach a steady state value of around 90% after two weeks' exposure. Measurements of carbon dioxide tension (PCO_2) reveal an initial, rapidly-developing hypocapnea which progresses more slowly after day 3 until at 14 days a mean PCO_2 of approximately 20 mm Hg. is reached. Arterial pH reflects this respiratory alkalosis. During this time the renal excretion of bicarbonate and fixed base is accelerated (4) and partially compensates for the hypoxia-induced respiratory alkalosis. The final data point on the pH curve, plotted with a dotted line, may well be erroneous since it represents the mean of only five subjects whose variation was great. The 14 day value was not significantly different from that at sea level.

Although not included in Figure 3, the hemoglobin concentration and hematocrit increase so that somewhat after two weeks, O_2 content has essentially returned to pre-altitude values (5) in the face of reduced saturation.

Respiratory Control with CO_2 Signaling

Earlier work with high altitude natives by Hurtado (6) and with sea level residents at high altitude by Severinghaus (7) has shown CO_2 response curves to be shifted to the left under conditions of chronic hypoxia. This simply means respiratory control is adequate in chronically hypoxic, hypocapnic individuals, i.e., there has been a shift in respiratory set-point to CO_2. It is important to determine how rapidly this set-point shift occurs if respiratory control is suspected as a limiting factor in natural acclimitization.

Respiratory control system response to CO_2 signaling was studied using incremental increases and decreases of inspired CO_2. Increments of 7.6 mm Hg. CO_2 were employed at sea level and Pikes Peak. Oxygen tension, however, was kept at sea level equivalent at both altitudes to rule out hypoxic drive of ventilation. Arterial PCO_2 and ventilation were measured simultaneously under steady state conditions. Hysteretic loops describing ventilation as a function of PCO_2 were constructed such that: (a) position of loops on the abcissa indicates respiratory "set-point" to CO_2;

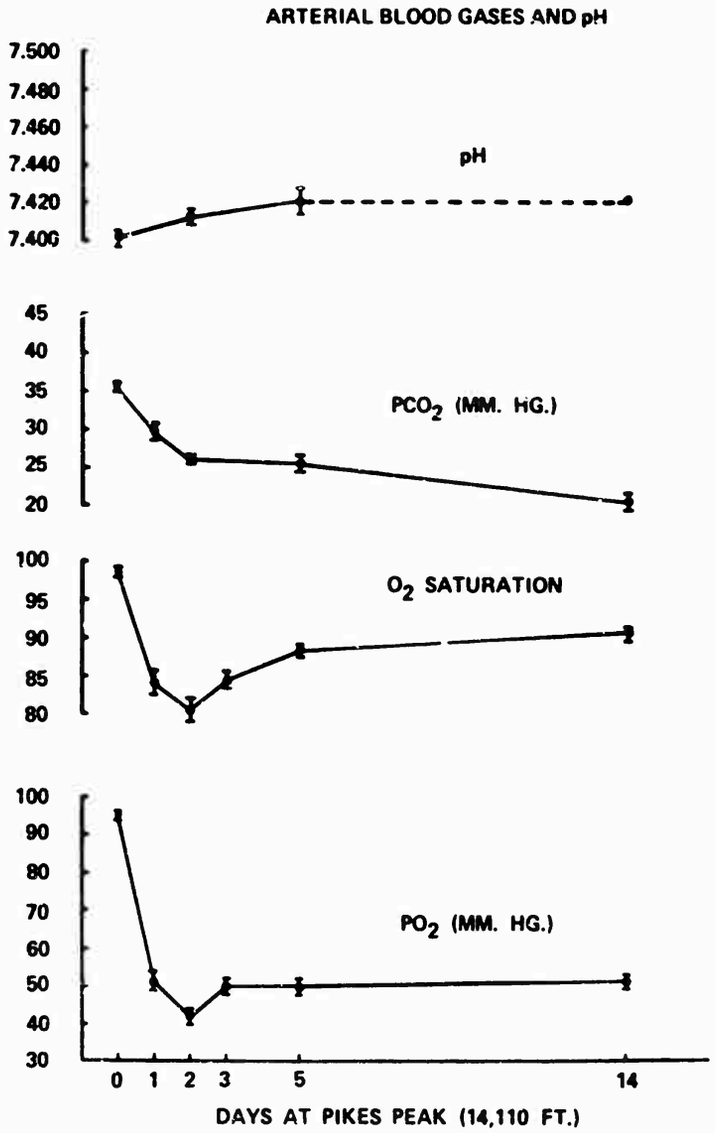

Figure 3. Values plotted are as mean ± S. E. M.

(b) slope of loops indicates respiratory sensitivity to CO_2; and (c) area inscribed by the loops indicates control system efficiency, i.e., the less hystersis in the loop, the more perfect the control system. Figure 4 contains the results of these experiments with each loop being constructed from the mean values obtained from eight subjects. Measurements were made at sea level and on the 2nd and 5th day at Pikes Peak.

The salient features of Figure 4 may be summarized. First, subjects responded to CO_2 signaling at a "set-point" which is nearly equivalent to resting PCO_2 at both low and high altitude. Prealtitude levels of ventilation (1.00 on the ordinate) were reached after 10 minutes of breathing air with sea level equivalent of O_2 (initial downward deflection of right limb on the loops at Pikes Peak). This decrease in ventilation at altitude was accompanied by only a slight elevationn of PCO_2 and presumably repre-

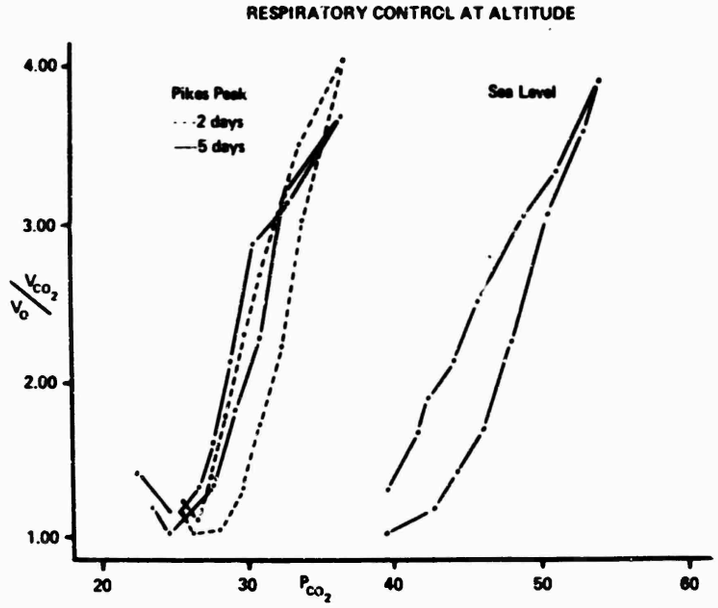

Figure 4. Hysteretic loops representing ventilation as a function of arterial PO_2. Means of 8 subjects breathing 160 mm Hg. inspired PO_2 with 7.6 mm Hg. increments inspired PCO_2. Ordinate represents ratio of ventilation during CO_2 breathing to that at rest with 160 mm Hg. O_2.

sents the degree of ventilatory drive by the hypoxia. It appears, therefore, that the shift in "set-point" to CO_2 stimulation is reasonably complete by the 2nd day of hypoxia. Second, the slopes of the CO_2 response loops were not significantly affected on Pikes Peak. This strongly suggests no change in sensitivity to CO_2, i.e., a given increase in PCO_2 results in the same increase in ventilation at both altitudes. Nevertheless, it must be stated that there is considerable individual variation in this measurement. Some subjects do show obvious increases in loop slope while the majority do not. Perhaps it is unwise to make sweeping generalizations based on average responses of such small groups. Finally, the degree of hysteresis appears to diminish throughout the study. A two-tailed sign test of loop areas showed some tendency toward more perfect control. This tendency was slight, as can be seen by inspection of average loops. Probably, the reduction in hysteresis is a consequence of practice effects on the procedure rather than any real improvement in perfection of the control system. In any case, it seems safe to conclude that respiratory response to CO_2 is not a major contributing factor in the pathogenesis of acute mountain sickness, since it has already reached a stable "set-point" when symptoms are maximal. Stated more simply, the respiratory center has "learned to live with the hypocapnea" when subjects are sickest.

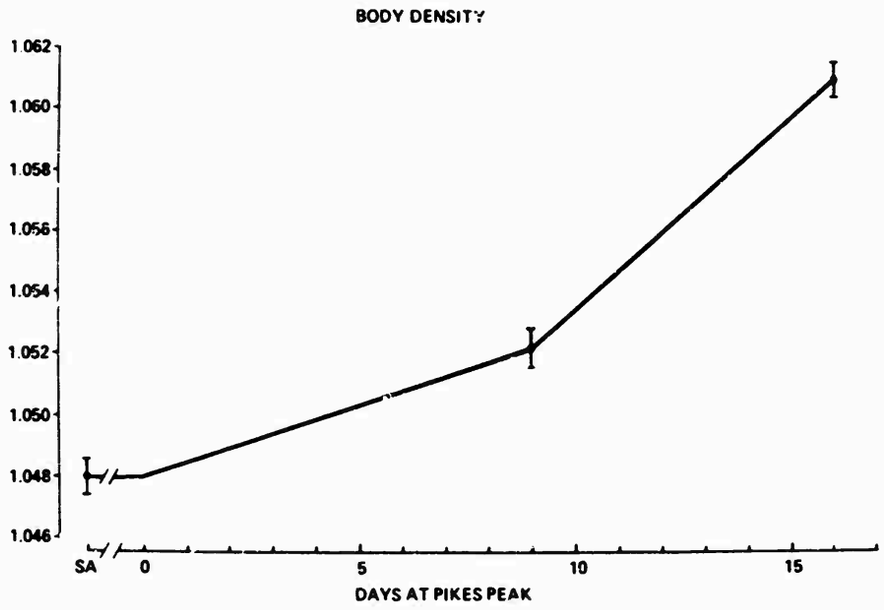

Figure 5. Body density by water displacement. Correction made for residual lung volume by nitrogen wash-out. Mean values ± S. E. M. From Hannon and Chinn (8). SA = measurements made at San Antonio, Texas (sea level).

Body Composition and Fluid Compartments

Measurements of body composition and fluid spaces were made on a nine-man group of volunteers over 15 days at Pikes Peak (8). Figure 5 contains the means of body density measured with a whole body densitometer involving the water displacement principle. Values were determined after maximal expiration and corrections made for residual lung volume (nitrogen wash-out method).

The steady increase in body density was highly significant ($P<.01$) after 15 days' exposure to altitude. This degree of increase in density could occur if there were: (a) a marked increase in lean body mass, which is highly unlikely since body weight decreased also; (b) a severe hypohydration; or, (c) a significant loss of body fat.

Figure 6 summarizes changes found in body composition calculated from body weight and body density by the method of Chinn and Allen (9). These measurements were made only at 9 and 15 days of exposure since they required transporting subjects from Pikes Peak to a laboratory in Fort Collins, Colorado. Body weight showed the usual loss encountered in studies of this duration amounting to a mean loss of 2.6 kg. after 15 days. Calculation of total body water showed a tendency to increase but the change was not significant. Body fat decreased and appeared to be respon-

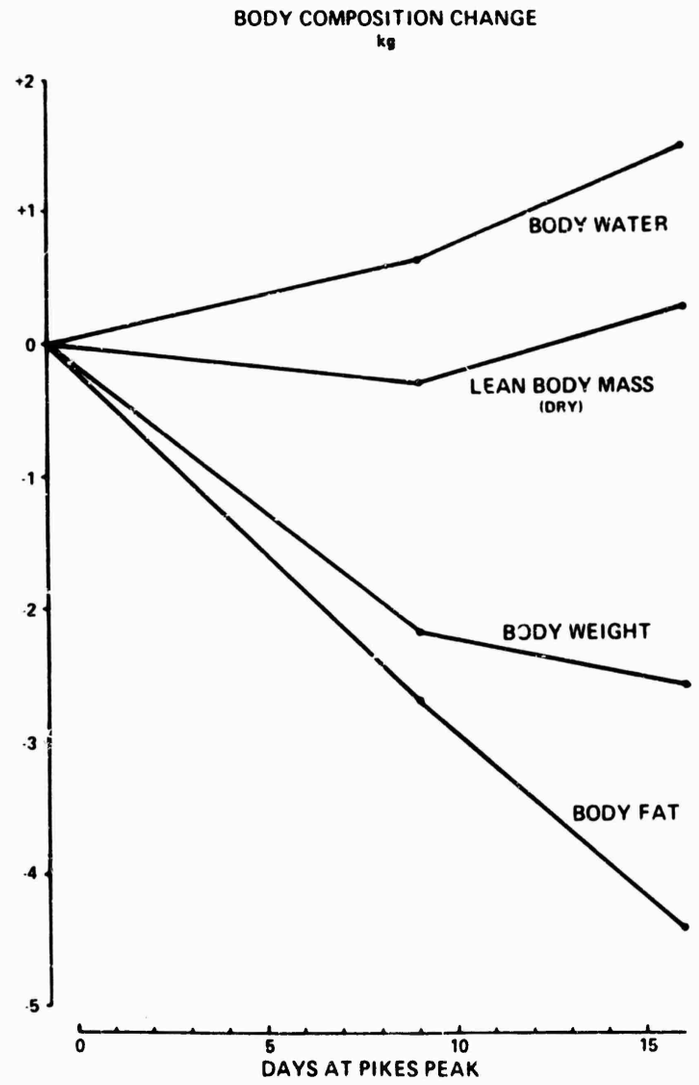

Figure 6. Mean values plotted. Lean body mass calculated by difference. From Hannon and Chinn (8).

sible for the loss of weight. Lean body mass predicted in this manner showed no significant change. This component is ordinarily very constant and would be expected to change only very slowly and under the most severe, debilitating conditions. The loss of body fat stores during hypoxic exposure may seem paradoxical in a sense. Combustion of lipid requires greater amounts of oxygen mole for mole, than carbohydrate oxidation. It does not seem advantageous for the system to do this in a state of oxygen deficiency, but oxygen is available to cells, obviously, and one is forced to the conclusion that lipid mobilization and oxidation does take place during hypoxia.

Experiments with rats on various diets at 11,400 feet have been reported (10) in which total body fat was measured by direct methods. Those data (table 1) reveal a significant depletion of total body fat in three weeks compared to controls at Denver altitude (5,300 ft.).

Table 1. Percent of total ether extractable fat in rat carcasses. Mean values ± Std. Dev. Summarized from Chinn (10) and unpublished data.

		DENVER	ALTITUDE
DIET	n	%BODY FAT	%BODY FAT
HIGH-FAT	8	13.50 ± 1.05	8.30 ± 0.77‡
HIGH-CARB.	8	6.79 ± 1.36	5.01 ± 1.00+
HIGH-PROT.	8	7.20 ± 1.71	5.27 ± 1.02+
PURINA CHOW	6	6.23 ± 0.87	5.99 ± 0.52*

*Non-significant
+Significant at 2% level
‡Significant at 0.1% level

Figure 7 contains mean values of plasma volume at sea level (San Antonio, Texas) and after 3, 8 and 15 days on Pikes Peak observed in these subjects. Plasma volumes were determined by conventional procedures with Evans Blue dye. The 18% reduction by day 15 is in close agreement with the plasma volume loss at high altitude frequently reported and recently reviewed (11). Much speculation has been made regarding reduction of plasma volume during chronic hypoxia and dehydration has often been suggested as a responsible factor. Figure 8 shows results of measurements of total body water calculated from the volume of distribution of 4-amino antipyrene (4-AA) in the same subjects at sea level and 1, 3, 8 and 15 days at high altitude. 4-AA was given intravenously and plasma concentrations serially sampled over five hours were extrapolated to zero time for calculating volume of distribution. The tendency toward increased total body water volume was significant by analysis of variance ($P<.05$) by the 15th day. Figure 6 shows a marked similarity of values for body water changes estimated by two methods (body densitometry and 4-AA). The apparent decrease seen (Figure 8) after one day's exposure was not significant, but might well reflect a slight initial hypohydration. This would explain the initial small rise of hematocrit commonly reported in studies of this type (11). The data here argue strongly against any chronic hypohydration at altitude and one is forced to seek another explanation for the chronic reduction in plasma volume.

Extracellular space was estimated in these subjects by intravenous infection of sodium thiocyanate with serial sampling over

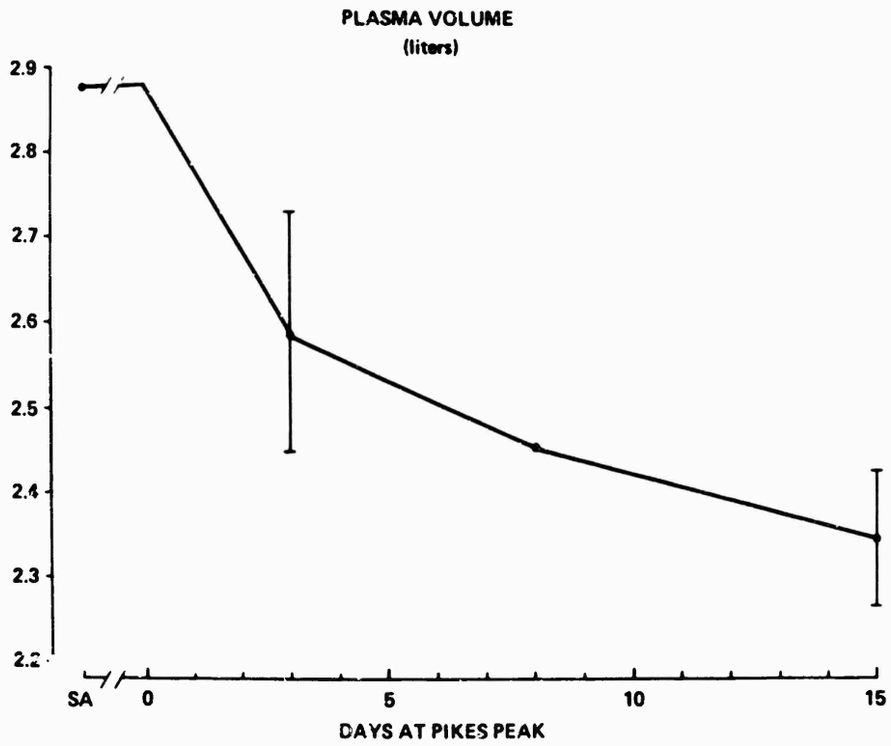

Figure 7. Plasma volume determined by Evans Blue dye. Mean values with maximum and minimum Std. Dev. From Hannon and China (8).

five hours and extrapolation to zero time. The results are plotted as mean values in Figure 9. A rapid initial decrease in extracellular volume is seen which reached a maximum at eight days on the mountain and tended to recover partially at 15 days. The magnitude of reduction at eight days was nearly three liters which was significant by analysis of variance ($P<.01$). In view of these data, plasma volume loss apparently reflects the overall change in total extracellular fluid volume.

If extracellular volume is decreased while total body water volume is unchanged or slightly increased, one can calculate intracellular volume by difference (i.e., total body water - extracellular water) and see an expanded intracellular compartment. This is presented in Figure 10. Once again, the marked change is most rapid during the first three days of altitude stress. At maximum it amounts to a three-liter increase on day 8 and tends to stabilize there throughout the next seven days. Similar findings in rats have been reported (10). Table 2 summarizes these findings which were based on chloride space. Thus, two methods of estimating intracellular water, in two species of animals (man and rat), indicate chronic hypoxia with hypocapnea causes an expansion of intracellular volume at the expense of the extracellular compartment.

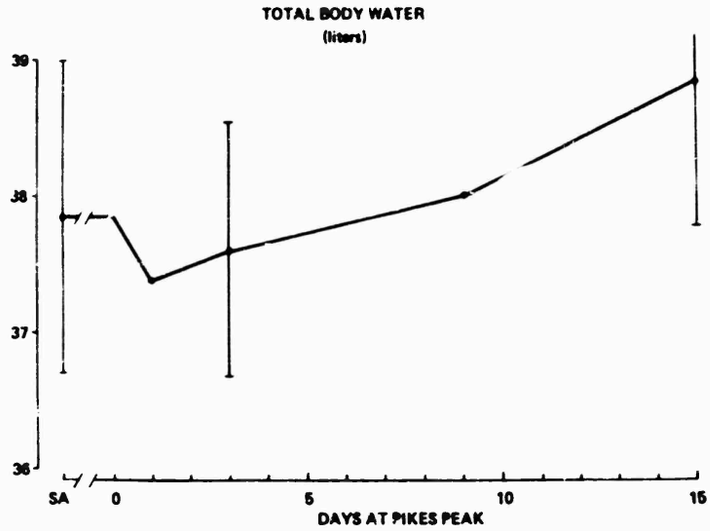

Figure 8. Body water estimated by volume of 4-aminoanti-pyrine distribution. Mean values with representative Std. Dev. From Hannon and Chinn (8).

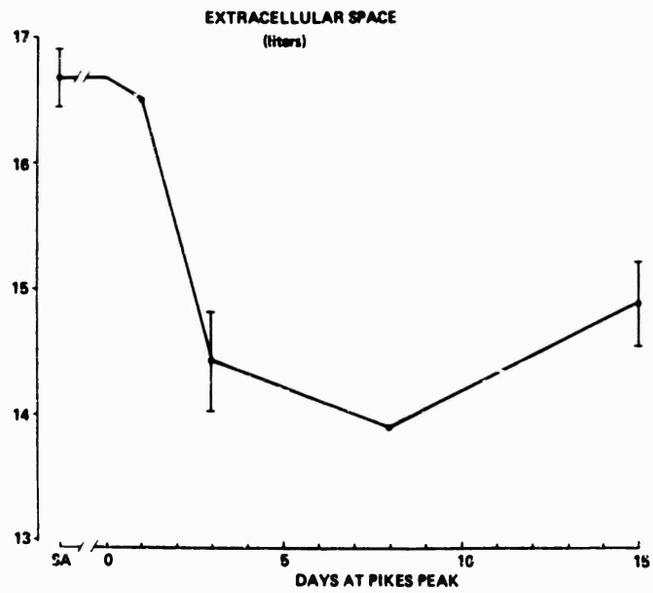

Figure 9. Extracellular space estimated by thiocyanate. Mean values with representative Std. Dev. From Hannon and Chinn (8).

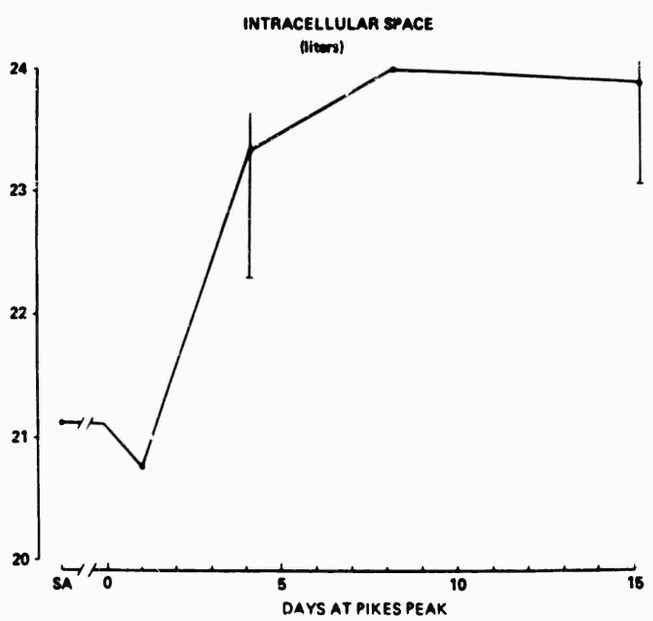

Figure 10. Intracellular space calculated from total body water and thiocyanate space by difference. Mean values with representative Std. Dev. From Hannon and Chinn (8).

Table 2. Percentages of intracellular water in rats, calculated from chloride space and total body potassium. From Chinn (10).

DIET	n	DENVER	CLIMAX	%CHANGE
HIGH-FAT	8	57.66 ± 3.08[a]	62.76 ± 6.35	+8.84[b]
HIGH PROTEIN	8	55.03 ± 2.50	60.46 ± 1.29	+9.87[d]
HIGH CHO	8	55.85 ± 1.90	64.54 ± 3.18	+15.56[d]
PURINA CHOW	6	58.01 ± 4.10	67.04 ± 4.09	+15.57[c]

[a]standard deviation
[b]significant at 5% level
[c]significant at 1% level
[d]significant at .1% level

Figure 11 summarizes these fluid shifts in the nine men at Pikes Peak. An initial hypohydration at day 1 is suggested by decreases of body water, extracellular and intracellular water, although the reductions were not statistically significant. At best, one can conclude only a very slight hypohydration. Then very quickly, two days later, a marked recompartmentalization of water is evident. The shift of fluid is maximal by the 8th day of exposure and amounts to a three-liter expansion of intracellular water with a parallel reduction in extracellular water. Plasma volume reduction was 550 cc or 18% at maximum. It is interesting that the three-liter reduction of extracellular volume reported here amounted to 16%, the same relative magnitude seen in plasma volume reduction. This suggests a passive shift of fluid from the vascular system toward a shrinking interstitial space from which fluid is moving into intracellular space. The implications of such a fluid shift are quite considerable in terms of altered physicochemical kinetics of intracellular reactions. If intracellular dilution occurs as a result of this fluid shift, a major component of adaptation to high altitude may lie in intermediary metabolic adjustments to an altered intracellular milieu.

Another question, perhaps more pertinent to this discussion, is whether such an altered distribution of water might be responsible for the symptomatology of acute mountain sickness. The temporal relationship of fluid shifting to symptom incidence (Figures 1 and 11) suggests that altered water compartmentalization per se is not well correlated with symptoms since the latter have subsided some four days earlier than establishment of maximal water shifts. As with other systems noted here, however, maximal symptom incidence coincides closely with the period of greatest water flux, i.e., during the first three days of altitude exposure.

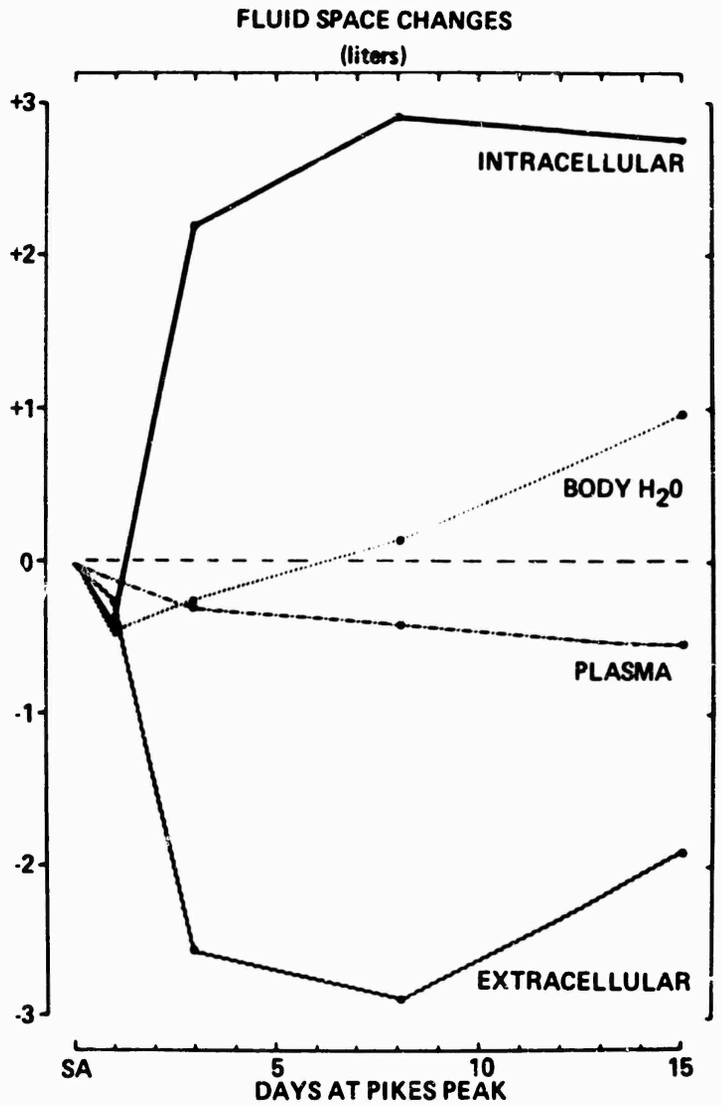

Figure 11. Summary of fluid shifts. Mean values. From Hannon and Chinn (8).

The data in Figure 11 do not indicate whether fluid shifts are permanent or merely transient at high altitude since the particular study involved only 15 days. An attempt to resolve this point of contention was made using existing data on body fluid compartments at various altitudes. Figure 12 contains these data. Data points at 6,000 feet are from Gopalan *et al.* (12) using urea for total body and thiocyanate for extracellular volume in men. Data points at 14,900 feet are those of Picon-Reategui (13) based on antipyrine and sucrose space. The remainder are values measured at sea level, Denver (5,300 ft.), Climax, Colorado (11,400 ft.) and Pikes Peak (14,110 ft.) by members of this laboratory. Each data point plotted, therefore, represents space estimates on natives or at least partially acclimated men or rats who exhibited no typical picture of acute mountain sickness. It seems, therefore, that a stabilized recompartmentalization of water is a consequence of chronic altitude exposure.

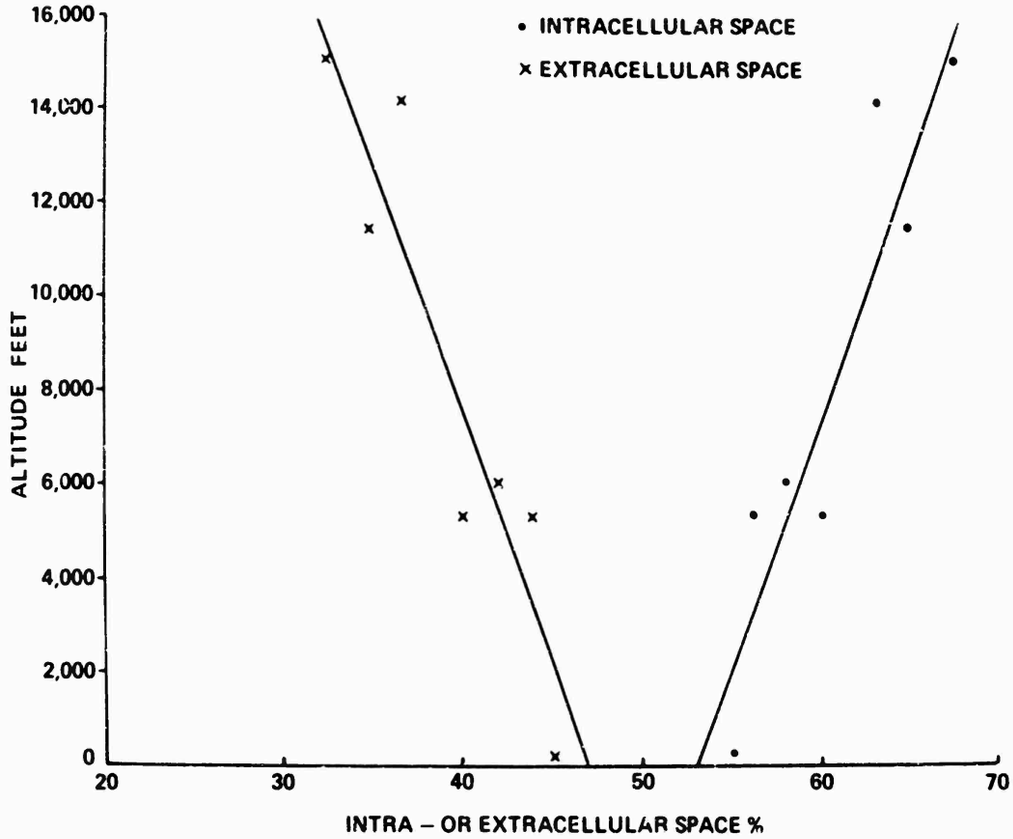

Figure 12. Effect of altitude on percentages of intra- and extracellular spaces. Mean values from separate experiments. From Chinn (10).

CONCLUSION

Since maximal symptomatology of acute mountain sickness occurs during the early stages of exposure, when most body characteristics are *changing* maximally, it seems most logical to suspect these symptoms are the subjective reactions to the entire spectrum of specific and nonspecific responses the host undergoes in reaching a new steady-state to cope with the unusual environment imposed upon it. It fits, in the broad sense, the general concept of stress originally proposed by Selye. Certainly a specific biochemical lesion may be primarily responsible for a given symptom or cluster of symptoms, but as Dr. Carson will point out in the next presentation, the interaction of multiple factors resulting in a rather nonspecific clinical syndrome more nearly typifies the picture of acute mountain sickness.

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A DISCUSSION OF SOME CLINICAL ASPECTS OF ACUTE MOUNTAIN SICKNESS

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It would seem most appropriate to begin with a definition and description of acute mountain sickness (AMS). The clinical point of view is emphasized since symptomatology may bear little or no relation to the duration and severity of physiologic alterations or changes in psychomotor performance which are observed at high altitude.

We consider AMS to be a definite clinical syndrome or complex of symptoms which occur to some degree in all unacclimatized individuals who rapidly ascend to high terrestrial elevations. Significant symptoms usually become manifest only after several hours of exposure, reach their peak severity within the first twenty-four to forty-eight hours, and then gradually recede over the ensuing two to four days. The syndrome may be so mild that the individual is virtually unaffected or so severe that he is temporarily incapacitated. We have been particularly impressed with the great individual variability in responses which are observed. This is not difficult to understand if one considers AMS, like any other illness, to be the overt expression of a host reaction pattern to one or more evoking stimuli. In many instances, this reaction pattern may depend more on the past and present state of the host than on the primary inciting factors. We shall come back to this point shortly.

The following will serve as a description of the AMS syndrome:

"... There is a sense of overwhelming oppression which rapidly takes the spirit out of men... Trifling work is fatiguing and more burdensome work rapidly leads to exhaustion. A throbbing headache may develop and reach cruel intensity. Dizziness occurs, accentuated in the standing position. Dyspnea may be a problem... Nausea, vomiting and loss of appetite are common-

place. Lack of coordination reduces the efficiency. . . Apathy may be interrupted by outbursts of irritability. Judgment and morale decline. . . Unwillingness to continue work or the onset of physical disability may rapidly disorganize a well-disc plined and efficient unit. A severe and alarming, albeit usually innocuous, illness has produced almost complete ineffectiveness" (1).

This particular description depicts the effects as well as the symptoms of AMS, yet it was written to relate what happens to normal men who are exposed, *not to high altitude* but rather, to high ambient temperature. The remarkable similarity in responses to such dissimilar stress situations points out the nonspecific aspect of man's adaptive capabilities.

The importance of the individual in determining the observed reactions to stressful stimuli has been alluded to previously. This can be illustrated by the results of some of our past studies on the effects of various drugs in reducing the severity of symptoms of AMS. We have found that two psychotropic drugs, codeine and desoxyephedrine, are as effective in reducing symptomatology (measured by a subject self-rating questionnaire) as acetazolamide (Fig. 1). The effects (or lack thereof) of these three agents on the altitude-induced decrement in short term memory, as measured by performance of the Digit Symbol Substitution Test (Table 1), also demonstrates some of the discrepancies between clinical and other (in this case psychological) methods for evaluating the effects of acute altitude exposure.

There is apparently no physiologic parameter that remains unaltered in response to acute altitude exposure. Dr. Shields has pointed out in the preceding discussion that there appears to be a close temporal relationship between the rate and degree of physiological changes and the severity of the clinical syndrome of AMS. In other words, subjects appear sickest when maximal physiological alterations are occuring. We believe, therefore, that we are dealing with a complex series of interactions between many variables where any number of such interactions may predominate at any given time or in any given individual in producing the overall reaction observed. For example, we know that a major compensatory response to hypoxia is hyperventilation with resultant hypocapnic alkalosis. Wayne (2) has shown that voluntary hyperventilation at ground level produces qualitatively similar symptoms to those experienced upon acute exposure to 25,000 feet simulated altitude. On the other hand, hypoxia per se as produced by carbon monoxide inhalation can result in virtually all the symptoms we see with AMS before any marked changes in respiration are apparent. Thus the symptoms of AMS may be due in part

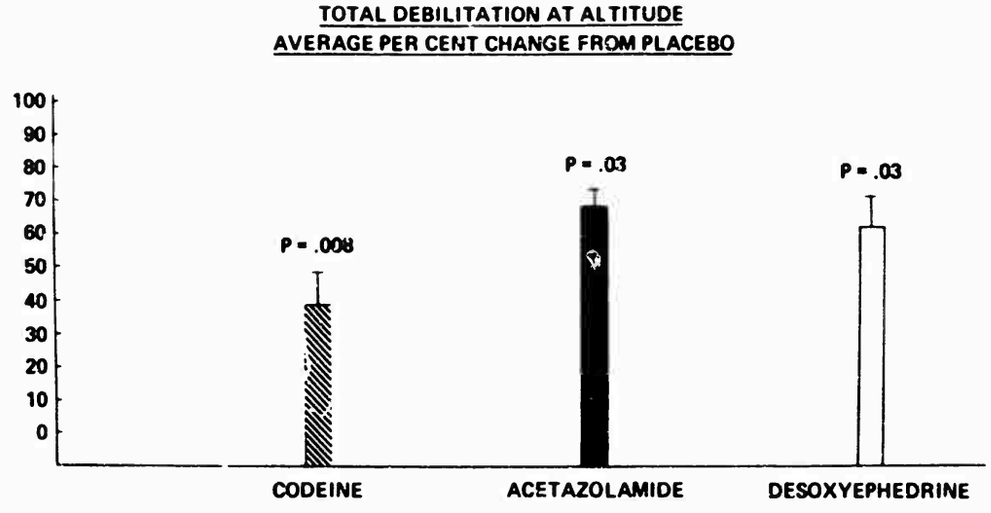

Figure 1 *Effects of three drugs on symptomatology of acute mountain sickness.*

Bars represent total scores on a 26 item symptom questionnaire expressed as a percentage of appropriate placebo scores. All drugs were administered orally. Codeine and desoxyephedrine study was conducted in a chamber at 15,000 feet simulated altitude, acetazolamide study on Pikes Peak, Colo. (14,100 feet).

to hypoxia or secondarily to respiratory alkalosis or to a combination of both.

Although AMS may be considered more or less a nonspecific reaction, certain of the component symptoms may well have specific mechanisms involved in their production. It has been our experience on Pikes Peak, Colorado, 14,100 feet above sea level, that virtually all subjects develop headaches of variable severity during the first 48 hours of exposure. The headache is usually described as pounding or throbbing in character, and is frontal or bitemporal in location. It is aggravated by bending over and when severe may be associated with photophobia. This clinical pattern is

Table I. **EFFECTS OF THREE AGENTS ON DIGIT SYMBOL SUBSTITUTION TEST AT 14,000-15,000 FT.**

	% of Appropriate Placebo*	
Codeine	117.8	(P<.01)
Desoxyephedrine	101.7	(N.S.)
Acetazolamide	96.5	(N.S.)

**Higher score signified more correct responses.*

quite characteristic of most headaches of a vascular origin, i.e. vasodilitation with pressure on adjacent nerves and stimulation of dural and arterial neural plexsuses with subsequent pain. We attempted to confirm our clinical impression with a double blind drug study this past August on Pikes Peak using ergotamine tartrate or saline in a group of 12 subjects. Since ergotamine has no analgesic, sedative, or narcotic properties it is beneficial only for those headaches characterized by vasodilitation (3).

Subjects who complained of moderate to severe headache were given 0.5 ml injections of either ergotamine (0.25 mgm) or saline. During the first 48 hours of exposure four subjects received ergotamine on nine occasions and three subjects received saline on five occasions. The results are shown graphically in Figure 2. Sixty-seven percent of the ergotamine injections gave seventy-five percent or better relief of pain within one hour as compared to forty percent of the saline injections. It should be pointed out that we administered only half the usual dose of ergotamine in order to

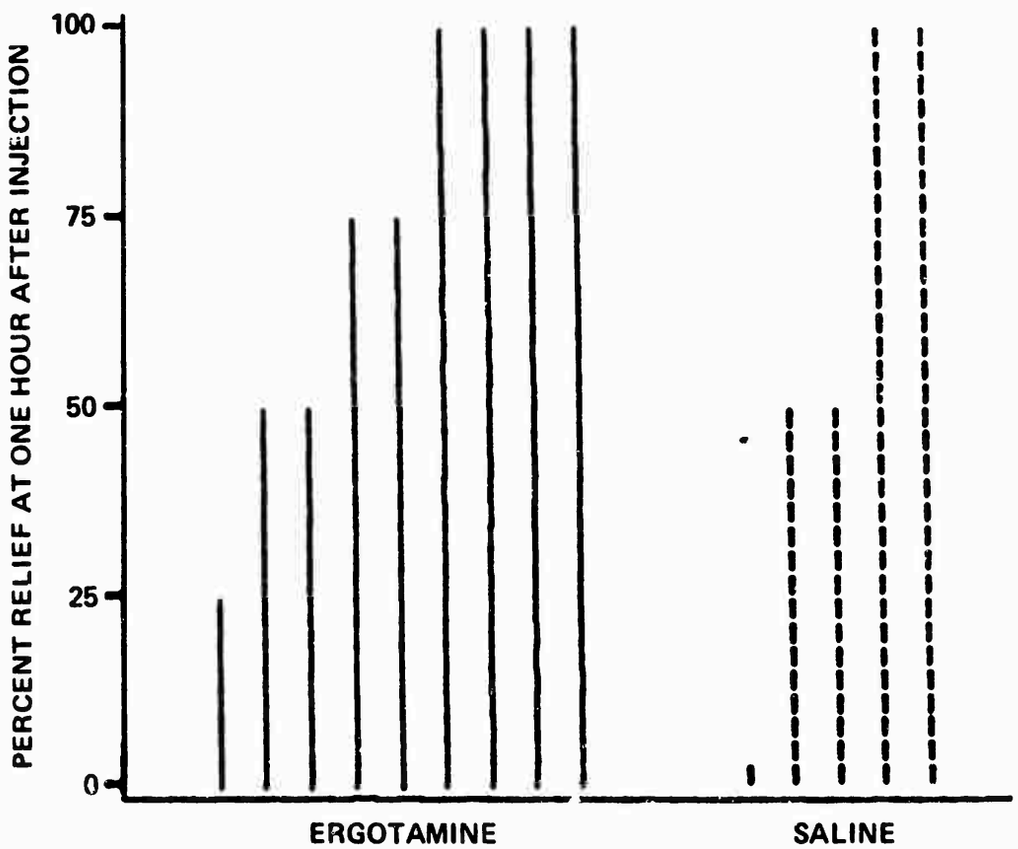

Figure 2 *Effects of injection of ergotamine tartrate or saline on high altitude induced headache.*

Data represents responses of four subjects to ergotamine and of three subjects to saline during the first forty-eight hours of exposure to 14,000 feet altitude.

avoid an excessive vasoconstrictor response under hypoxic conditions. Perhaps we might have observed even better symptomatic relief with a larger dose. In any case, we believe the data are quite suggestive that ergotamine is effective in ameliorating altitude induced headaches.

Because of the potential importance of AMS to the Army, the Physiology Division, U. S. Army Medical Research and Nutrition Laboratory, has directed a major portion of its research program over the past few years to the study of this problem. One of our major concerns has been that of establishing a reliable measure or estimate of the severity of AMS in any individual subject. A major criticism of many previously published papers reporting the effects of various measures in alleviating this syndrome is a lack of such a measure. In 1965 Major Evans of this laboratory developed a subject self-rating symptom questionnaire for AMS which we call The General High Altitude Questionaire (GHAQ). The GHAQ was found to be sensitive to both elevation and duration of altitude exposure (4). In addition to providing an estimate of the severity of each symptom of AMS, by adding all symptom changes from baseline, an over-all illness score can be obtained. Until this summer there was some doubt in our minds as to the validity of employing such an overall score as an index of how "sick" the subject really is. However, over the past few months we compared the GHAQ with two other methods of estimation namely, clinical evaluation and a paired comparison technique.

Clinically, the subjects were placed into one of three categories:

Group I: Only mildly affected. Would not anticipate any significant loss of time from duty status because of illness.

Group II: Moderately ill. Short periods of time lost from duty to be expected.

Group III: Severe and persistent symptoms. Medical observation and care would be required for a two to three day period.

The paired comparison technique, like the GHAQ allows quantitative investigation of subjective experiences but by a different approach. A history of each subject's past illnesses is first obtained by interview and then a series of pairs of these illnesses is made up so that each illness is paired with every other illness. Subjects are then asked to indicate which illness of each pair made them feel the sickest. In this manner a rank order of severity of a subject's previous illnesses can be determined. The subject's ranking of the severity of his acute high altitude experience compared

to his previous illnesses is then obtained by the addition of another set of comparisons. Since this is done during the high altitude exposure, we are really comparing the subjects estimate of severity of his current symptoms with his memory of previous illnesses. We have found that subjects are quite consistent in their ranking both at sea level and at high altitude. A numerical score is determined by dividing the number of illnesses which the subject ranks as more severe than AMS by the total number of illnesses being compared.

The responses to the GHAQ were evaluated for each subject by taking the difference between the mean score for all twenty two items averaged over three days at sea level and the mean score for a similar period at high altitude.

The paired comparison and GHAQ scores were then arranged in numerical rank order where the highest rank corresponded to the highest score in the former case and the lowest score in the latter case. Thus the higher rank orders represent the least affected subjects. Comparisons of the three methods are presented in Figures 3

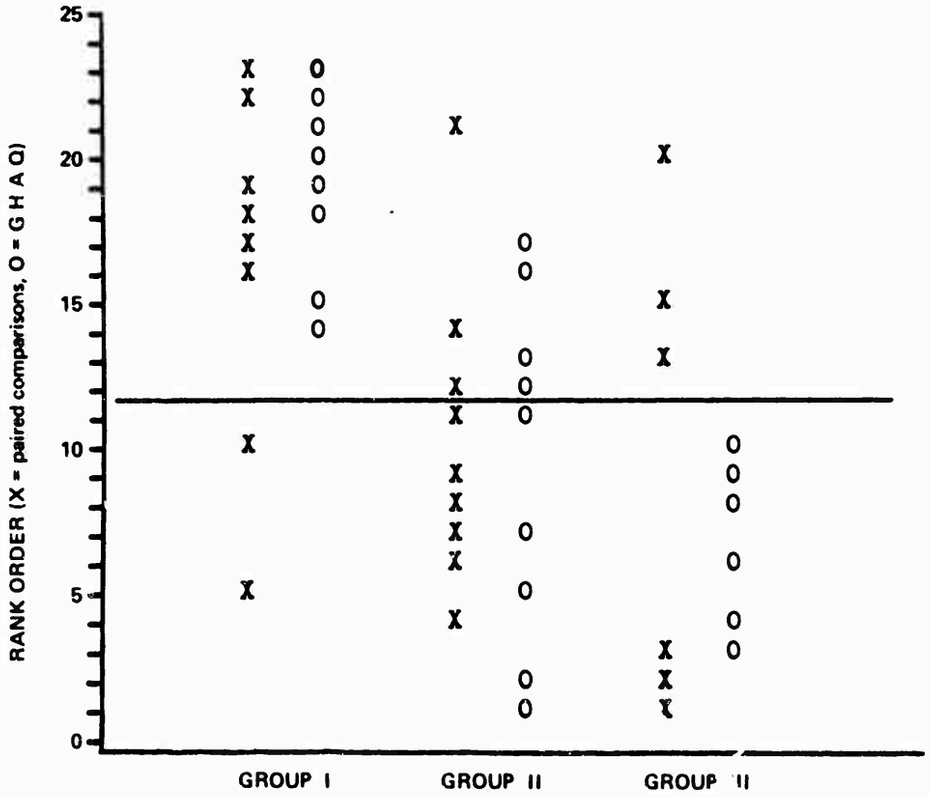

Figure 3 *Comparison of three methods used to estimate severity of acute mountain sickness.*

Horizontal line represents median rank order. Data obtained on 23 subjects from a study conducted in August, 1967 on Pikes Peak, Colo. (14,100 feet). See text for details.

and 4. Figure 3 represents data obtained on 23 subjects during a study in August 1967; Figure 4 on 29 subjects during October 1967. Inspection of these figures reveals the remarkably good correlation between the three separate estimates of the severity of AMS in these subjects. In short, we now feel reasonably confident of our ability to estimate the severity of AMS and thus to determine whether any proposed ameliorative measure does indeed reduce the severity of this syndrome.

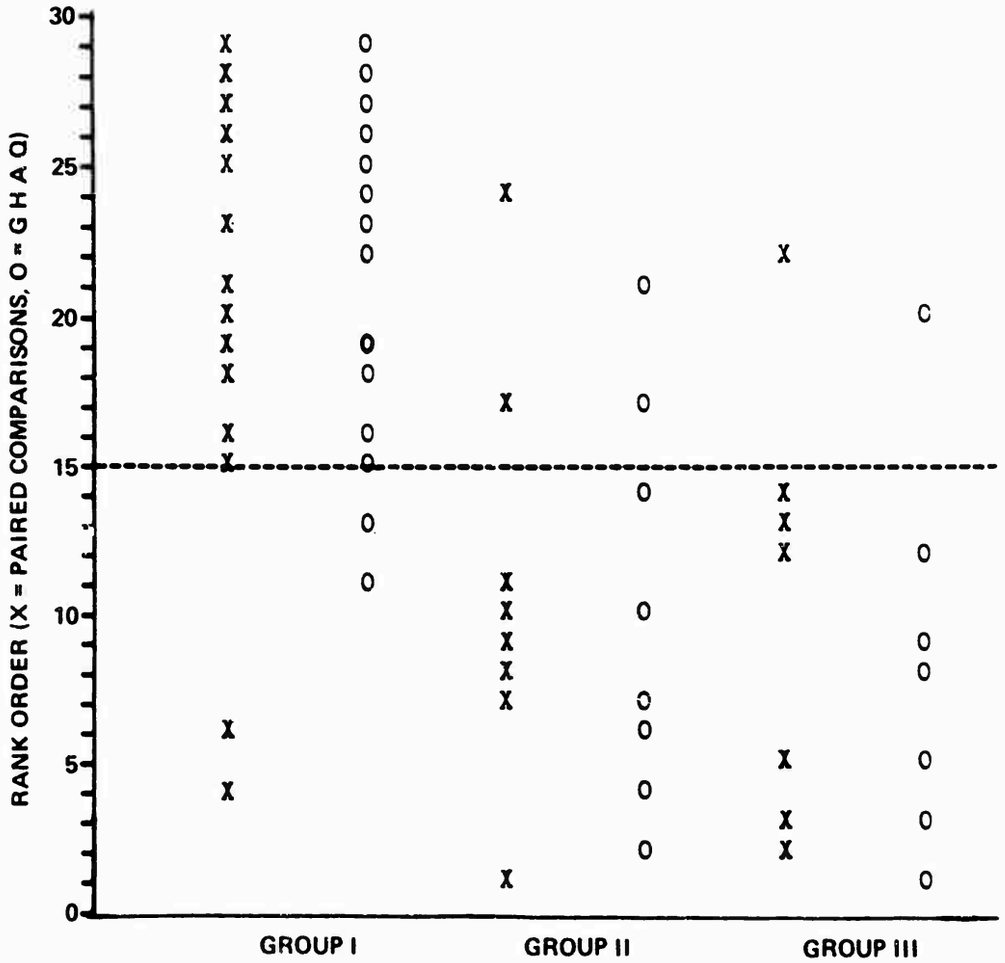

Figure 4 *Comparison of three methods used to estimate severity of acute mountain sickness.*

Horizontal line represents median rank order. Data obtained on 29 subjects from a study conducted in October, 1967 on Pikes Peak, Colo. (14,100 feet). See text for details.

SUMMARY

Acute mountain sickness is defined and described from a clinical point of view. The nonspecific nature of the overall response to the stress of high altitude exposure and the importance of the host state as well as the evoking stimuli in determining the overt manifestations of this syndrome are emphasized.

Data are presented which suggest that altitude induced headaches may be due in part to vasodilitation.

Three methods of estimating the severity of acute mountain sickness along with evidence demonstrating their validity are discussed.

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ACUTE MOUNTAIN SICKNESS IN HIMALAYAN TERRAIN: CLINICAL AND PHYSIOLOGICAL STUDIES

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Because of our commitments in the Himalayan terrain, troops are shuttled frequently between the sea level and 18,000 feet. Hence, acute mountain sickness is a constant challenge to us. In the last 5 years, over 2000 subjects between the ages of 18 and 53 were incapacitated with the illness.

The incidence of acute mountain sickness in large groups of men arriving at altitudes between 11,000 feet and 18,000 feet, under identical circumstances, varied from 1.01 to 83.33 per thousand. Also, an individual predisposed to acute mountain sickness invariably suffered from the illness on every trip to the altitude. Its severity, however, varied each time.

There was a definite time-lag, which ranged from 6 to 96 hours, between arrival at high altitude and onset of the symptoms (Fig 1).

Physiologic Study

The present study was designed to observe the acute circulatory response to high altitude hypoxia and explore to what extent shifts in the circulating blood volumes, if any, could be related to the time lag and clinical features of acute mountain sickness.

Thirty healthy volunteers were selected from the Indian Army. They were between 17 and 32 years of age (average 21.5 years) and had never been exposed to high altitudes. Sea level data were obtained at Delhi (height 650 ft.). Right heart catheterization was performed by positioning a number 7 cardiac catheter in the pulmonary artery just below the valve. The left atrium was entered by the percutaneous transseptal method (1). The right brachial artery was cannulated to obtain arterial blood pressures and dye curves. Consecutive dye dilution curves were obtained directly on a poly-

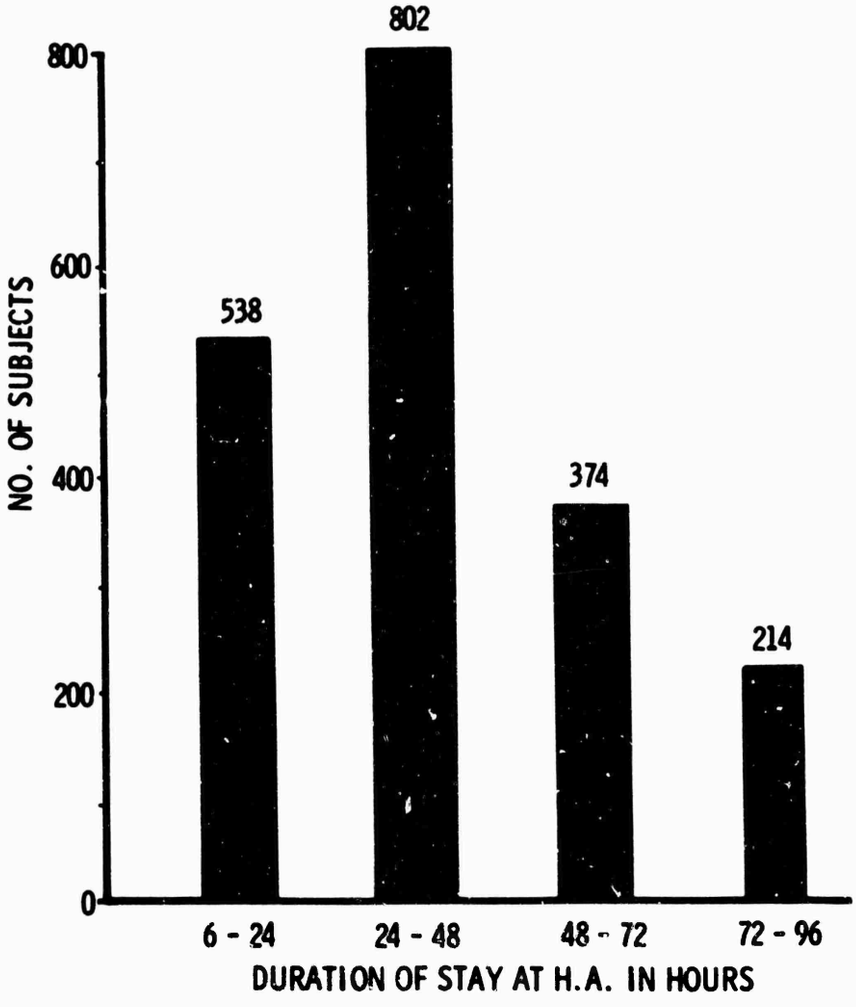

Figure 1 *Relating the time lag between the onset of the illness and arrival at the altitude in 1928 subjects.*

viso channel through a continuous recording densitometer (Colson) by injecting 5 mg of indocyanine green dye into the main pulmonary artery and then into the left atrium. The difference in the mean transit times of the two resulting curves was taken as pulmonary transit time. The cardiac output was measured from the dilution curves by the formula of Hamilton *et al.* (2). The volume of blood between the pulmonary artery and the left atrium was obtained by multiplying the pulmonary mean transit time by the average cardiac output and represented the pulmonary blood volume. Similarly the volume of blood between the pulmonary and brachial arteries was estimated by multiplying the pulmonary artery to brachial artery mean transit time by the average cardiac output and this gave the central blood volume (3). The total blood volume was determined by Evans blue dye method. Cerebral blood flow was estimated by nitrous oxide technique of Kety and

Schmidt (4). Peripheral blood flow was measured in the right forearm by venous occlusion plethysmography (5). All pressures were recorded through Statham P23AA strain gauge manometers on a 4-channel single gun photographic system (6). Arterial blood pH, PCO_2 and PO_2 were determined using electrodes (Beckman). Cerebral blood flow and pulmonary blood volume were estimated in the alternate subject, all other parameters were studied in all the subjects. For high altitude study, the team of investigators (nine doctors and four technicians) with the equipment were air lifted to an Army general hospital at 12,000 ft. a week earlier for acclimatization. The subjects were subsequently flown in three batches at intervals of five days so that it was possible to observe the acute response in five to six subjects each day from day 1 to day 5 after arrival at the altitude. Peripheral blood flow, however, was estimated in four subjects from each batch (total twelve subjects) daily from day 1 to 10. Physiologic studies at Delhi and at the altitude were performed under identical conditions regarding room temperature, equipment and observers.

Results (Table 1, Figs. 2, 3) While there was no significant change in the total blood volume, peripheral blood flow diminished from the beginning, and remained so for the next seven days. On giving 100 per cent oxygen the diminished peripheral flow could be somewhat restored. The cerebral blood flow increased by 40 per cent within 12 to 36 hours and approached normal values by the 5th day. Between 48 and 72 hours the pulmonary blood volume increased by 80 per cent, and the central blood volume increased only by 28 per cent. The arterial blood pH increased and PCO_2 and PO_2 fell from the beginning.

Clinical Profiles

Altitude and Severity. No correlation between the severity of illness and increasing altitude was found. Mild, moderate and severe grades of incapacity occurred at all altitudes between 11,000 feet and 18,000 feet. Wintry weather and activity on arrival at high altitude, however, aggravated the illness.

Effect of Acclimatization. The symptoms were worse after air travel. By road journey, the severity of symptoms depended on the stages of ascent and the time spent for acclimatization at each stage. Usually, one week each at 8,000, 11,000 and 14,000 feet was considered adequate for acclimatization for altitudes between 8,000 and 11,000 feet, 11,000 and 14,000 feet, and 14,000 and 18,000 feet, respectively. Rarely, at 14,000 feet, acclimatization had to be prolonged for three weeks or even more.

Table 1—CIRCULATORY RESPONSE TO ACUTE HIGH ALTITUDE HYPOXIA

PARAMETERS		TOTAL NO.	12-36 hrs		48-72 hrs		84-130 hrs	
Total blood volume ml/m^2	C HA	27	2960 2880	(11)	3110 3440	(9)	2760 2930	(7)
Peripheral blood flow ml/100 ml/mt tissue	C HA	12	4.4 3.6	(12)	4.4 3.4	(12)	4.4 3.8	(12)
Cerebral blood flow ml/100 G brain/mt	C HA	13	55 77	(5)	57 70	(3)	55 57	(5)
Central blood volume ml/m^2	C HA	20	726 759	(8)	690 881	(6)	678 595	(6)
Pulmonary blood volume ml/m^2	C HA	12	251 340	(5)	270 493	(4)	226 237	(3)
Arterial blood mm Hg								
pH	C→HA	27	7.41→7.47		7.41→7.46		7.41→7.45	
PCO_2			39.0→30.8	(9)	39.0→31.0	(9)	39.0→30.8	(9)
PO_2			87.0→53.0		87→52		87→52	

C = control data at 650 ft. HA = data at 12,000 ft.
Numbers in parenthesis indicate data of the number of subjects observed during the period

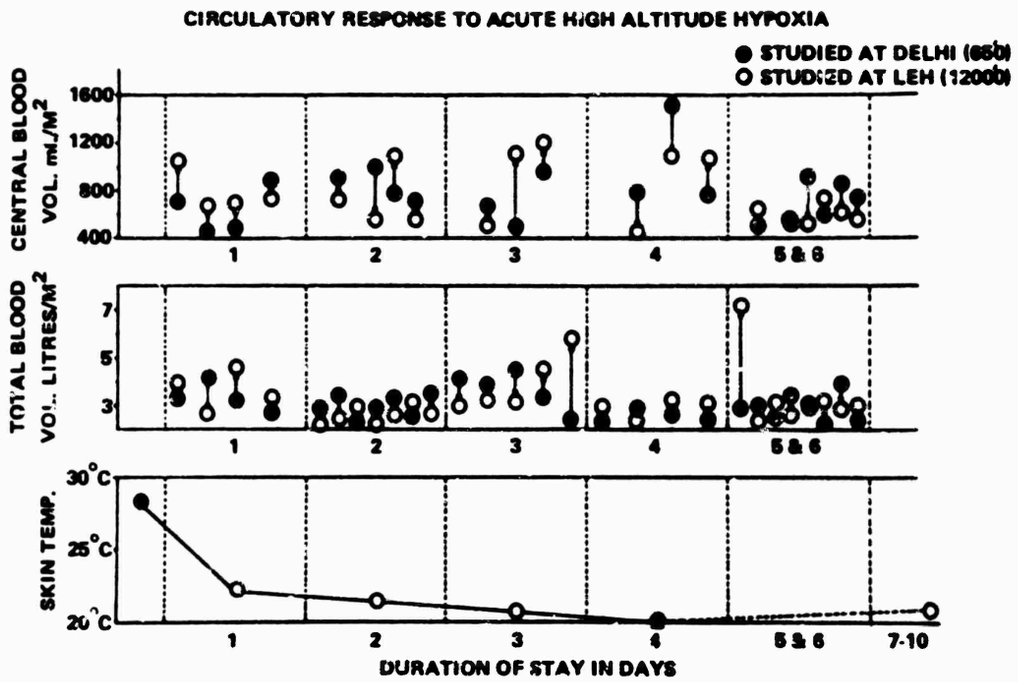

Figure 2 *Depicting the immediate circulatory response from day 1 to day 6 after arrival at the altitude. Peripheral blood flow (skin temperature) is shown here as the average values obtained in 12 subjects studied every day for 10 days. Each line joining closed circle to open circle represents the observations at sea level and altitude in one subject.*

The peripheral flow decreases from the first day, total blood volume does not change significantly and the central blood volume increases on day 3 and day 4.

Anti-diuresis. On arrival at high altitude and during illness, predisposed individuals suffered from an antidiuresis, whereas immune individuals passed urine freely. Thus, under identical conditions regarding altitude, bed rest, food intake (composition, sodium content, calories) and fluid, the effective diuresis (fluid intake minus fluid output) in 118 known predisposed test subjects on the first day of their arrival at the altitude was -1100 ml to +437 ml against 930 ml to 4700 ml in 46 immune individuals. Also, improvement in symptoms was preceded by diuresis which continued for from 2 to 10 days.

A controlled trial is now in progress in which 30,000 subjects have been studied to date. Half of them were acclimatized for 10 to 14 days at 9,000 feet before proceeding to 12,000 feet, and the other half were directly airlifted from sea level to 12,000 feet with diuretic prophylaxis (Frusemide 80 mgm on arrival at the altitude and 2 more doses every 12 hours). The induced diuresis has been very effective in the prevention of the illness in general as well as

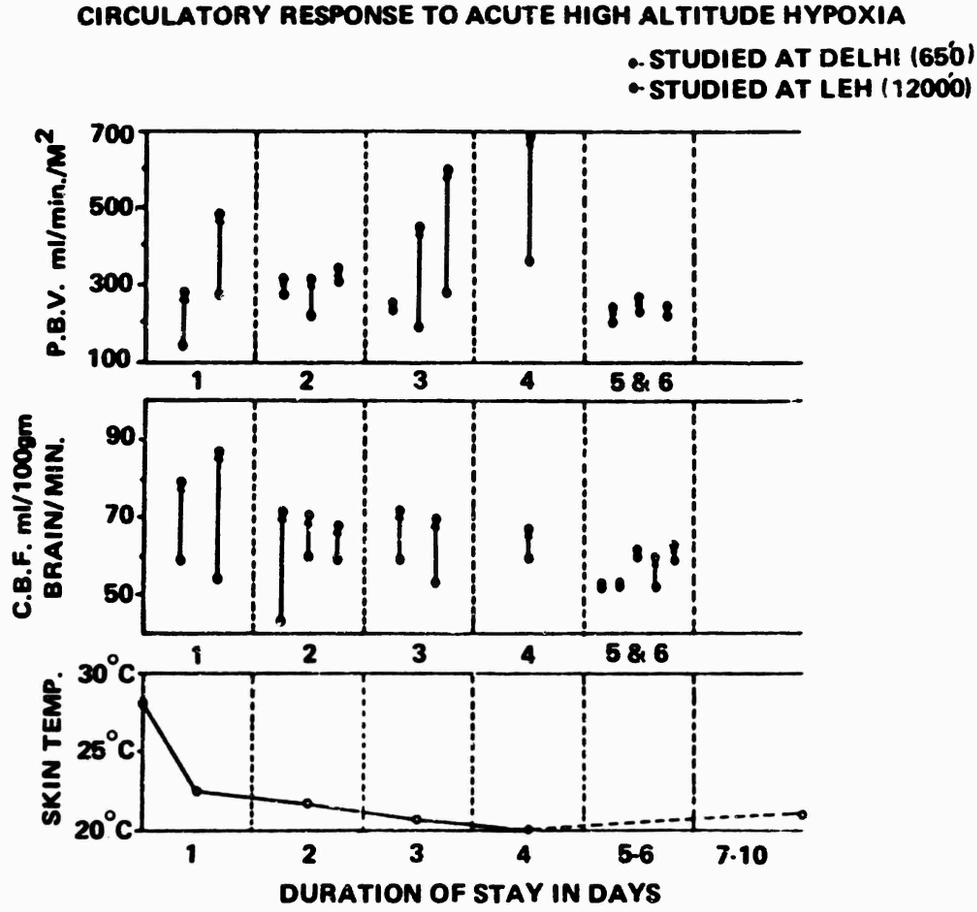

Figure 3 *Showing the immediate increase in cerebral blood flow (CBF) from day 1 and pulmonary blood volume (PBV) increasing on days 3 and 4*

mitigating or aborting it in known susceptibles. The results obtained so far are as good if not better than the acclimatization group.

Clinical Types (Table 2) In an analysis of 849 untreated cases, three clinical types were apparent:

a) Cerebral: Complaining of headache, insomnia, hysteria, apathy

b) Pulmonary: Complaining of breathlessness, chest pain, cough. On examination showed basal crepitations.

c) Hypoxia: Complaining of cramps, anorexia, flatulance.

Recovery Most of the subjects recovered within two to five days, though some went to the subchronic and finally to chronic forms. In severe cerebral form papilledema and other neurological complications were seen. Detailed history of one such subject is shown in Figure 4.

A 28 year old healthy soldier on arrival at 12,000 feet had acute mountain sickness. Headache, vomiting and blurred vision

Table 2 — ACUTE MOUNTAIN SICKNESS
(showing clinical profiles in 849 untreated subjects)

Cerebral		Pulmonary		Hypoxic	
Headache	525	Breathlessness	684	Anorexia	285
Giddiness	114	Pain in chest	126	Vomiting	112
Vomiting	112	Cough	121	Cramps	92
Apathy	93	Rales	280	Insomnia	85

continued for more than 15 days. Examination showed bilateral papilledema (4 diopters), right sided sixth and seventh nerve palsies and cerebrospinal fluid pressure of 500 mm H_2O. He was evacuated to a base hospital for investigation of a space occupying lesion. All investigations, including electroencephalogram and carotid angiograms, were negative. On histologic examination of the biopsy, the brain was found to be edematous (Fig. 5). Patient recovered uneventfully.

Necropsy Findings. Three patients died from neurological complications and the predominant necropsy findings in two were cerebral edema and edema of the lungs.

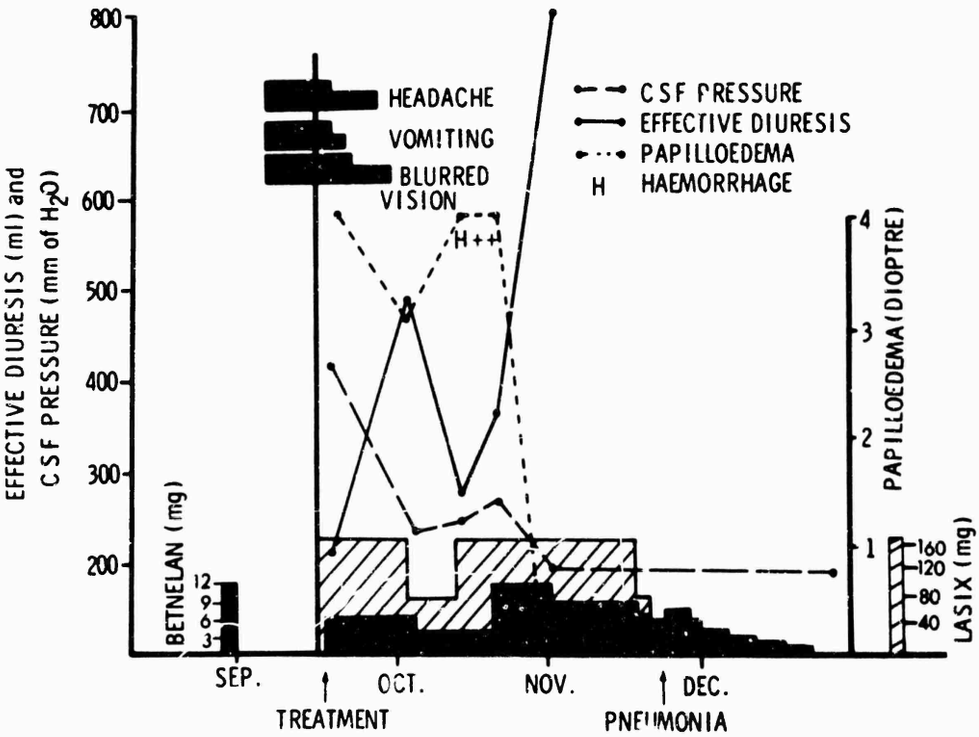

Figure 4 *Detailing the clinical course of a severe case of acute mountain sickness progressing from acute to subacute form.*

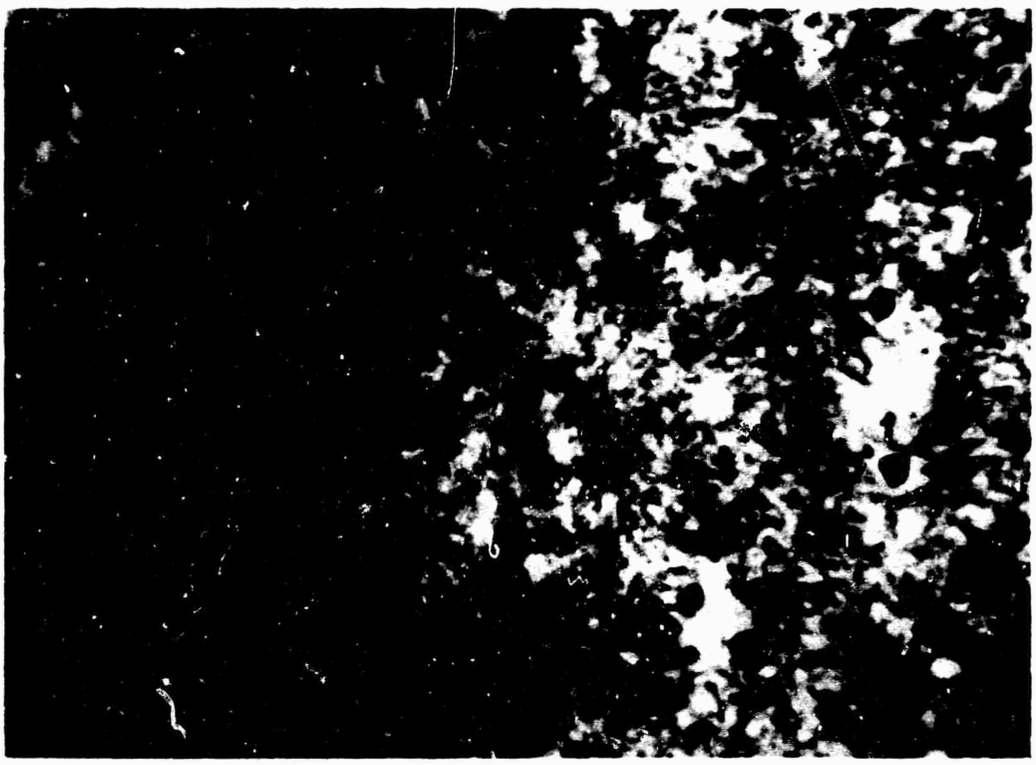

Figure 5 *Brain – biopsy of the same subject (as Fig. 4) showing edema of the brain.*

Discussion

The immediate increase in the cerebral blood flow in high altitude hypoxia was also observed by Severinghaus *et al.* (7). They found a 33 per cent increase in the cerebral blood flow estimated in six men within 6 to 12 hours of arrival at 12,500 feet. We could also grossly relate the intensity of the headache of the sufferer to the greater increase in their cerebral blood flow. Thus the three subjects who had the severest headaches had the maximum increase in their cerebral blood flows. Blood acid-base changes observed by Severinghaus (7) showed similar patterns in the elevation of arterial blood pH and fall in PCO_2 and PO_2. Reduction in the peripheral blood flow has been observed in acute hypoxia by breathing 7.5% oxygen (8) and also in congestive heart failure (9). The disproportionate increase in the pulmonary blood volume compared to the central blood volume (and no increase in the total blood volume) may lead to pulmonary congestion. Yu *et al.* (10) on the other hand, by giving 12 percent oxygen to 16 patients with heart disease found the average central and pulmonary blood volume values to decrease by 36 and 48 ml/m^2. The two groups are not comparable as our subjects were healthy young soldiers and it was not induced hypoxia of only 10 to 15 minutes duration. Furthermore, the present observations cannot be critically reviewed as comparable data on shifts in the circulating

blood volumes due to high altitude hypoxia are not available. Decrease in the peripheral and increase in the cerebral blood flows, fall in the arterial blood PO_2 and PCO_2 with concomittant rise in pH can be related to the early onset of hyperventilation and respiratory alkalosis, throbbing headache and muscular cramps. Marked increase in the pulmonary blood volume between 48 to 72 hours may in part account for the maximum incidence of high altitude pulmonary edema during this period. It is concluded that time lag for the onset of the illnesses and such features as headache, muscular cramps and pulmonary congestion as seen in acute mountain sickness may be related to the shifts in the circulating blood volumes and fall in the arterial PO_2 and PCO_2 with rise in pH.

Acknowledgments

We are grateful to General A. K. Dev, Director General, Armed Forces Medical Services, and Professor K. L. Wig, Director, All India Institute of Medical Sciences, for their enthusiasm and support for this study. We acknowledge our indebtedness to the volunteers (Subedor Patil and his men) without whose cheerful co-operation this study would not have been possible. We thank Doctors Guleria, Khanna, Talwar, Wood, Manchanda, Pande, Kaushik and Subba for their excellent work under difficult and trying conditions.

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GENERAL DISCUSSION

DR. ROY: These three papers are open for questions and discussion.

DR. STAUB: Dr. Shields, have you in any of your studies on body water measured plasma osmotic pressure? Have you considered measuring total pulmonary water? It would be interesting to me whether there might be some pulmonary edema.

Dr. Carson, are there any differences in high altitude sickness between officers and enlisted men or between enlisted men with different backgrounds, that is, whether they come from high or low altitude or know what may happen at high altitude?

Finally, to anyone who may have information – have any studies been made of antihistaminics, particularly chlortrimeton (chloramphenamine), in the prevention or treatment of high altitude sickness? We will present some data this afternoon on the role of histamines in the pulmonary circulation at high altitude.

To Dr. Roy: I was told just before coming here by Dr. Milledge, who had spent some time in one of the Indian Army hospitals at high altitude in the Himalayas, that the incidence of acute mountain sickness and pulmonary edema apparently depends on the local commander's policy; that at the place where Dr. Milledge was, newly-arriving troops were not allowed to do anything for four days. There was concern if they even got out of bed; and I just wondered whether the variable incidence depends somewhat on what the local commander allows his troops to do.

DR. ROY: Dr. Staub, can I answer the last question first because it is very simple to answer. When I said the incidence varied between 1.1 and 83.3 per thousand, it referred, as I said, to people who are not acclimatized, people who did not receive any drugs; people who were suddenly brought to a high altitude and

put to routine duties of a soldier. Our knowledge at that time was obviously inadequate.

Now, of course, there is a definite policy. Even when our good friend Dr. Wood arrived there, he was put in quarantine for 72 hours. I am sure with the revised policy the incidence is much less. Dr. Shields, would you like to answer the first question, please?

DR. SHIELDS: Dr. Staub, the answer to your first question, i.e., we have not made any measurements of pulmonary water. We have measured plasma osmolality in young college-age females on Pikes Peak. It decreased about ten milliosmols by seven days of exposure, roughly parallel to the fall in serum sodium and potassium. Normal values were re-established between one and two months, while sodium and potassium levels remained low throughout the two and one-half months on Pikes Peak.

In the females there was a slight increase in the protein osmotic pressure. I wonder whether I can call for some help from Dr. Surks, who probably has more data on that in other subject groups?

DR. SURKS: In the previous studies, marked elevation of plasma protein occurred during the first week to ten days and these seemed to decrease after about two weeks down to control levels (1). This has been confirmed in rats and again in humans (2).

DR. CARSON: In regard to Dr. Staub's question about antihistamines, I am not aware of any controlled studies using these drugs for acute mountain sickness. Since most of these compounds have some sedative properties, they might be effective in this regard as well.

Concerning the question of differences in background or rank of subjects, we have not carried out a controlled study of acute mountain sickness using officer personnel. All our field studies have utilized enlisted personnel, volunteers from various army posts. We also attempt to obtain subjects who have not had previous high altitude exposure, although this is not always possible. This past August we found it necessary to take two subjects who had resided at 8,000 to 10,000 feet but had not been exposed to these elevations for about a year. One of these subjects became quite ill on Pikes Peak while the other did not.

DR. ROY: The Indian Army has used various antihistamines, including chloramphenamine. Results were not encouraging.

DR. MONCLOA: We too have found the same decrease in extracellular space measured with radiosulphate. We observed a decrease of 1.4 liters after 30 hours of exposure to high altitude (Malpartida, M., et al. (3)) with associated decrease in body weight. However, the correlation coefficient between these decreases were

not statistically insignificant, a fact that can be explained taking into consideration the other variables studied by Dr. Shields.

You have an increase in body water, and at the same time a decrease in body weight. Would you not need a very important decrease in solids to account for this effect? Or do you have any alternative explanation?

DR. SHIELDS: We feel that the decrease in body weight is primarily due to loss of body lipid rather than body water, that is, mobilization of fat stores. We have some data to support this in addition to calculation of body fat which I presented. In the females, we found a decrease in skinfold thickness at suprailiac, umbilical, subscapular, brachial and thigh areas. This, of course, represents a diminution of subcutaneous adipose tissue. I would remind you that the increase in total body water was very slight. Quantitatively, it does not amount to anything like the magnitude of fluid shifting toward intracellular compartments. I would suspect that losing a water-poor tissue, such as adipose tissue, might partially answer your question.

DR. MONCLOA: In rats it has been reported that the body water content decreases (Picon-Reategui, et al. (4)). Do you find in your rats the same phenomenon or is there any species difference?

DR. SHIELDS: Our data on water content of rats and men are roughly equivalent, but I would not make too much of this because the altitudes of measurement were different.

DR. BASS: I have a question or two for Dr. Shields. Am I to understand then, that you wound up with relative hypo-osmolality in both extra- and intracellular fluids? Another question: Is the time of distribution of the injected tracer the same at altitude as it is at the sea level? This latter question, of course, relates to the possibility that, considering the cardiovascular changes at altitude, you might have an artifactual effect on calculated volumes of distribution.

DR. SHIELDS: Let me address myself to your second question first. The time-disappearance curves of sodium thiocyanate and 4-aminoantipyrene were almost identical at Pikes Peak and sea level. There seemed to be a somewhat more rapid mixing at altitude, but we could demonstrate no difference in disappearance, which was surprising to us. The first question was about hypo-osmolality in extracellular and intracellular fluid. In the absence of a measurement of intracellular osmolality in these men I can, of course, only conjecture that if membrane ion permeability is intact at that point in time – for example, at eight days when fluid shifts were maximal – then I would suspect, as a first approximation, an intracellular hypo-osmolality. This, I repeat, is

mainly supposition and certainly bears more study because of its implications. There is measurable hypo-osmolality of serum early in exposure.

COL. HANSEN: Dr. Roy, I thought your findings on cerebrospinal fluid pressure were very interesting. Do you have serial measurements on patients or measurements on people who were not ill?

DR. ROY: We have measurements on both groups and also on the group which had suffered acute mountain sickness after they recovered. There is a definite difference. The pressure decreases as the patient gets better.

DR. BILLINGS: I have one comment, and a question for Dr. Roy. Regarding the changes, or apparent changes in body fat, in 25 young men at 12,800 feet for from 17 to 20 days, we found evidence of marked mobilization of lipids; very considerable increases in all subjects in cholesterol and (in 23 out of 25) in phospholipid, and approximately the same in the esterified fatty acids. We were not able to measure NEFA because we had to hold on to the specimens for a while. The only way we have been able to explain these to our satisfaction is in terms of very considerable mobilization of lipids and, therefore, presumably of utilization. We are trying to follow this up at the present time. The possibility that these changes were coincidental is at the vanishing point, and we are not able to find enough difference in the diet to account for this. This is in the presence of only one-pound average decrease in body weight over the 20 days.

One question for you, sir: Have you done any cerebrospinal fluid bicarbonate studies in these people on whom you have done cerebrospinal pressures? There has been some interesting work recently presented by Brown and others in this area.

DR. ROY: I can answer that easily – the answer is no. Now, I am just going to divert for 30 seconds. We have some data on chronic exposure to high altitude, at 16,000 feet, where soldiers were kept for two years without any break. In not one single subject did the cholesterol or phospholipids reach more than two-thirds the value of the average army person. The subjects were on a 4,800 calorie, high fat diet.

DR. BILLINGS: Were there weight losses or shifts in body fat?

DR. ROY: There was no weight loss.

DR. McFARLAND: Dr. Roy, do you have controls for the pathological studies that you showed – is this characteristic of high altitude or is this characteristic of those people who died? Have you made such slides on those who had been killed by accident or not demonstrating this pathology?

DR. ROY: I have eight slides with me. Six of them belong to the two people who died, and two are brain biopsies of the soldier who recovered. I do not have any slides at the moment of high altitude accidental deaths. But I do know such people do not show cerebral edema.

CPT. WHITTEN: I should like to comment on the changes in serum lipids which Dr. Billings talked about. Just recently we analyzed three groups of subjects. NEFA values go up at day 3. They are higher at day 7 and even higher at day 14. This parallels very closely the increase in catecholamine excretion which Dr. Surks has shown. So, it would seem there is some mobilization of depot fat, perhaps in response to norepinephrine activation of lipase. With regard to phospholipid and cholesterol levels, we have measured these and we have irregular values in about 25 subjects now and there is not significant difference. I am presently analyzing serum lipid profiles on ten subjects from our most recent altitude study.

DR. ROY: Is this acute response?

CPT. WHITTEN: This is an acute response.

DR. DEXTER: Dr. Roy, in reference to the cerebrospinal fluid pressure, there are obviously two possible causes that come to mind. One is that the patient may have had an elevated venous pressure in which case the cerebral spinal fluid pressure must keep above it, and the other is cerebral edema. My question is: Was there any relationship between the cerebrospinal fluid elevation of pressure and the venous pressure or right atrial pressure.

DR. ROY: There is no relationship between the cerebrospinal fluid and central venous pressures. But the CSF pressure could be related to the severity of the illness, as demonstrated by the case discussed earlier.

DR. DEXTER: You mentioned that you had looked upon this cerebral and pulmonary problem as possibly representing the same underlying process. Would you care to elaborate further?

DR. ROY: When people are suddenly exposed to high altitude hypoxia, definite shifts in the blood volumes occur; total blood volume does not change, peripheral flow diminishes, cerebral flow increases and pulmonary blood volume increases disproportionately.

DR. VISSCHER: The well-known retention of fixed acids in hyperventilation states would indicate that there might be a change in the osmotically active particle content of the cells. Dr. Shields have you made complete inorganic ion balance studies on your subjects while they are undergoing these shifts of water from extracellular to intracellular spaces? With the magnitude of the

shifts, of course, there would have to be a very large magnitude of ion shift as well, and if there is any significant change in the total osmotic pressure I should think that the balance studies should tell you whether the body has lost salt. What were the actual figures for the change in osmolality?

DR. SHIELDS: The electrolyte balance study you refer to has just been completed. The data are not yet reduced.

DR. VISSCHER: You do have some information as to what the actual osmolality change was?

DR. SHIELDS: Yes, but I don't remember the absolute values. I wonder if I may call on Dr. Hannon for that?

DR. HANNON: In young women exposed for a two and one-half month period on Pikes Peak (14,110 feet) we found a small, but statistically significant, decrease in serum osmolality. The maximum change was observed on the seventh day of exposure where a value of 275 milliosmols was obtained. This was about 10 m-osm below the low altitude value and was attributable to electrolyte losses. Serum sodium and potassium showed decreases of 9 and 0.6 meq/l, respectively, while chloride and phosphate showed increases of 7 and 1 meq/l, respectively. Plasma protein increased slightly in a linear fashion for the entire period of exposure, but probably had little effect on the early changes in osmolality. Bicarbonate levels, which we did not measure, presumably were reduced and contributed to the decrease in osmolality.

DR. ROBINSON: Dr. Shields, was any account made of balance between the calorie intake and weight loss of the subject, and was any estimate made of the daily energy expenditure of the subject?

DR. SHIELDS: There was no estimate of daily energy expended. Caloric deficit, of course, does occur and we have measured this.

There are published data available on rats at altitude. These data can best be summarized as there being a weight loss greater than one would predict from the caloric deficit. There seems to be, at least in the rat, a relative reduction in efficiency of caloric utilization. I believe there are others here who could perhaps shed some light on these data in men.

MR. CONSOLAZIO: In all of our altitude studies with men we have measured energy intake, and in all instances we have observed a decrease in intake during high altitude exposure. This caloric deficit has ranged from 500 to 1500 Calories/day. In our last study, the daily intakes averaged 3300 Calories/day at sea level and approximately 1800 Calories/day at altitude (Pikes Peak (4300 Meters)). The body weight loss of two groups averaged 5.0

and 4.5 kg/man during 12 days of altitude exposure which could not be accounted for by the calorie deficit. This great body weight loss was in part due to body fat (as observed by body density values) which decreased markedly during altitude exposure.

At high altitude, we have observed great hypohydration. The subjects were in negative water balance during altitude exposure. This finding has been quite consistent in every study that we have conducted up to the present time.

DR. SURKS: I think it is very attractive to associate the major changes in cerebrospinal fluid pressure and blood flow to the symptomatology of altitude. I would just like to enter a note of caution that at the end of blood flow and pressure, there are cells and tissues and that, undoubtedly, the most dramatic change we have seen today is the marked shift of water into cells. This has been observed in two or three separate studies. Not only is water shifting but I am certain that when the appropriate measurements are made we will find definite shifts in oxidizable substrates, hormones, electrolytes, p_H changes, etc. Now, this also implies that intracellular organelles are going to be diluted by this influx of water into the cell. This might then lead to marked shifts in association of various hormones which are known to be physicochemically bound to different subcellular particles, and thereby alter the effects of these hormones in microsomes, nuclei, mitochondria, etc. I feel that this area of investigation is just beginning to open up but I think when we talk about blood flow and pressure changes, we should keep this in mind.

DR. WEINSTEIN: Dr. Roy, you mentioned that acute mountain sickness was very often present in people who did not diurese and you emphasized this point. Would you elaborate on that?

DR. ROY: I will give you just one example. We have two very good army officers, both medical specialists, who have been up to the mountains about six to eight times. One of them, upon reaching high altitude, rushes to the bathroom; the other does not. The latter always gets into trouble.

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THE EFFECTS OF CARBONIC ANHYDRASE INHIBITION ON THE RESPONSES OF MEN TO 14,000 FEET SIMULATED ALTITUDE: 1. CHANGES CAUSED BY ACETAZOLAMIDE AFTER 24 HOURS AT ALTITUDE

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If a man is taken rapidly to an altitude of 14,000 feet, his ventilation increases immediately. During the next several hours, a further increase is seen and ventilation will continue to increase slightly for several more days or even weeks. The primary stimulus to increase breathing is the hypoxic stimulation of carotid and aortic chemoreceptors. The ventilatory response to this stimulation is modified, however, by the acid-base balance of other chemoreceptors in the central nervous system (1) as well as that existing at the peripheral chemoreceptors (2). As the pH at both of these sites is restored toward its initial value before ascent, the secondary and slower increase in ventilation takes place with time at altitude.

When carbonic anhydrase is inhibited in the renal tubules, it causes increased renal bicarbonate excretion and it is thus possible to anticipate the normal compensatory response of the kidneys to respiratory alkalosis by several days. Because renal carbonic anhydrase inhibition mimics a normal physiologic process known to take place with altitude acclimatization, treatment with drugs such as acetazolamide is an attractive approach to achieving early acclimatization. We knew from previous experiments (3) that pretreatment with the inhibitor acetazolamide did nearly compensate the respiratory alkalosis of men at altitude with respect to arterial pH. This apparently was beneficial in that ventilation and end-tidal PO_2 were increased in treated subjects. We also noticed that the largest effect occurred after 24 hours at altitude and this led us to speculate that the full benefit of a lower arterial pH might be delayed until the chemical environment of the CNS chemoreceptors was readjusted in the manner postulated by Severinghaus et al. (1). We wished to see, then, what effect pretreatment with

acetazolamide had on cerebrospinal fluid composition after 24 hours at altitude. Because acetazolamide has been shown to reduce CSF flow (4) and because choroid plexus is rich in carbonic anhydrase, there was reason to suspect some direct effect of acetazolamide on CSF composition.

Forty-seven healthy men, ranging in age from 19 to 38 years, were studied in a decompression chamber during 24 hours at pressure altitudes of either 3,000 feet (681 mm. Hg) or 14,000 feet (447 mm. Hg). They were divided into 4 groups according to the altitude and whether they were given placebo or acetazolamide. The drug or placebo was given in two doses of two 250-mg. capsules, one the evening before and one the morning of ascent. The experiments were conducted as a "double blind". The chamber was decompressed to the desired altitude in 30 min.

End-tidal PCO_2 was measured 1 hour after ascent and every 2 hours thereafter except during the time allotted for sleep. Different curves (Fig. 1) were found for the 4 combinations of experimental variables. Even without hypoxia, acetazolamide-treated subjects had a lower end-tidal PCO_2 and, presumably, a greater resting ventilation. Hypoxia displaced both placebo and drug groups downward, the drug group still having lower PCO_2 on the average. During the 24 hours or so at the higher altitude, PCO_2 continued to decrease. Between 5 and 9 hours at 14,000 feet, there is a change in slope of the curves, and PCO_2 decreases faster thereafter. This may be related to the time required for the readjustment of cerebrospinal fluid (CSF) pH toward a more normal value, thereby partially relieving the central chemoreceptors from the inhibitory effect of respiratory alkalosis. After 24 hours at 14,000 feet, the placebo group decreased end-tidal PCO_2 from 33 to 30 mm. Hg on the average whereas the acetazolamide group went from 32 to 26 mm. Hg.

Twenty-four-hour urine samples were collected from each subject and analyzed for potassium, sodium, and 17-hydroxycorticosteroids (17-OHCS) (Table I). Acetzolamide significantly increased potassium excretion ($P<.01$) but did not significantly affect sodium excretion. Excretion of 17-OHCS was significantly higher with altitude but was not affected by the treatment. The diuretic effect of the drug was evident and amounted to about 500 ml. in 24 hours. The effect was probably complete at that time and no further diuresis would be expected unless more drug were given.

At the end of their 24-hour stay at altitude, arterial blood and cerebrospinal fluid samples were taken and analyzed for PO_2, PCO_2, pH, and bicarbonate. In addition, lactate levels in CSF were

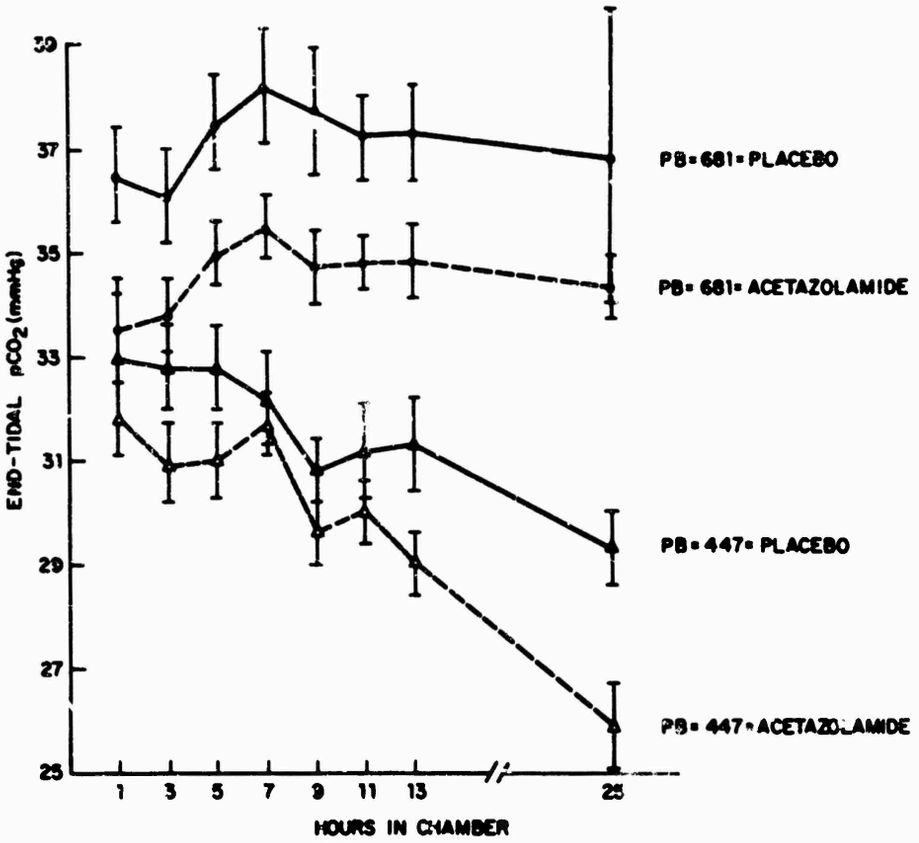

Figure 1. Mean values ± 1 S. E. M. of end-tidal PCO_2 as a function of time at altitude.

Table I. Average values ± 1 S. D. of variables measured in 24-hour collections of urine

	14,000 ft		3,000 ft	
	Acetazolamide	Placebo	Acetazolamide	Placebo
Potassium (mEq. /24 hrs.)	110.3±24.1	66.4 ± 20.0**	137.6 ± 23.1	61.1 ± 26.9**
Sodium (mEq. /24 hrs.)	216.5±74.9	183.0 ± 90.0	220.1 ± 81.8	242.8 ± 73.6
17-OHCS† (Mg. /24 hrs.)	7.3±2.5	7.2 ± 4.9	4.6 ± 3.4	4.1 ± 1.6
Volume (cc. /24 hr.)	1910±23	1279 ± 18*	2049 ± 15	1544 ± 20*

* $P < .05$
** $P < .01$

measured (Table II). Before either sample was drawn, the end-tidal PCO_2 was stabilized at the level that prevailed before the sample needle was introduced. The total CO_2 content of CSF was measured manometrically and from it and the measured pH value, PCO_2 was calculated to compare with the value obtained directly by CO_2 electrode. In several instances, in spite of all precautions, small bubbles of air leaked into CSF samples. In a poorly buffered solution like CSF, even with prompt elimination of bubbles, contamination with air may have caused falsely high pH values and, in fact, the CSF pH at 3,000 feet was slightly higher on the average than the usual value of 7.32. The CSF gas tensions must also be regarded as suspect for the same reason. Sampling error would not affect the bicarbonate measurably, however, and the accuracy of its measurement is attested to by the close correspondence of measured and calculated values for CSF PCO_2. In CSF, acetazolamide significantly decreased bicarbonate at both altitudes. The treatment did not affect CSF lactate levels but altitude significantly increased CSF lactate.

The changes in arterial blood were similar to those found before (3). The drug significantly decreased PCO_2, pH, bicarbonate, and the standard bicarbonate. The average difference of 6 mm. Hg in arterial PO_2 at 3,000 feet was statistically significant ($P<.05$) but at 14,000 feet, the difference of almost 5 mm. Hg was not ($P<.10$).

The close correspondence of CSF bicarbonate and arterial bicarbonate has been pointed out by Fencl et al. (5). We also obtained a linear relationship between CSF and arterial bicarbonate (Fig. 2) with the slope of the calculated regression line at 3,000 feet (681 mm. Hg) being similar to that obtained by them during chronic metabolic acidosis and alkalosis. Acetazolamide decreased both CSF and arterial bicarbonate, but the same proportion was maintained as for placebo subjects.

High altitude did not change the slope of the line significantly but the whole line was displaced by about 3 mM./liter. The increase in CSF lactate at 14,000 feet accounted for less than one-third of this displacement and the remainder must be explained by other means; possibly the active regulation of CSF acid-base balance as proposed by Severinghaus et al. (1).

Because acetazolamide did not affect the slope of the line relating CSF and arterial bicarbonate at 24 hours, we believe that there was no direct effect of the drug on CSF composition by that time. An earlier direct effect cannot be ruled out, however. Both CSF and arterial bicarbonate were lower with the drug and this is the direction of change that would be expected in untreated subjects

Table II. Average values ± 1 S. D. measured in arterial blood and CSF after 24 hours at altitude

	14,000 ft.		3,000 ft.	
	Acetazolamide	Placebo	Acetazolamide	Placebo
Cerebrospinal Fluid				
P_{O_2} (mm. Hg)	34.7 ± 6.2	32.7 ± 3.3	42.3 ± 5.7	41.3 ± 10.2
Meas P_{CO_2} (mm. Hg)	34.3 ± 4.9	35.9 ± 2.3	41.7 ± 3.4	48.0 ± 4.2*
Calc P_{CO_2} (mm. Hg)	34.2 ± 4.2	36.3 ± 2.7	41.4 ± 1.7	47.0 ± 4.5**
pH	7.376 ± .035	7.387 ± .033	7.359 ± .017	7.360 ± .012
Lactate (mg. %)†	18.4 ± 3.0	19.8 ± 3.0	13.4 ± 1.3	12.4 ± 1.1
HCO_3^- (mM./liter)	19.04 ± 0.69	20.72 ± 1.00**	22.30 ± 0.85	25.09 ± 0.60**
Arterial Blood				
P_{O_2} (mm. Hg)	46.6 ± 5.3	41.8 ± 3.0	86.4 ± 7.3	80.1 ± 7.2*
P_{CO_2} (mm. Hg)	26.6 ± 1.7	30.5 ± 2.7**	34.8 ± 2.7	38.2 ± 2.5**
pH	7.423 ± .030	7.466 ± .042**	7.351 ± .020	7.420 ± .028**
HCO_3^- (mM./liter)	17.42 ± .09	22.30 ± 1.50**	19.55 ± 1.66	25.09 ± 1.58**
Std. HCO_3^- (mM./liter)	19.99 ± .06	23.66 ± 1.20**	20.32 ± 1.00	24.37 ± 1.00**

* $P < .05$
** $P < .01$

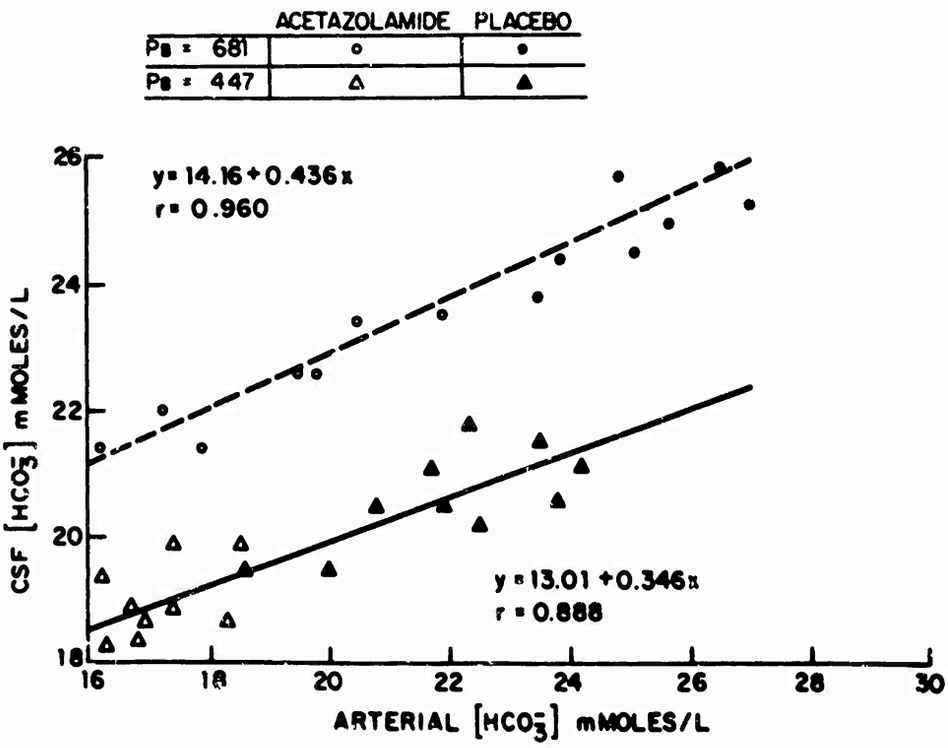

Figure 2. Individual values of CSF HCO_3^- plotted against arterial HCO_3^-

as respiratory acclimatization progressed with more time at altitude.

Of the several ways by which we might have assessed the state of well-being of the subjects at 14,000 feet, we chose to rely on interrogation of the subjects and on personal observation before either subjects or investigators knew who had received acetazolamide or placebo. Each subject was given a numerical ranking of 1 to 4 in relation to the other 3 subjects in the chamber during any single experiment. The summary of these rankings is presented in Figure 3. Those given a rank of 1 were obviously sick with vomiting, nausea, and severe headache singly or in combination. Those given a rank of 4 were symptom-free or nearly so. The intermediate rankings are less well discriminated. If only the extremes are considered, 5 of the 12 subjects who were given placebo were very sick, but only 1 drug-treated subject was that ill. On the other end of the scale, 4 of 11 drug-treated subjects were symptom-free but only 1 of those given placebo was that well. The trend of the observations does indicate some advantage to those subjects treated with acetazolamide prior to altitude exposure.

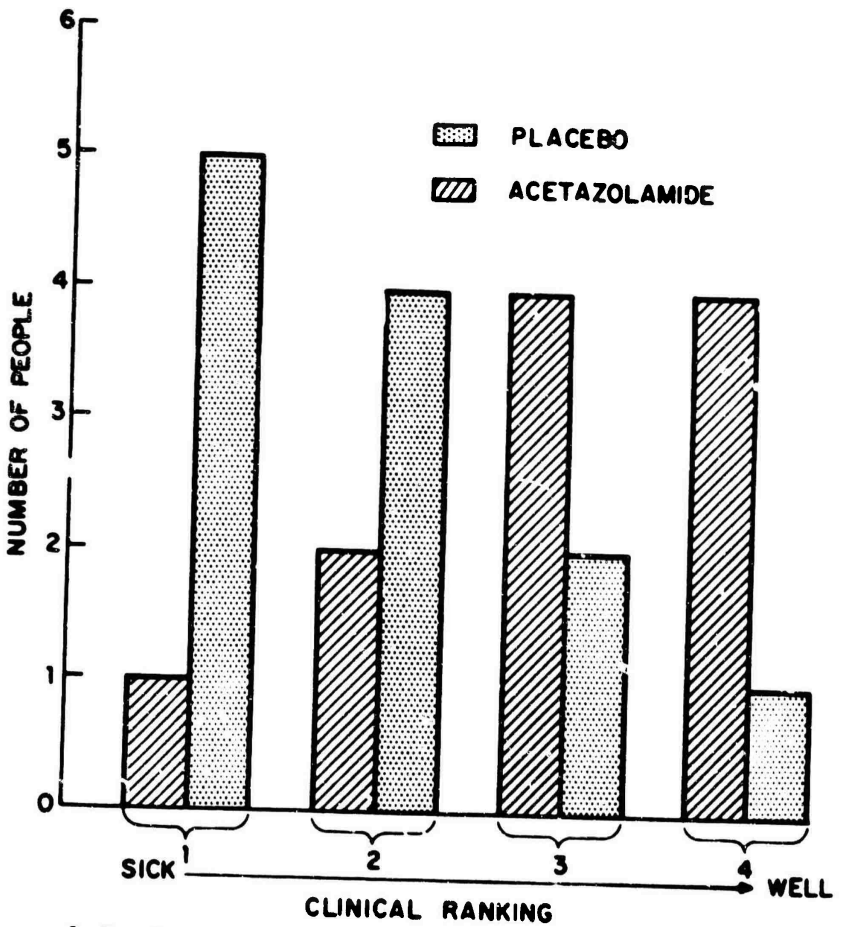

Figure 3. Ranking of subjects after 24 hours at 14,000 feet according to their state of well-being.

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HASTENING RESPIRATORY ACCLIMATIZATION TO ALTITUDE WITH BENZOLAMIDE (CI 11,366)

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The data presented by Dr. Cain demonstrated that the use of carbonic anhydrase inhibitors would aid altitude accommodation. It has been suggested that the beneficial effects of acetazolamide might be enhanced by increasing the dose of the drug. Unfortunately, as Dr. Cain will attest, large doses of acetazolamide, in the order of 25 mg/kg body weight will produce side effects similar to those of acute mountain sickness. Travis et al. (1) reported in 1964 that it was possible to give a new carbonic anhydrase inhibitor, benzolamide, in approximately 10 times the effective dose of acetazolamide with respect to renal tubular inhibition of carbonic anhydrase without fear of causing significant enzyme inhibition in the red blood cell. Mani and Weinstein (2) have shown that benzolamide improves the performance of rats during hypoxia. Therefore, we undertook a study to explore the usefulness and mechanisms of action of benzolamide in aiding accommodation of men to altitude.

A total of 23 active-duty military men were used. In each experiment, two to four subjects were placed in a low pressure chamber at 14,000 ft. simulated altitude for 72 hours. A total of 500 mg. of benzolamide or a lactose placebo was given orally in a "double-blind" fashion prior to going to altitude. The dose was divided so that five 50 mg. gelatin capsules were taken 12 hours before, and another five 1 hour before entering the chamber. After a minimum of 4 weeks each subject was studied again with reversal of those receiving drug and placebo. CO_2 response curves on nine of the subjects were determined immediately before going to altitude and in the afternoon of the 1st, 2nd, and 3rd days at 14,000

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ft. At the end of 24 and 72 hours at altitude samples of arterial blood and cerebrospinal fluid (CSF) were obtained. Three 24-hour urine volumes were collected from each subject while he was at altitude. During each experiment the subjects were ranked according to their apparent state of well-being. In addition the subjects themselves were asked to indicate a preference between the two runs.

The results of the CSF data are shown in Table I.

After 24 hours at 14,000 ft., benzolamide had significantly lowered the calculated PCO_2 and the HCO_3^-. These differences persisted in the 72 hour samples and were in the same direction and of virtually the same magnitude as those seen after prior treatment with acetazolamide.

Between 24 and 72 hours there had been a rise in PO_2 and pH while the calculated PCO_2, HCO_3^-, and lactate all decreased significantly in both treated and untreated subjects. The fall in CSF lactate between 24 and 72 hours is especially interesting. We have shown that the increase in CSF lactate occurring during the first 24 hours at altitude accounts for less than 1/3 of the CSF HCO_3^- loss (3). The fact that the lactate fell between 24 and 72 hours while HCO_3^- was also dropping would indicate that CSF lactate plays little if any role in the CSF HCO_3^- concentration after the

Table I. Analyses of cerebrospinal fluid, sampled after 24 and 72 hours at a simulated altitude of 14,000 feet

	24 Hours		72 Hours	
Cerebrospinal Fluid	Benzolamide	Placebo	Benzolamide	Placebo
P_{O_2} (mm. Hg) †	29.7 ± 1.8	27.8 ± 1.7	32.2 ± 1.6	31.4 ± 1.7
Meas. P_{CO_2} (mm. Hg)	38.0 ± 1.0	38.7 ± 0.8	36.3 ± 0.9	37.2 ± 0.8
Calc. P_{CO_2} (mm. Hg) ††	37.3 ± 1.0	40.8 ± 0.9*	35.2 ± 0.9	36.5 ± 0.9*
pH †	7.357 ± .008	7.348 ± .008	7.362 ± .008	7.373 ± .008
Lactate (mg. %) † †	17.4 ± 0.6	18.2 ± 0.5	15.8 ± 0.5	17.1 ± 0.6
HCO_3^- (mM./liter) ††	20.26 ± 0.21	21.41 ± 0.20**	19.21 ± 0.20	20.24 ± 0.20**
Chloride (mEq./liter)	130.3 ± 1.0	128.7 ± 0.6	131.1 ± 0.8	129.2 ± 0.7

* $P < .05$ between benzolamide and placebo
** $P < .01$ " " " "
† $P < .05$ between 24- and 72-hour value
†† $P < .01$ " " " " " "

first 24 hours at altitude. The decrease in lactate is probably related to improving cerebral oxygenation as manifested by the rising CSF PO_2.

The results of the arterial blood data are summarized in Table II.

Looking at the 24 hour benzolamide and placebo data first, benzolamide raised the PO_2 while lowering PCO_2, pH, HCO_3^-, and std. HCO_3^-. Once again all of the 24 hour differences persisted up to 72 hours and were very similar to those already reported with acetazolamide. The only changes occurring between 24 and 72 hours were a rise in both PO_2 and Hct. The latter was not statistically significant ($.05 < p < .10$).

The urine data are shown on Table III.

Taking each 24 hour collection period separately, there was a significantly higher potassium excretion in the drug-treated group after the first 24 hours at altitude. This was comparable to the kaluresis seen in the acetazolamide-treated subjects. There were two differences in the 24 hour benzolamide vs. placebo data when compared with the acetazolamide vs. placebo findings for the same collection period. The first was the lack of a significant diuresis in the benzolamide group; although the urine volumes were higher on the average in the drug-treated subjects. The second is the signif-

Table II. Analyses of arterial blood, sampled after 24 and 72 hours at a simulated altitude of 14,000 feet

	24 Hours		72 Hours	
Arterial Blood	Benzolamide	Placebo	Benzolamide	Placebo
P_{O_2} (mm. Hg) †	45.6 ± 1.6	41.1 ± 1.4*	49.3 ± 1.5	44.4 ± 1.5*
P_{CO_2} (mm. Hg)	26.7 ± 0.9	28.5 ± 0.7*	25.8 ± 0.8	27.3 ± 0.9*
pH	7.437 ± .008	7.493 ± .006**	7.445 ± .008	7.501 ± .007**
HCO_3^- (mM./liter)	18.11 ± 0.50	22.33 ± 0.35**	17.94 ± 0.45	21.47 ± 0.40**
Std. HCO_3^- (mM./liter)	21.33 ± 0.31	25.06 ± 0.26**	21.33 ± 0.32	24.27 ± 0.25**
Hct. (%)	45.6 ± 1.0	41.1 ± 0.9	49.3 ± 1.0	44.4 ± 1.0

* $P < .05$ between benzolamide and placebo

** $P < .01$ " " " "

† $P < .05$ between 24- and 72-hour value

Table III. Analyses of 24-hour urine samples collected during 24, 48, and 72 hours at simulated altitude of 14,000 feet

	24 Hours		48 Hours		72 Hrs.	
	Benzolamide	Placebo	Benzolamide	Placebo	Benzolamide	Placebo
SODIUM (mEq./24 hrs.)	185.0 ± 17.1	173.9 ± 12.8	99.0 ± 15.0	140.5 ± 10.2	91.2 ± 13.1	126.0 ± 8.6
POTASSIUM (mEq./24 hrs.)	69.0 ± 4.8	41.5 ± 3.5**	50.5 ± 4.5	35.5 ± 3.3**	36.7 ± 5.0	39.7 ± 3.7
CHLORIDE (mEq./24 hrs.)	126.0 ± 14.3	126.7 ± 11.2	99.1 ± 9.7	93.1 ± 8.6	91.6 ± 8.5	90.6 ± 8.0
17-OHCS (Mg./24 hrs.)	4.4 ± 0.6	5.4 ± 0.4*	6.1 ± 0.7	6.7 ± 0.5*	4.7 ± 0.5	5.6 ± 0.3*
VOLUME (cc./24 hrs.)	1702 ± 142	1196 ± 164	1196 ± 110	1024 ± 108	921 ± 72	986 ± 65

* $P < .05$ between benzolamide and placebo

** $P < .01$ " " " "

icantly higher 17-hydroxycorticosteroid (17-OHCS) excretion in the untreated subjects. Insofar as the excretion of this hormone is indicative of stress, the subjects given a placebo underwent more stress than those given benzolamide.

No changes occurred in the relationships between the two groups of subjects during the second collection period. However, between 48 and 72 hours only the difference in the 17-OHCS excretion levels remain while those between volume and potassium disappear. This may indicate the loss of some drug effect after 48 hours and point to the necessity of giving additional doses at that time.

In general there was a significant decrease in the excretion of all the urine variables during the period of altitude exposure, the major exception to this being the rise in 17-OHCS excretion occurring on the 2nd day. This fall in excretion was probably due to the marked reduction in oral intake on the part of almost all the subjects and, along with the increase in the arterial Hct., indicates some degree of dehydration.

Figure 1 summarizes the clinical ranking of the subjects as well as the subject's own evaluation of the two runs.

In contrast to the acetazolamide study no separation of benzolamide and placebo-treated subjects could be obtained on the basis of my rankings. We feel this is more a reflection of the

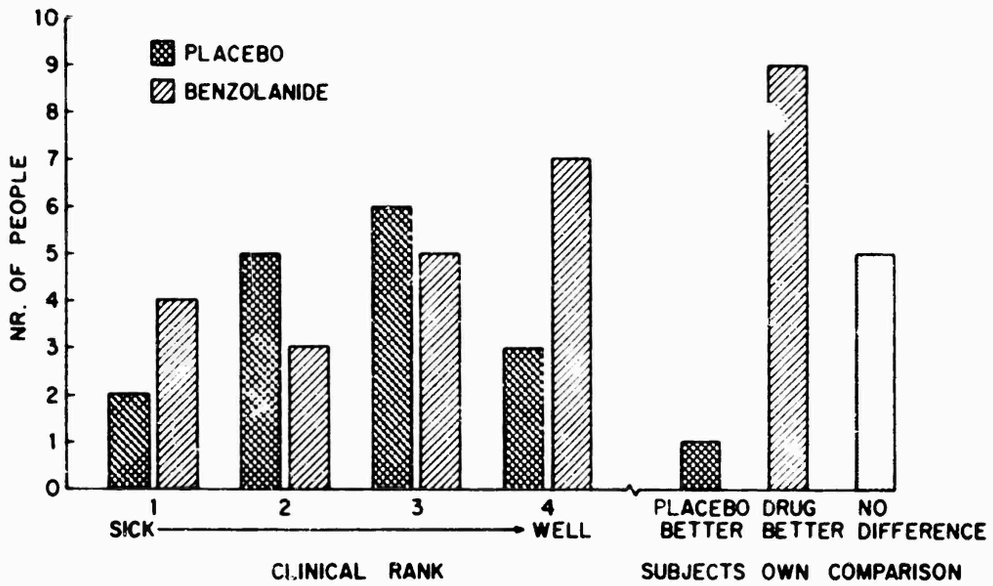

Figure 1. Clinical, rankings and subject's own evaluation of the flights.

difficulties inherent in having an outside observer evaluate someone for the presence or absence of acute altitude sickness under these conditions rather than a lack of any benefit from the drug. The subjects themselves expressed a clear-cut preference for the drug runs and this is supported by the significantly higher 17-OHCS excretion in the untreated group.

Figure 2 illustrates the results obtained from the CO_2 response curves.

The ground level curves obtained prior to going to altitude (labeled G.L.) are essentially identical for both groups of subjects. After 24 hours at altitude the curve for the untreated subjects had not changed significantly from its ground level position. The benzolamide curve on the other hand, had moved to the left and upward to a position achieved by the placebo-treated subjects only after 48 hours. This relationship persisted throughout the course of the altitude exposure.

This illustrates one of the major effects which carbonic anhydrase inhibitors have on altitude accommodation, namely the ability to speed up the normal process of acclimatization by 24 to 48 hours.

It appears that if a large number of people are taken to altitude, 3 distinct groups will appear. A small percentage will not be adversely affected by altitude. A slightly larger number will be made ill no matter what preventatives they take. Finally the majority will be helped to some degree by prior administration of the drug. Although not perfectly effective in preventing the signs

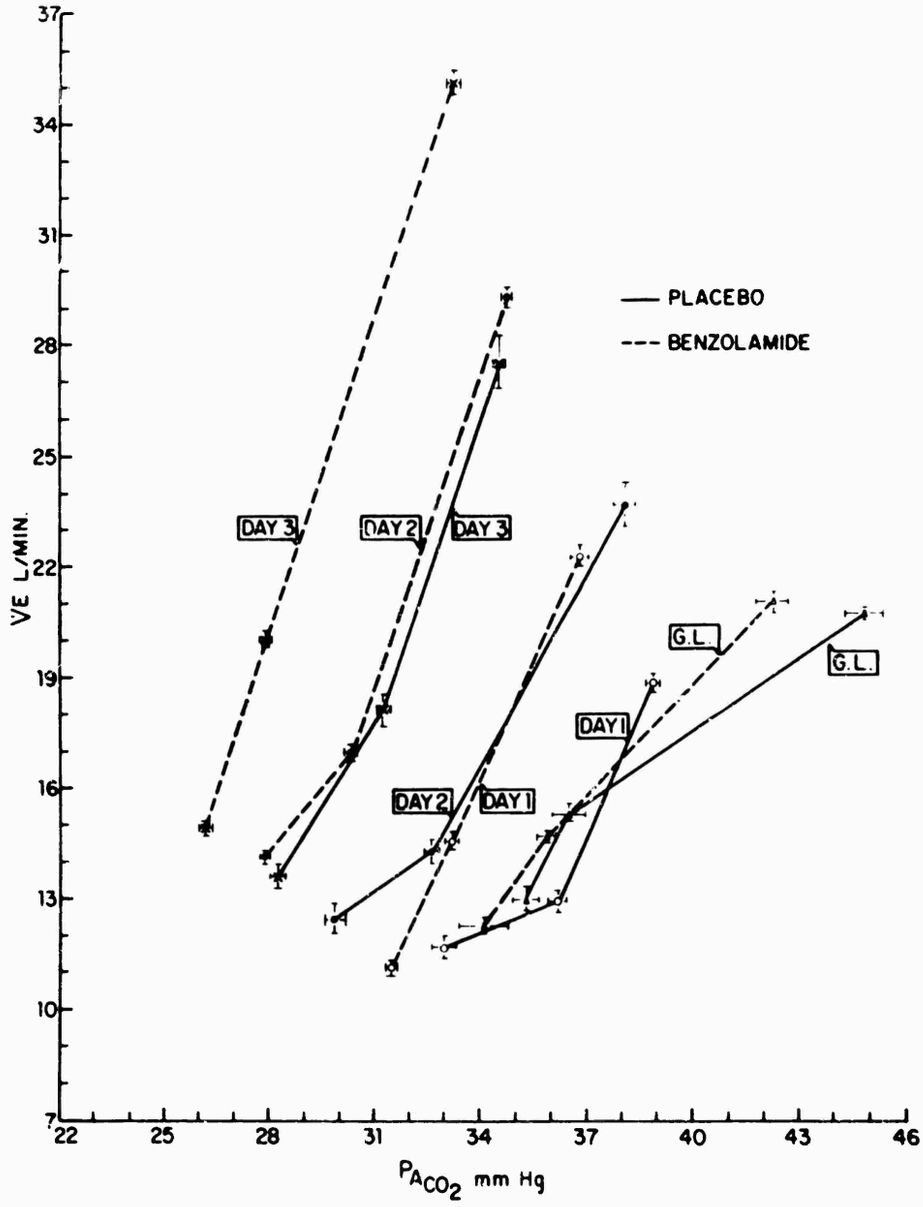

Figure 2 Average CO_2 response curves. Each point represents a mean value + 1 S. E. M.

and symptoms of acute altitude sickness this study with benzolamide offers additional evidence that pretreatment with carbonic anhydrase inhibitors does aid some subjects, and certainly hastens respiratory features of altitude accommodation. Benzolamide is not clearly better in either respect than acetazolamide.

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EVALUATION OF ACUTE MOUNTAIN SICKNESS AT 12,000 FEET ALTITUDE AND THE EFFECT OF ACETAZOLAMIDE

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The assessment of acute mountain sickness, especially if considered as a step toward understanding and control of this condition, poses a challenge. The problem of acute mountain sickness although long recognized is still unsolved. It has moved from that of a contingent disability to one of practical military importance. Considered from an even broader point of view, acute mountain sickness, in common with numerous other conditions, is a disorder with predominantly subjective manifestations. In conditions of this nature, the approaches to quantitative assessment are truly challenged by a tantalizing array of difficulties. Simple, as well as complex, some of these difficulties can be overlooked by the enthusiastic clinician and by the non-clinical investigator alike.

There may be relatively little difficulty in recognizing extremes of subjective sensation and endowing these with tangibility, or in estimating the disability which severe symptoms are likely to induce. When symptoms range from most mild to less than intolerable, the difficulty of grading or quantitation increases the more deeply it is approached, and the finer the resolution one strives to obtain. With reluctance it must frequently be admitted that in the absence of a primary standard of comparison, and without measures of the reliability of estimation, even the construction of a weighted index of over-all illness frequently approaches an exercise in futility.

In order to be able to make comparisons among the growing number of agents which have been suggested for the alleviation of symptoms of acute mountain sickness, and in order to determine the relation between the effects of different levels of altitude, training and procedures, etc., and the severity of this condition, it is necessary to use tools which are capable of achieving these

sufficiently fine degrees of discrimination. It is here that the assessment of subjective states finds its greatest need and greatest difficulty.

Some aspects of a field study approach to an evaluation of the effects of acetazolamide on acute mountain sickness will be presented in order to illustrate this problem and invite its discussion. This work was carried out during the summer of 1966 on Mt. Evans, Colorado, at an altitude of 12,800 feet, and represents the participation of numerous members of the USARIEM staff. Subjects of this study were 43 soldiers of the U. S. Special Forces. These young men are not to be considered representative either of the average soldier or of the average university student. Details of the experiment are reported elsewhere (1).

Since we did not begin with set criteria to provide a predefinition of acute mountain sickness, description and evaluation were concurrently elicited. For this purpose, we acquired two types of information. The first was the traditional clinical method of evaluation in which a physician obtains a history from, examines a "patient", and formulates a judgment as to the presence and severity of symptoms and of illness. This was modified in these 3 respects: (a) in order to provide uniformity of sampling, all of the individuals at risk were seen each day – these were called "subjects", (b) to aid uniformity of observation, an outline was provided which designated minimum topical coverage, (c) to introduce replication, two physicians alternated in examination of each subject.

The second type of information was that obtained by a self-administered short form questionnaire given twice a day. This contained 83 questions. Twenty of these were chosen as being unlikely to evoke a positive response from the experience, and thirteen others were chosen where a positive response would be unlikely to be due to reduced barometric pressure alone. These were included as null items to serve in part as a validating check. With some reluctance, a scoring method was adopted. This was based on the intensity and duration, which were indicated by the answers, and it was intentionally made non-linear. The difference between scores at altitude and at sea level is referred to as the altitude effect, while the number of positive answers is referred to as the response frequency.

It can readily be noted that these two types of evaluation – the clinical appraisal and the questionnaire, are far from independent. Their major difference lies in the extraction, clarification and distillation process which, in the clinical method, is complex and involves two human transfers, and in the questionnaire approach is

simple, with but one human transfer. Concordance in results obtained with the two types of inquiry might lend encouragement to the idea that results of either were real and were not spurious. However, a sobering realization of their common source, and of the virtually unknown and uncontrollable effects of the large variables – which influence the recorded assessment of subjective sensation or experience including receptor sensitivity, perception, recognition, attention, interpretation responsiveness and communication must discount any such claim. It would appear valid, nevertheless, to conclude that agreement in the two methods indicates that the more easily administered questionnaire could be substituted for the clinical evaluation, not only in this instance but possibly in others, and where clinical evaluation of adequate numbers of subjects was not feasible.

From the questionnaire, responses to twenty-four questions showed substantive over-all altitude effect or drug effect. These were selected for summary and analysis, and grouped into 10 symptom categories of 1-5 questions each (Figure 1.). Adverse effects of altitude in the 22 subjects who received placebos were reflected by averaged answers in these categories. In decreasing order of severity per question, nasal symptoms (congestion and rhinorrhea) and dizziness, were highest. Following were the closely grouped categories of headache, respiratory symptoms (dyspnea, cough), insomnia, impairment of general well-being or affect, and upper gastrointestinal distress (anorexia, nausea, and loss of taste). Scoring less were lower gastrointestinal distress (flatulence, constipation), feeling cold, and polyuria.

Effects tended to be greatest after 12-36 hours at altitude, presenting in this order: dizziness, affect, nasal symptoms, headache, upper gastrointestinal symptoms, feeling cold, respiratory symptoms, insomnia, lower gastrointestinal symptoms and polyuria. The number of questions in each category is indicated. With each day providing two tests on 22 subjects, each daily point represents the mean of 44-220 scores and each 4-day average point is the mean of 176-880 scores, expressed as percent of maximum possible score. Selecting 5 of these categories as a group (Group A), and plotting their daily averages, a trend of the time-intensity course of symptoms may be depicted, showing an early peak and decline. However, if the other 5 categories are grouped (Group B), a different trend is indicated where the severity level is more sustained. (Here each point represents the mean of over 500 entries). These same general relationships, with minor variation, are demonstrable when the frequencies of positive responses are plotted instead of the altitude effect scores (Fig. 2).

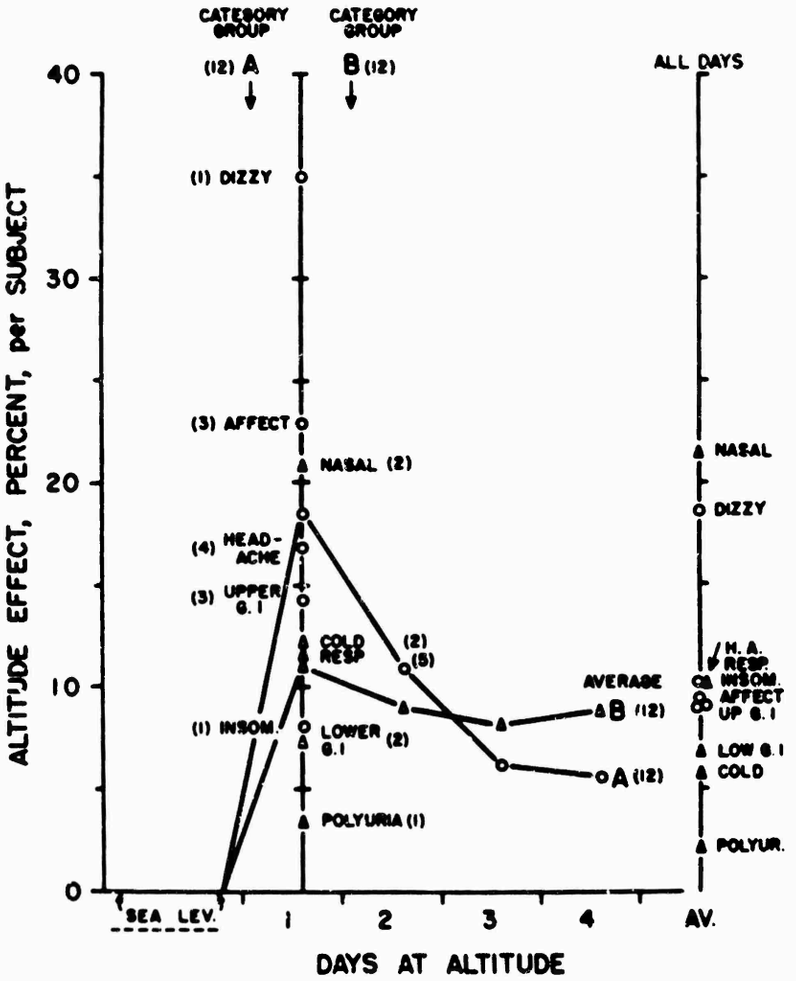

Figure 1. The effect of altitude on response to questionnaire is presented for 24 questions in two groups and 10 categories. Ordinate represents mean of difference between altitude and sea level score on 22 subjects, expressed as percent of maximum possible score. Averages for 12-24 hours and 12-96 hours are indicated for each category (the number of questions in each category are given in parentheses). Daily averages for each category group are indicated over the period at altitude.

It is evident to begin with that the patterns of responses and trends will vary if questions are weighted by their number or content. The General High Altitude Questionnaire used by Shields et al (2) Carson et al (3) and Evans (4), has multiple questions dealing with the category of activity which are scored as separate questions: "lively", "active", "energetic", "vigorous", "(not) sleepy", "(not) drowsy", "(not) lazy", "(not) tired", "refreshed". In a total of 26 questions these and other included redundancies can result in inadvertent but discernible weighting which may be

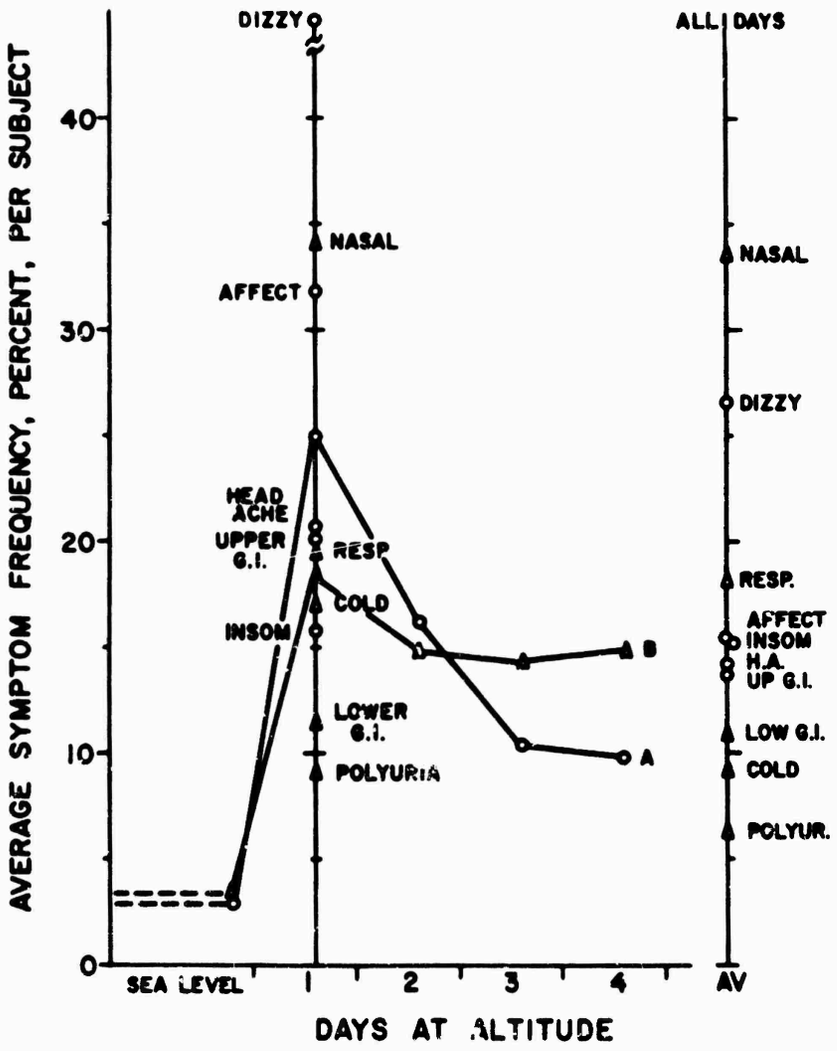

Figure 2. As in Figure 1, where ordinate represents mean response frequency expressed as percent of maximum response frequency.

undesirable for general use. Nevertheless it is considerably more of a problem to devise a way to determine how the meaning of any question is weighted in the mind of the subjects, and what variation in response arises from the differences in comprehension, "set" and background of the subjects. The questionnaire used in this study was not constructed with any plan or knowledge of optimal weighting, and although it may not be a sensitive or reliable tool with which to search for small differences, it has been capable of eliciting two useful results. This quasi-amorphous instrument has served firstly to identify certain group differences in the study for which it was developed (but not pretested). Secondly, certain individual differences within the group may be promulgated from its findings.

As has been pointed out, the trend obtained for one category group appeared to differ from that obtained for another, a logical consequence of the fact that exposure to 12,800 feet altitude may have a variety of effects. With the exception of respiratory symptoms, the second group either consists of relatively minor and non-disabling symptoms, of effects appearing with relatively less intensity, or associated with mountain environment but not due to reduced barometric pressure. The first group contains the major, disabling and more intensely reported adverse manifestations of mild hypoxia.

Comparing the responses of the 22 untreated subjects with 21 subjects simultaneously exposed but pre-treated with acetazolamide, it is readily indicated (Fig. 3) that the drug treated subjects had consistently and sizably lesser altitude effect by score or frequency with respect to the symptoms of the first group, i.e., dizziness, headache, insomnia, affect, upper gastrointestinal distress. From this it would seem likely that the drug ameliorated the symptoms of acute mountain sickness. However, the right half of the figure indicates, perhaps to a lesser extent, that the drug treated subjects experienced a greater adverse effect of altitude at least with respect to these symptoms categories. It was this difference with regard to drug effect which actually determined the grouping of categories. Since acetazolamide at sea level can induce noticeable dyspnea on exertion, the greater increase in respiratory symptoms of the treated subjects were judged to be due to this. The first grouping (Group A) is favored as descriptively appropriate to mountain sickness, and the second (Group B) as related to coincidental or side effects of drug.

Before further consideration of the questionnaire evidence for a beneficial action of the treatment, it is appropriate to comment on the extent of agreement between the questionnaire and the clinical evaluation (Figure 4). Over a comparable time period (between 12 and 36 hours at altitude) the incidence and severity of headache revealed to and recorded by the physician are shown in relation to the averaged altitude effect designated by the questionnaire for all subjects both placebo and drug treated. There is a recognizable consistency, with several notable exceptions, and the effect of drug in reducing headache can be identified from the clinical evaluation as well as from the questionnaire score. In Figure 5 the over-all average effect, indicated by 12 questions in 5 categories (Group A) for the entire altitude period (96 items per subject), is plotted for each subject against the replicated clinical appraisals of two physicians - one on the 4th, and the other on the 5th day at altitude. There is a satisfactory degree of concordance in the clini-

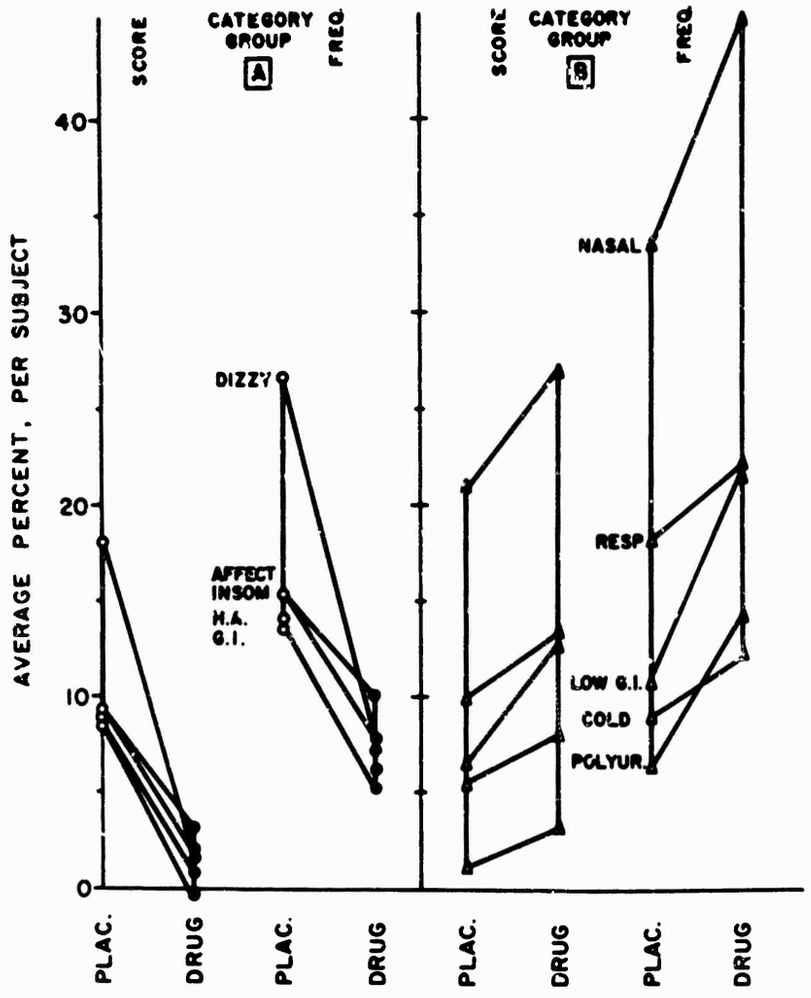

Figure 3. Effect of acetazolamide on symptoms from questionnaire analysis by category and in category groups. Ordinates as in Figures 1 and 2. First and third segments of figure refer to altitude effect (score), second and fourth segments refer to number of responses (frequency). Each segment indicates means of 22 control subjects (placebo, on the left) and 21 subjects pretreated with acetazolamide (drug, on the right).

cal estimates (with occasional exceptions) in view of the lack of either grading trials, or predefinition of mountain sickness. Again, the general consistency of clinical and questionnaire estimates of acute mountain sickness shown on the scatter plot serves as a background to highlight a) the variance about any prediction, b) the occasional gross discrepancy, and to indicate that the influence of drug can be deduced by the generally lower position of the drug treated subjects on either coordinate scale.

Returning to the evidence that drug was beneficial for some symptoms, Figure 6 compares the questionnaire altitude effect for

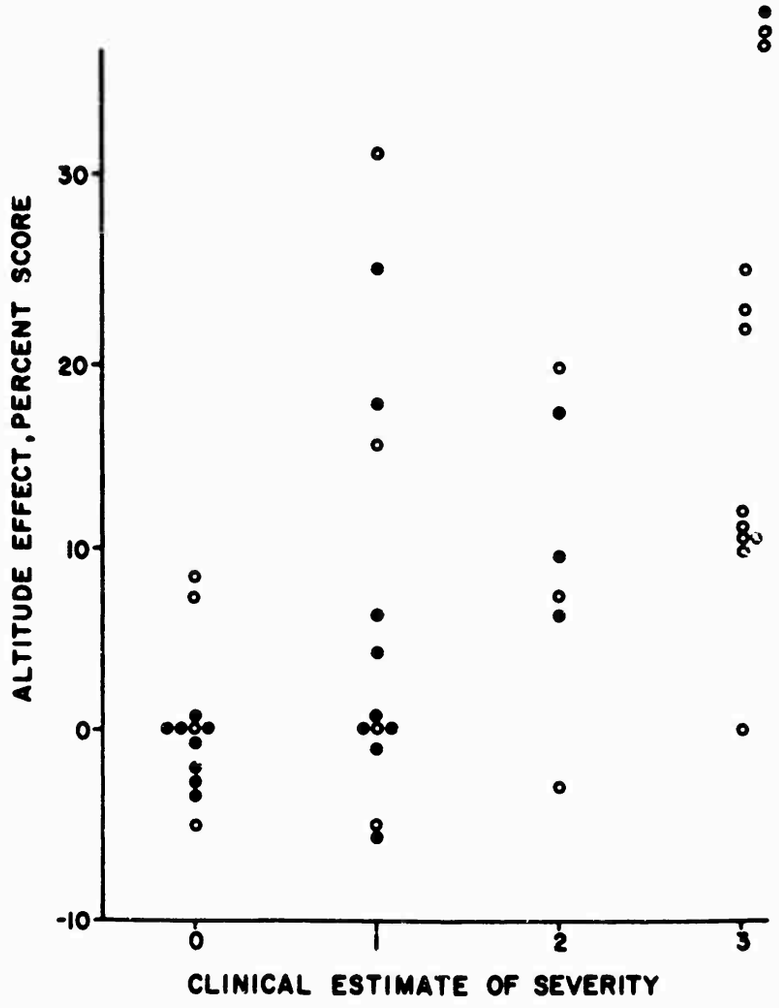

Figure 4. Comparison of questionnaire and clinical estimates of headache severity after one day at altitude, for 44 subjects (solid dots represent drug treated, open circles placebo treated,.

12 questions in the control subjects (open circles) with the effect in the treated subjects (closed circles) showing each subject for 2 of the periods at altitude and for the over-all average. The distribution of the values is noticeably asymmetrical. For this reason the median values are indicated by the horizontal lines, for each day at altitude and for the average of all days. These, as well as the distributions, again show the consistently lower altitude effect reported by the drug treated subjects. Differences in the sum of the rank order of the scores for the two sets of subjects provide an appropriate statistical test of the differences in the mean (Wilcoxon) and indicate this to be significant for each day and all days at altitude ($P < .01$). Similar treatment for the question category of headache (Fig. 7) again shows the drug effect, although not as persistent.

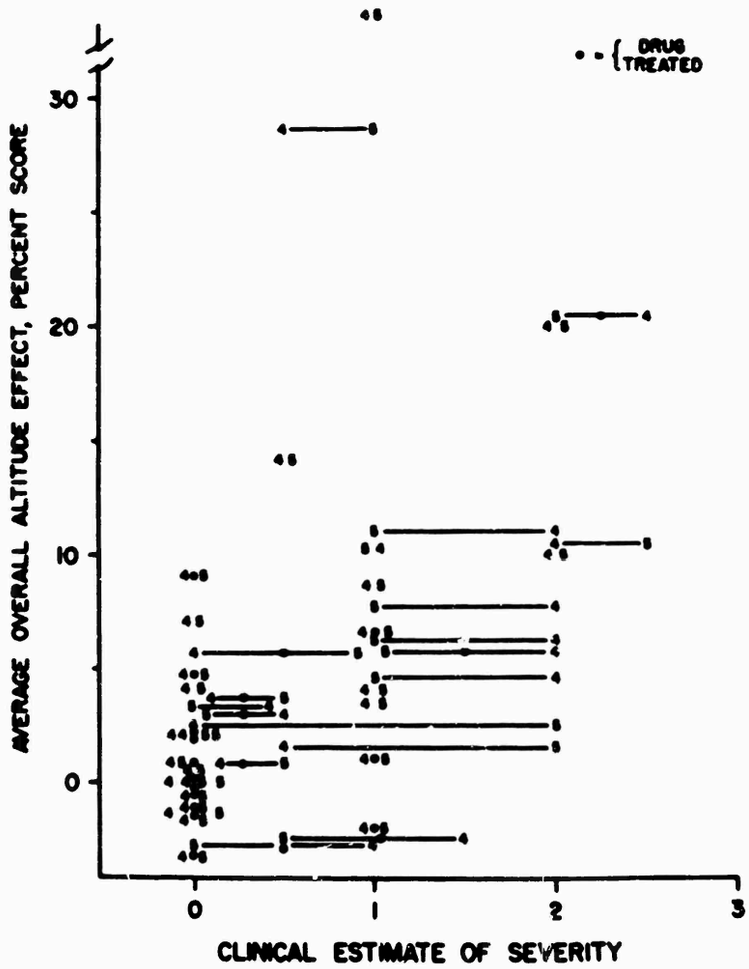

Figure 5. Comparison of questionnaire (average of 12 questions) and clinical estimates of over-all acute mountain sickness. Paired numbers indicate 4th and 5th day clinical estimates made by separate observers. Dots indicate subjects given drug.

Figure 8 provides an example of the use of this approach to deduce individual differences within the control subjects. Here the rank of the altitude effect of headache (all days) is compared with the arterialized blood CO_2 tension, and a direct relationship is noted. The rank (Spearman) correlation coefficient of .70 is statistically significant ($P < .01$). The correlation provides meaningful insight into and support of an hypothesis to explain the mechanism of acute mountain sickness (5).

In summary, through the questionnaire approach, the manifestations and course of acute mountain sickness have been described, the effects of a drug quantitated and symptom severity has been related to a biochemical measurement. An awareness of

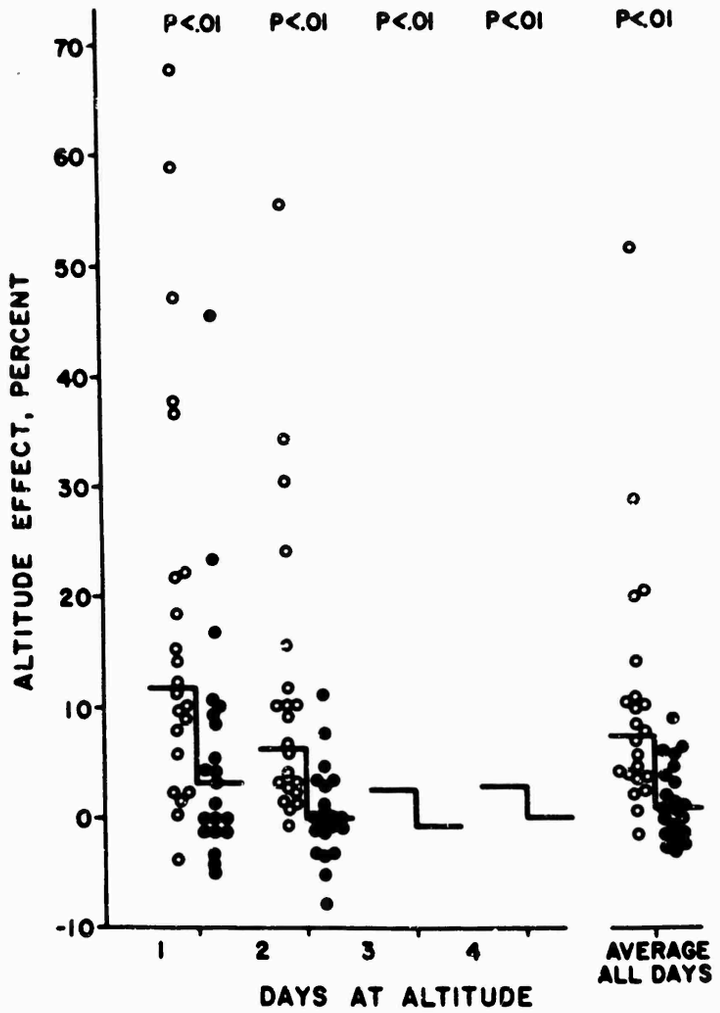

Figure 6. Distribution of questionnaire altitude effect for average of 12 questions by individuals in 22 placebo (open circle) and 21 drug (solid dots) treated subjects for 12-24, 36-48, and 12-96 hour periods at altitude; median values for averages for each time period and treatment.

the uncertainties and difficulties in assessment of subjective states leads to caution in interpretation, to search for means of testing the validity of this approach and to question whether it can be expected to detect more subtle differences, which are for the reason of their subtlety even more important to discern.

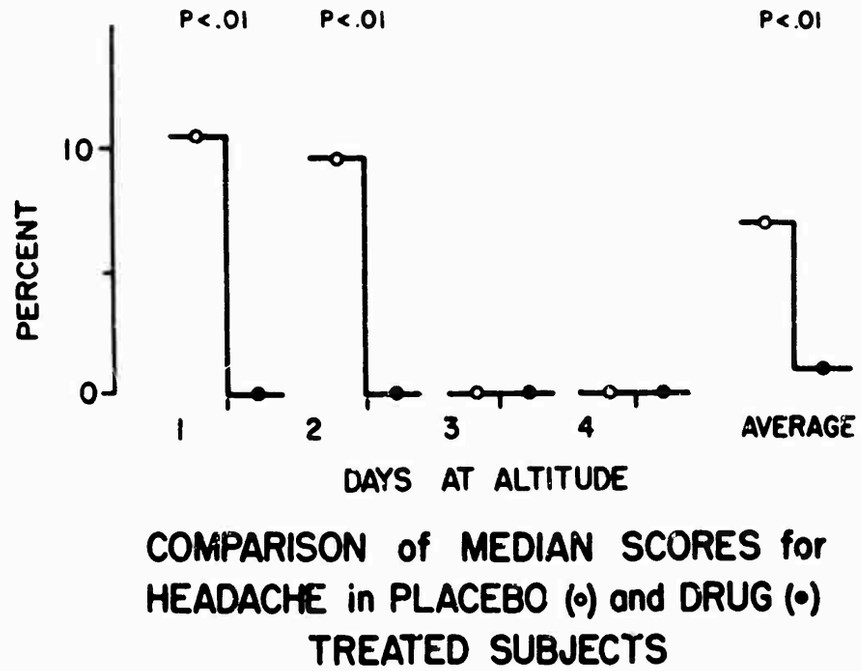

Figure 7. Median values as in Figure 6, for headache (average of 4 questions).

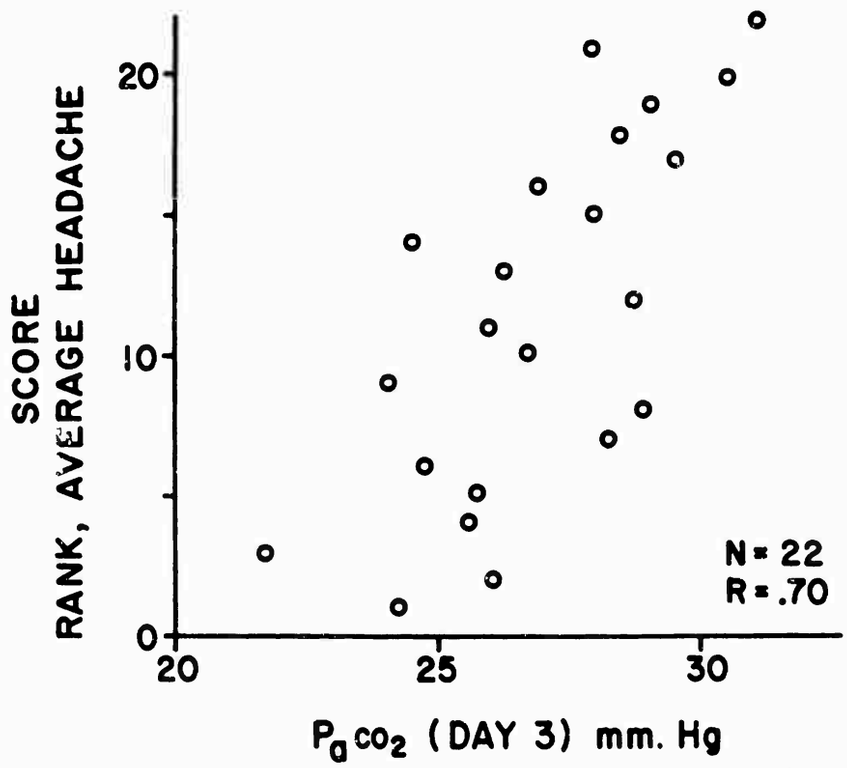

Figure 8. Scatter plot to show relation between rank of effect of altitude on headache for period at altitude, and arterial CO_2 tension on the 3rd day at altitude in 22 control (placebo treated) subjects at 12,800 feet elevation. The rank correlation coefficient (.70) is significant at $P<.01$.

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METHODOLOGICAL COMMENTS ON ASSESSMENT OF SUBJECTIVE STATES IN MAN WITH REFERENCES TO STUDIES OF ALTITUDE SICKNESS

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1967

Assessment of subjective states is employed in studies of many phenomena. Studies of altitude sickness, fatigue, sleep deprivation, pain, and human psychopharmacology, for example, consistently employ subjective information. In studies of altitude sickness investigators have asked questions such as the following: What are the subjective effects of altitude sickness? How do these effects covary? How does each vary with variation in altitude, exposure-time, rate of ascent, and characteristics of the subjects tested?

For present purposes we will define subjective information as "information concerning the subject's physical and psychological condition which the subject transmits by responding to questions, rating scales, or check lists". This definition excludes directly observable behavior and objectively measurable performances on tests of sensory, mental, psychomotor, or physical functions, although inferences regarding subjective states may, of course, be drawn from such performances.

The assumptions made by the investigator of subjective responses are: first, that the subject possesses information concerning his physical and psychological condition; second, that he can and will transmit this information to the investigator; and third, that the investigator can correctly interpret what the subject transmits. Even when the subject is conscious, rational, cooperative, and in all ways able and willing to communicate with the investigator, obstacles to the valid transmission of information from subject to investigator are numerous and must be guarded against. Hence, procedures for reducing bias and experimental error (and for assessing error which cannot be eliminated) are necessary for dependable study of subjective responses. In human psychopharmacology, for example, use of the double blind procedure,

placebos, and statistical assessment of results are generally considered essential. The present discussion will deal briefly with three topics: methods of eliciting subjective information; problems of control in such studies; and use of statistical analyses.

Methods

Interviews, written narratives, questionnaires, rating scales, and check lists have all been used to study subjective responses. Each approach has certain advantages and disadvantages. Interviews permit the investigator latitude for exploration of ambiguous subjective responses and may surpass other methods for assessment of subtle or emotionally-charged information; however, interviews are time-consuming and favor introduction of bias stemming from the investigator's conscious and unconscious expectations and wishes. Narratives are useful during initial exploration to assure coverage of relevant subjective states and they, like interviews, promote clarity and depth of communication. However, their open-ended design requires time-consuming coding of responses and does not guarantee that all subjects will consider the same subjective states in their self-evaluations. Rating scales, check lists, and questionnaires which require simple answers are taken easily and quickly by subjects and they increase the chances that cooperative subjects will consider the same subjective areas when responding, but they may not enlist the subject's concentration and interest as effectively as interviews or questions requiring narrative replies. Check lists which simply ask the subject whether or not he has a particular symptom (for example, a headache) are very economical of subject response time and hence permit broad coverage quickly. However, they do not permit assessment of degrees of a particular symptom or subjective state as do rating scales.

A procedure we have found useful in drug studies (references 4, 5, 6) is to employ interview and narrative responses to identify the relevant subjective areas during periods of pilot study, and then employ check lists, rating scales, and specific questions for the investigation proper, where data are to be assessed by statistical methods.

Problems of Control

Bias can stem from many sources, and controls of various sorts are needed to avoid such error. The double blind procedure is intended to reduce error due to expectations and desires (conscious and unconscious) of subject and investigator. However, cues

available to the subject or investigator may render the double blind procedure infeasible. For example, some side effects of certain drugs are readily recognizable by subjects and investigators. Similarly, as noted by Evans (3), cues such as how matches burn may destroy the double blind nature of chamber studies of altitude sickness. Clearly, it would be difficult to maintain the double blind procedure in prolonged studies of altitude sickness where variation in altitude is real rather than simulated. Under such conditions an investigator might reduce bias by selecting subjects who are naive concerning the changes which are likely to accompany changes in altitude. Information concerning presence or absence of bias can sometimes be secured by careful interrogation of subjects after completion of the study.

Use of matched control and experimental groups, and use of the same subjects under both experimental and control conditions, are strategies employed to reduce error due to individual differences in response resulting from variation among subjects regarding such variables as age, sex, physical condition, and temperament. These approaches are intended to guard against comparing experimental and control conditions in unequated groups and, in addition, they often increase the experiment's efficiency by reducing the standard error. In investigations where the same subjects are studied under both control and experimental conditions, order effects must be controlled by counterbalancing. This is a procedure which requires that half of the subjects receive the experimental treatment first and the control treatment second, while the other half receive the two treatments in the reverse order.* Learning, boredom, carry-over effects and other order effects can be prevented from biasing the comparison of control and experimental conditions by such counterbalancing. In addition, evaluation of counterbalanced data by analysis of variance permits the investigator to increase precision of measurement by extracting the variance due to order effects from the error term used to asses the statistical significance of the experimental effect. Studies of performance are perhaps more likely to show significant variation due to order effects than are studies of subjective states. Nevertheless, a counterbalanced design used in conjunction with analysis of variance is a desirable safeguard in any study where experimental and control treatments are administered to the same subjects on different occasions. In studies of altitude sickness, as in studies of psychopharmacology, bias and experimental error are likely to be reduced more effectively by the "own control"

**Counterbalancing can also be used in studies with more than two treatments. See Smith and Beecher, (6).*

approach than by the "matched subjects" approach. However, when it is impractical to study a subject more than once, the "matched subjects" approach can often be helpful.

Randomized assignment of subjects to experimental and control treatments is an essential feature of experimental designs where the same subjects are not given both treatments. It guards against conscious or unconscious construction of experimental and control groups which are unequated with regard to the criterion being measured. In addition, randomized assignment of subjects is an assumption on which statistical analytic procedures are based. When matched pairs of subjects are compared (e.g., twins), it is important to assign treatments randomly because the investigator can never be certain that matched pairs are matched on all relevant variables. When counterbalanced designs are used and each subject receives both treatments, order of treatment should be assigned randomly, especially if time trends may be operative.

A famous example of bias due to failure to employ proper randomization is the study of change in height and weight of 20,000 children in Lanarkshire, Scotland. Half of the children were given milk daily for three months and half (the control subjects) were not. Unfortunately, the comparison between experimental and control groups regarding growth was biased by the fact that taller and heavier children were more often assigned to the control group, which did not receive milk. Corrections for such failure of matching are available, but it is always hard to tell how well they will work in the presence of bias. However, if experimental and control groups which are thought to be matched on all important relevant variables are found not to be matched after the study is completed, statistical adjustments can be applied to reduce the bias introduced. A method frequently employed for this purpose is analysis of covariance.

Statistical Analyses

Today virtually all investigators of subjective states employ statistical analyses. Tests of significance enable the investigator to make a quantitative estimate of the probable reproducibility of his results. Confidence limits enable him to make an informed quantitative estimate of the range within which the true experimental effect falls. Thus tests of significance, in association with probability theory, provide the investigator something more substantial than opinion and faith to guide interpretation of his results. This, of course, is highly desirable, but it is also important to know what tests of significance do not do. Tests of significance concern unsystematic error, not bias, and if appropriate controls do not

eliminate bias, tests of significance are pointless and misleading. Control of bias depends on careful planning and selection of an appropriate experimental design. Assuming that such bias is eliminated by randomization and other appropriate controls and safeguards, the investigator may then use a test of significance to determine whether the observed experimental effect is large enough relative to its associated experimental error, to justify confidence in the reproducibility of that experimental effect. The experimental error just mentioned is determined by two factors: (a) the amount of variation from individual to individual regarding the criterion being measured and (b) the sample size. Given an experimental effect of a certain magnitude, the statistical significance of that effect increases as variation among individuals goes down and as sample size goes up. Thus, magnitude of the experimental effect, amount of subject-to-subject variation, and sample size all influence statistical significance. Failure to appreciate this can lead the investigator down the garden path.

At first blush it might seem reasonable for an investigator to try to determine the lowest altitude at which statistically significant deterioration in mental performance occurs. However, such an effort would be misdirected for several reasons – one being that progressive increases in sample size would change "the significant altitude" to progressively lower levels. Tests of significance do not provide an absolute assessment of an observed experimental effect; rather they permit such an effect to be assessed relative to the subject-to-subject variation associated with that experimental effect and relative to the sample size employed in the study. Perhaps this is why statisticians insist on a clear distinction between statistical significance and practical significance, where the latter is judged on the basis of size of the experimental effect alone, irrespective of sample size and amount of subject-to-subject variation. It also may account for the failure of statisticians to join investigators in worshipping the 0.05 level.

The investigator who tries to determine the lowest altitude at which deterioration of mental performance becomes statistically significant will encounter trouble for still other reasons – one being that a particular experimental effect (say change in altitude) will not influence all mental functions equally. In one of our own studies, for example, we assessed the effects of 14 mg of amphetamine sulfate on three different mental functions in 78 college students (8) and found that this agent dependably improved performance on a clerical test of digit-letter coding ($P<0.0001$), had no dependable effect on ability to solve calculus problems, and dependably impaired judgement ($P<0.01$). Such results generate

respect for cautious generalization. Caution must also, of course, be exercised regarding generalization from the sample studied to the population which it purports to represent.

The above comments provide a brief and necessarily sketchy coverage of methodological principles and practices. More detailed and technical treatments of these and related topics can be found in two excellent chapters in the forthcoming (1968) International Encyclopedia of the Social Sciences – one a chapter on experimental design by Cochran (1) and the other a chapter on nonsampling errors by Mosteller (4). The chapter on design of experiments by Wilson (1952, p. 36-68) also offers some helpful advice. The reader who wishes to explore these matters in still greater detail and complexity should consult Cochran and Cox (2).

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GENERAL DISCUSSION

DR. STAUB: Dr. Cain and Dr. Kronenberg, in our studies on the equilibration of CO_2, bicarbonate and oxygen within red cells with and without added acetazolamide (Nakamura, et al. (1)), there is a time lag of several seconds before equilibration of either O_2 or CO_2 is completed after the red cell carbonic anhydrase has been inhibited. My question is whether blood drawn from a subject under these conditions and allowed to equilibrate in a syringe or electrode cuvette is the same as blood arriving at the peripheral or pulmonary capillaries? If it is not, what deviations would true capillary blood show from the values obtained in the electrode cuvette? I would think the arterial CO_2 entering the cerebral capillaries would be lower than that measured in the electrode after equilibration was complete.

Have you noticed any effect of acetazolamide treatment on pulmonary vascular resistance? This could be a problem if vascular resistance rises at high altitude in response to the increased mixed venous blood PCO_2, as a result of carbonic anhydrase inhibition.

DR. CAIN: I do not think the equilibration time would be a factor in these studies for the reason that, at the relatively low dosage of the drugs which were used, there would still be adequate catalysis by uninhibited red cell carbonic anhydrase. Furthermore, by the end of 24 hours using these doses, I do not think there is much drug left in the circulating blood. I do not have any data on the pulmonary vascular pressures.

DR. TRAVIS: In Dr. Kronenberg's study, with the doses that were used there would be no red cell inhibition. That has been documented very thoroughly not only in experimental animals but also in our own studies in eight patients. We have measured the

CO_2 in every way you can measure it. We have also done drug studies on the blood and on plasma in these patients and correlated these with studies where we had intentionally inhibited red cell enzyme.

DR. WEINSTEIN: Do you have any information on the efficacy of carbonic anhydrase inhibition when you do not pretreat the animal with the drug? We found very marked differences in blood gases with benzolamide administration in pretreated animals versus non-pretreated animals. We found significant behavioral improvement, either when we pretreated animals or when we used high doses of the drug. This is specifically with benzolamide and studies of neural function. There are other situations in which we can demonstrate improvement in performance with low doses of the drug but for neural function we have found that pretreatment or high dosage is one of the necessary criteria.

DR. CAIN: We have not actually tried any other dosage schedules. We have always started with the pre-set metabolic acidosis. We need some information on what happens when you give this class of drugs after going to altitude.

DR. TRAVIS: I think this is quite an important issue to settle some place since the amount of pretreating you will need is at least two or three days. How long did you use?

DR. WEINSTEIN: We had pretreated for two days.

DR. GROVER: Do the doses of benzolamide which you are using interfere with the unloading of CO_2 during exercise?

DR. KRONENBERG: We have no data on that; we do not exercise our subjects.

DR. TRAVIS: One would have to go up to about five times the dose that Dr. Kronenberg used in order to affect the red cell enzyme. Complete inhibition is obtained at an intravenous dose of about 20 milligrams per kilogram. He was using about three mg/kg orally. Of the three in man given orally, only one-third is absorbed, so it is almost a 20 to 1 difference. You are way below getting inhibition in the red cell. Whether the acidosis itself would affect the unloading of CO_2 is another question.

DR. BILLINGS: Did not Carter (2) and Tomashefski (3), in early work at the School of Aerospace Medicine, use much higher doses injected intravenously? There were some exercise studies done in that early work and I frankly do not remember the finding in this area. But, they were using doses that were actually toxic.

DR. CAIN: Yes, as I remember they were using 100 milligrams per kilogram in dogs and I do not remember the exercise data but they certainly got large arterial differences which would speak of the red cell effect.

DR. BILLINGS: They also used fairly toxic dosages in humans. I do seem to recall some difficulty there.

DR. CAIN: Those were not reported. I have taken up to 50 milligrams per kilogram myself and it is extremely uncomfortable. Even at the low doses, perhaps you can call it a side effect, beer and coke do not taste very good.

MR. CONSOLAZIO: Most of the studies presented in this session deal with carbonic anhydrase inhibitors as they relate to the mountain sickness syndrome. I would like to present some information on the beneficial effects of high carbohydrate diets at high altitudes. Prior to World War II, Campbell (4,5) conducted studies showing the beneficial effects of high carbohydrate diet to hypoxia. Mitchell and Edman (6) critically reviewed these and other studies up to 1949 and showed the same beneficial effects. Recently we completed a study at an altitude of 14,000 feet (Pikes Peak (4300 meters)) to evaluate the effects of a high carbohydrate diet. We had two groups of young sea-level natives, a control group consuming a normal diet, and the second consuming approximately 70% of the calories in the form of carbohydrate. In past studies by our laboratory, the subjective mountain sickness symptoms were maximal at 36 hours of altitude exposure, but in this study we observed that the clinical symptomatology was maximal in 4 to 12 hours of exposure. We have used the same type of questionnaire that we have been talking about all morning.

Figure 1 shows the beneficial effects of a high carbohydrate diet. This group was less drowsy than the group consuming the normal diet. The normal carbohydrate group was more nauseated, was less energetic, and was more depressed. Cramping and headaches were approximately the same in both groups.

In Figure 2 one observes that the normal carbohydrate group had the greatest heart pounding, was more irritable, was more tired, and less happy than the high carbohydrate group. In Figure 3 the normal carbohydrate group was less lively and was more severely short of breath than the other group. Both groups felt that dizziness was approximately the same and both slept equally badly. This evidence suggests the great beneficial effects of a high carbohydrate diet at high altitude.

Work performance was measured on the treadmill at 3.5 mph on an 8% grade, carrying a 20 kg pack during all phases of the study. During sea level control studies and during sea level rehabilitation, all of the men completed the 15-minute walk. But at altitude the normal carbohydrate group averaged only 4 $\frac{1}{2}$ minutes, while the high carbohydrate group's time was more than doubled, averaging 9.8 minutes.

Figure 1. CLINICAL SYMPTOMS AT ALTITUDE

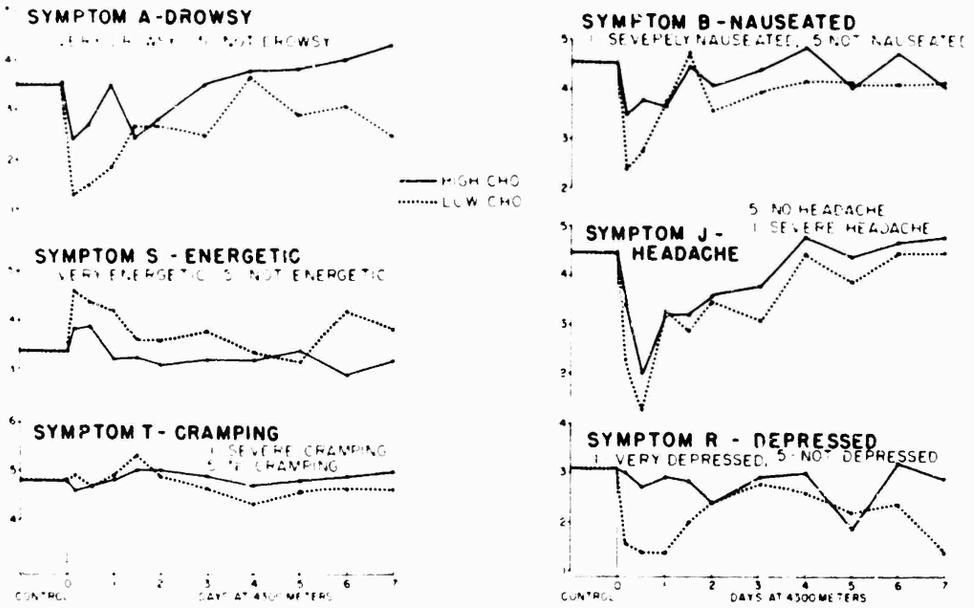


Figure 2. CLINICAL SYMPTOMS AT ALTITUDE

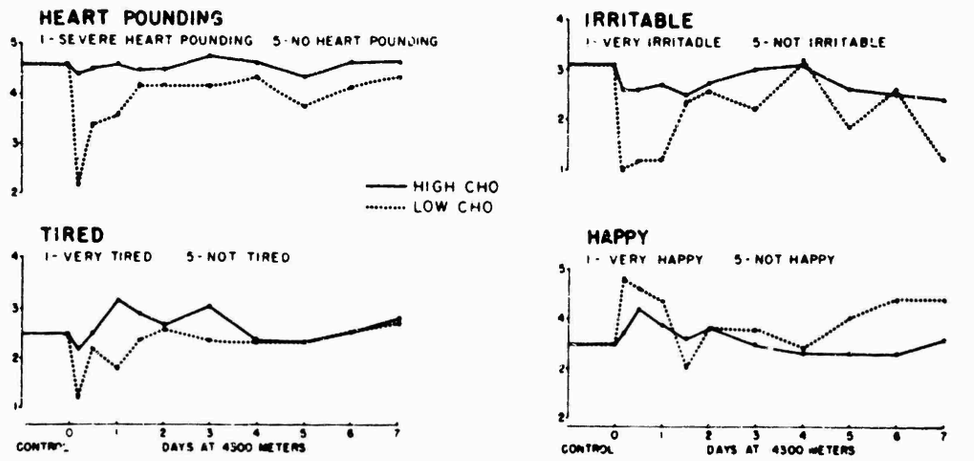
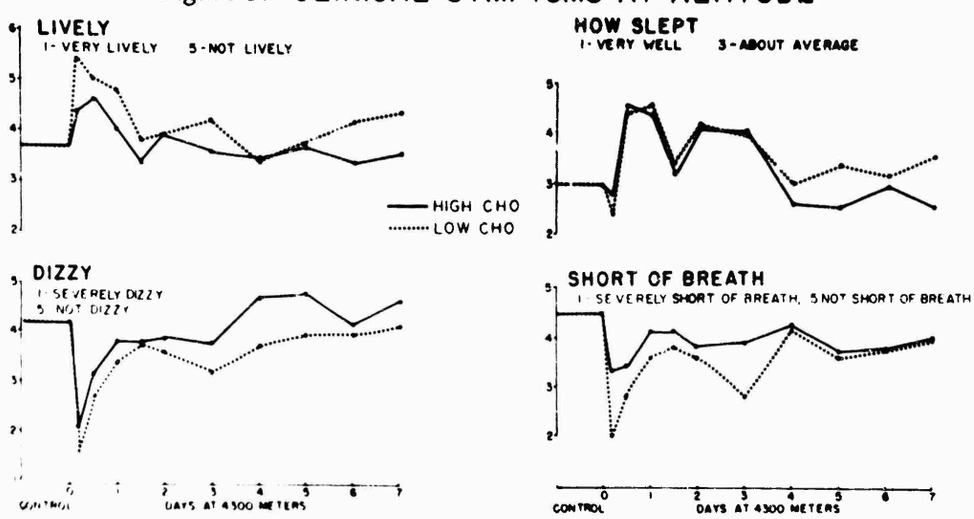


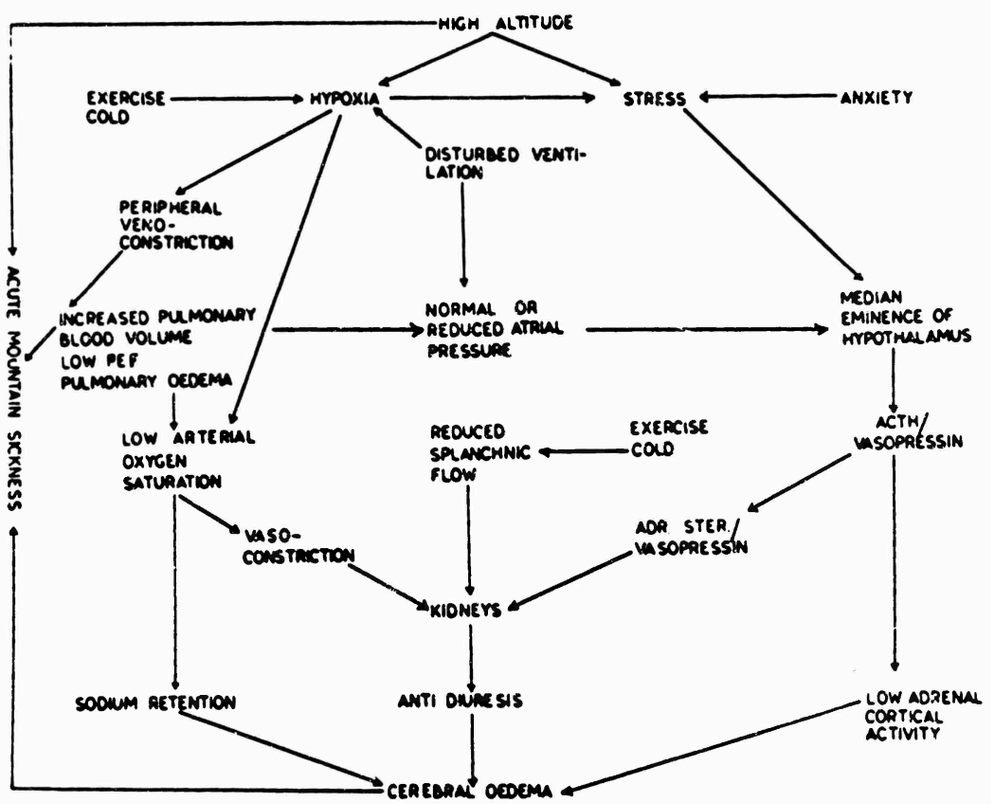
Figure 3. CLINICAL SYMPTOMS AT ALTITUDE



DR. MONGE: Dr. Landowne found a positive correlation between the evolution of headaches and PCO_2. I find this very interesting because I was expecting a negative one.

DR. LANDOWNE: I too expected a negative correlation. In Barcroft's paper from the 1921-22 Peruvian studies on a small number of subjects, although they felt that pulmonary diffusing capacity was related to symptoms, the CO_2 values fall in the same order. I think there are some unpublished observations from the group at Denver which also show a positive correlation.

DR. ROY: I would just like to show one slide to conclude – our philosophy of acute mountain sickness. This may look a little confusing but I think it is a very good appetizer for your lunch.



I would like to thank all the members of the panel who gave very lively and interesting deliberations. I also wish to thank the people who asked so many soul-searching questions, a number of which I know the panel members hedged, because precise answers were not known. But, as long as we appreciate and know our deficiencies there is always a bright future.

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PANEL

HIGH ALTITUDE PULMONARY EDEMA

Chairman: Maurice B. Visscher

BASIC FACTORS IN THE GENESIS OF PULMONARY EDEMA, AND A DIRECT STUDY OF THE EFFECTS OF HYPOXIA UPON EDEMOGENESIS

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It seems appropriate for this Panel to begin by a very short orientation in the basic pathophysiology of pulmonary edema. High altitude lung edema is obviously a special case of acute lung edema. The object of this meeting is really to ascertain what factors operate to precipitate this type of pathology.

Lung edema can be either interstitial or alveolar, or both, probably in sequence. The major factors controlling the net flux of water across capillary epithelia and the storage of water in interstitial spaces are well known. For a review see reference*. The pulmonary capillary blood pressure, the tissue pressure, the blood and tissue fluid colloid osmotic pressures, the state of permeability of the capillary-alveolar wall barriers, and the rate of lymphatic drainage are the critical factors in the case of lung edema.

Elevations in capillary blood pressure, depression of plasma protein osmotic pressure, or increases in permeability of wall barriers to plasma protein would obviously favor edemogenesis in the lung, as elsewhere. Obstruction to lymphatic drainage would also have a similar effect. These are the basic factors into which one should look for the causative mechanism for high altitude pulmonary edema. But one is interested in more than the identification of the direct causative factor or factors. One is perhaps even more interested in the mechanisms by which the immediate causative factor is made operative. For example, if the capillary blood pressure is elevated one must ask what in the high altitude situation has caused the elevation. Is there a sufficient increase in cardiac output to raise the pulmonary capillary pressure to values above the effective colloid osmotic pressure? Is there some

**Visscher, M. B. et al. The Physiology and Pharmacology of Pulmonary Edema. Pharmacological Reviews, 8: 389-434, 1956.*

decrease in cardiac work capacity at low oxygen tensions such that left atrial pressure rises, as would be predicted from the Starling law of the heart? In other words, is there some degree of heart failure? Or is there for some reason a pulmonary venoconstriction which alone or in combination with other changes, such as elevation in pulmonary flow, raises capillary pressure? Any one or a combination of these determinants might bring about acute pulmonary edema.

Another possible mechanism, namely an increase in membrane permeability to protein, requires analysis. If it occurs, to what might it be due? Low oxygen tension causing leaky membranes has long been considered a possibility, and I shall in a moment deal with direct observations on this problem. But are there other possibilities in the high altitude situation? Are such agents as histamine or serotonin liberated and do they influence capillary-alveolar wall permeability to protein?

Likewise if there is evidence of obstruction to interstitial fluid run-off in the lymphatics the most important question is how this might be brought about. Is the critical factor an increase in the net flux of water into the interstitial spaces from the capillary blood to levels which cannot be carried in available lymph channels?

These are questions which must be in the back of one's mind as one considers the problem of the pathogenesis of high altitude pulmonary edema. It seems very likely that this form of pathology may result from a combination of factors and not simply one, although one may perhaps be the major cause, as I believe will emerge from our discussions.

In any analysis of possible causes of a phenomenon it is helpful to eliminate, if it can be done, one or more of the theoretically possible causes. In order to attempt to do this I should like to present some data from studies of several of my recent graduate students and myself on the possible role of hypoxia in altering the permeability of the capillary-alveolar wall barriers to protein and the production of lung edema. Dr. Boyd Goetzman, Dr. Robert Goodale and Dr. Demetre Nicoloff have made these studies with my help which was mainly advisory.

Our interest was to provide a critical test of the thesis made popular by the late Cecil K. Drinker, that low oxygen tension, by itself, increases capillary permeability to protein. Our studies were of two types. In one we employed a sensitive method for continuous weighing of a lung undergoing perfusion and ventilation at various oxygen tensions. In the other type we measured by following a radioactive tracer the flux of albumin across the lung capillary-alveolar barriers while perfusing the lung vessels with

blood and "ventilating" the alveoli with suitable isotonic solution, all at several oxygen levels.

In our lung weight studies we established a perfusion rate which gave a slight progressive weight gain at normal oxygen tensions and then lowered the oxygen tension by ventilating with 95% N_2 and perfusing with blood or other fluid which was being deoxygenated in a gas exchanger. The result found was that substituting nitrogen for oxygen in the ventilating and in the blood gas equilibrating system did not in any case increase the rate of edema formation.

Furthermore when experiments were performed in which the critical perfusion pressure for induction of edema at high and low oxygen tensions were determined it was found that the average critical pressure for edemogenesis was higher at low than at high oxygen tension. In other words no support for the Drinker thesis was elicited in these studies.

However it was found that the critical pressure for edemogenesis was much lowered by metabolic poisons, of which sodium iodoacetate was one.

In the most critical type of experiment, namely studies of iodine (I^{131}) labelled albumin flux across the capillary-alveolar barrier it was found that changes in oxygen tension from a few mm. Hg to nine tenths of an atmosphere had no measurable effect upon the flux rates in either direction across those barriers. These results appear to prove beyond doubt that hypoxia per se of the degree involved is not a factor in high altitude pulmonary edema. The Drinker theory is undoubtedly wrong. His observations can be explained in entirely different ways. Especially it may be noted that he studied intact animals, and although he made no relevant measurements, other students of animals in similar situations have always shown heart failure to occur. It is unfortunate that his deductions, so poorly established, were accepted in dozens of textbooks of physiology and medicine and appear there today.

It should be a warning to prestigious investigators to be more careful of their logic. *Post hoc ergo propter hoc* is a most common fallacy into which, however, no scientist should allow himself to fall. Drinker made a great point of some observations Landis had made on capillary permeability in the frog mesentery. It is worth noting that the circumstances under which Landis found an undoubted effect of oxygen tension upon permeability of capillaries to protein were achieved only by boiling perfusion fluids to lower the solubility of gases, achieving virtually zero oxygen tension. No organism could survive at such oxygen tensions. At higher oxygen levels Landis found no effect of changes in O_2 tension upon capillary wall permeability to protein.

PULMONARY CIRCULATION AND PULMONARY EDEMA*

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The clinical study of pulmonary edema is difficult because it is a serious disease demanding us to "do something". Thus, as I read the available literature, I find that the clinical, radiologic and pathologic studies in high altitude edema occur quite late. In my limited experience, by the time pulmonary edema gives clinically apparent signs and symptoms it is rather far advanced. To resolve the pathophysiology of edema requires sequential studies of people before and after going to high altitude in order to detect those who develop acute edema before they are aware of it.

I. Acute Pulmonary Edema.

We began our study of acute edema to determine whether different forms of edema show different patterns of fluid accumulation (11). In anesthetized dogs we made two forms of edema: standard *high capillary pressure* edema after rapid fluid infusions and vasoconstrictor drugs, and *permeability* edema by rapid intravenous injection of the agent alloxan. Table I shows the many differences between these two forms of edema. Figure 1 shows in greater detail an important feature. The pulmonary capillary blood volume (Vc) is not increased in permeability edema indicating no significant change in pulmonary vascular pressures, particularly venous pressure. High pressure edema, however, shows a marked rise in Vc and the increase correlates well with the increase in pulmonary vascular pressure. This easy clinical measurement (much easier than cardiac catheterization) could be made daily on a large group of people going to high altitude and could settle the

*Much of the research reported here was supported by USPHS Grant HE-06285 and has been published in full elsewhere.

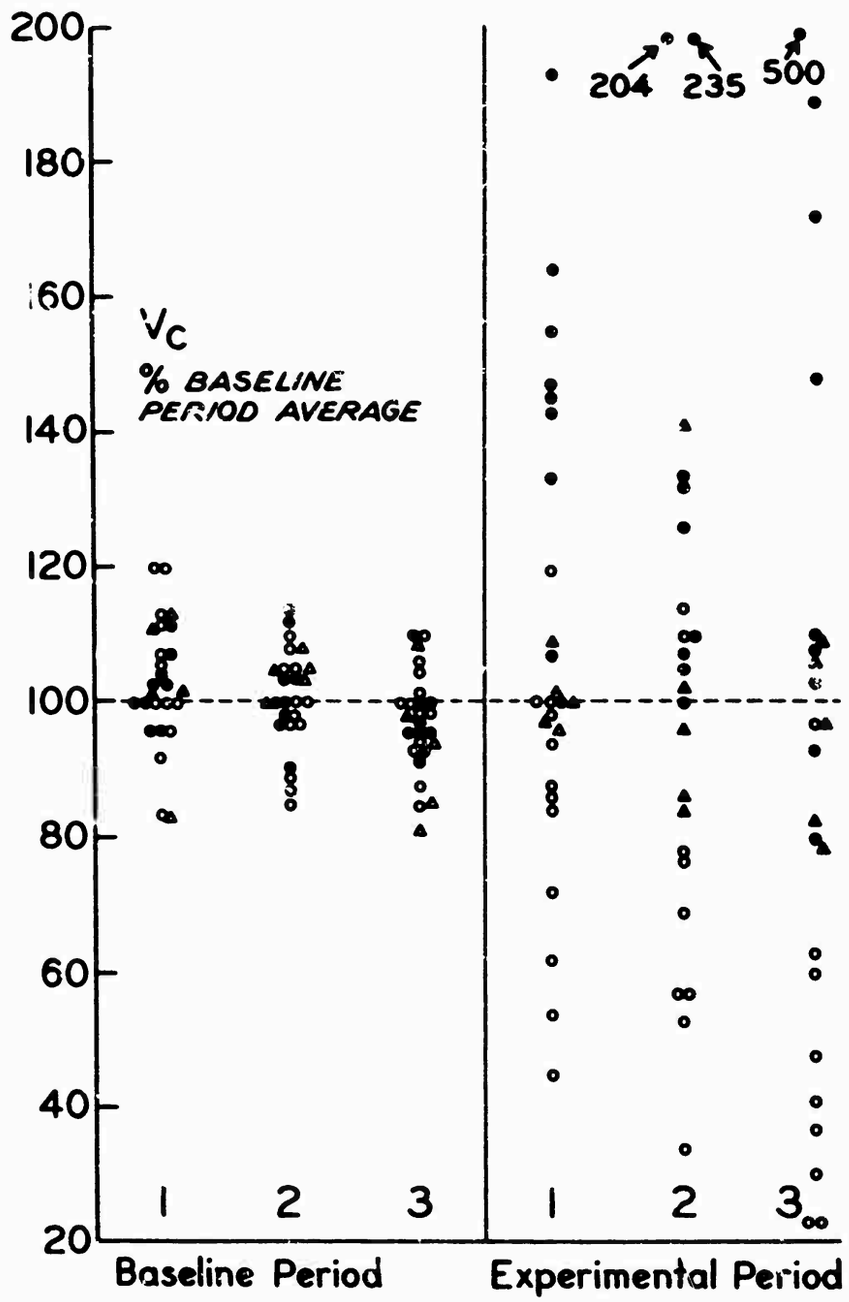

Figure 1. The time-course of pulmonary capillary blood volume changes (Vc%) in control dogs (△), high capillary pressure edema (●) and increased capillary permeability edema (○). The central vertical line separates a baseline control period and an experimental period in each dog. Each period is about 45 minutes. Vc was measured every 15 min. (1, 2, 3 and A, B, C). Five control dogs show no significant changes; nine high capillary pressure dogs show rapid, persistent increase in Vc; twelve dogs with increased permeability show no change or a decrease in Vc. (From reference 11. Reproduced by permission of Journal of Applied Physiology).

Table I. Differences between elevated hydrostatic pressure edema and alloxan edema

High Pressure	Alloxan
Pulmonary capillary pressure above 20-25 mmHg	Pulmonary capillary pressure below edomogenic level (even if $\overline{P}_{pa}=P_{cap}$)
Pressure persistently elevated as edema develops	Pressure transiently elevated during first 2-5 min; edema develops 30-60 min later
Pulmonary capillary blood volume increased	Pulmonary capillary blood volume decreased
Cardiac output usually increased	Cardiac output not much altered after initial transient phase
Central blood volume increased	Central blood volume decreased
Edema formation progressive as long as pressure elevated	Edema formation often fulminant
Alveolar capillaries throughout lung congested with red blood cells	Alveolar capillaries congested with red blood cells in lower zone; upper zone normal or anemic
Red cells in edema fluid; gross bleeding in severe edema	No red cells in edema fluid; no bleeding even in severest edema
Fluid-filled alveolar size decreased; moderately folded walls; occasional marginal atelectasis	Fluid-filled alveolar size decreased; slightly folded alveolar walls; no atelectasis

From reference 11. (Reproduced by permission of Journal of Applied Physiology)

problem as to whether significant capillary congestion occurs either normally or in relation to edema.

Returning to our original question, we were quite excited when we found that regardless of the initiating factor the edema fluid accumulated in a stereotyped fashion. The initial phase is fluid accumulation in the potential perivascular and peribronchial interstitial spaces (Fig. 2). These spaces are continuous with the alveolar wall interstitial space (7). The lymphatic capillaries are situated in them. They surround those vessels known to physiologists as *extra-alveolar vessels* which theoretically and by all available data have a subatmospheric pressure in them. Fluid leaking from very small vessels, presumably capillaries or venules shows up first here, not in the alveoli. The old ideas of Drinker (2) and Macklin (6) that fluid entered the alveoli first is no longer tenable.

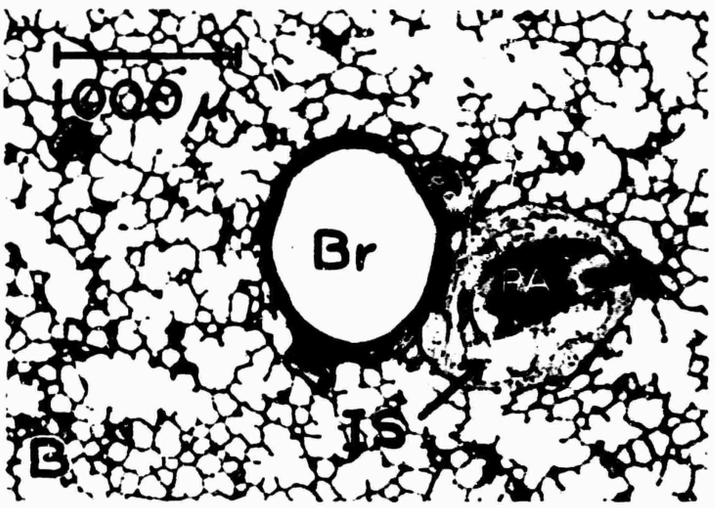

Figure 2. Frozen lung of dog, fixed, thin section. Early stage of acute pulmonary edema. Note the wide clear zone around the pulmonary artery. This is from the dependent part of the lung where the edema develops first. There is little or no alveolar fluid at this time. (From reference 11. Reproduced by permission of Journal of Applied Physiology).

These potential spaces have a large volume. Ideally, a volume of fluid equal to the pulmonary blood volume could be contained in them before alveolar fluid began to accumulate. Actually, because of the hydrostatic relations of the lung they are not all equally available for fluid so that is an overestimate. In this early phase there is no indication of any disturbance in the alveolar gas exchange areas. There are no blood-gas defects and clinically no rales can be heard. I am intrigued that there may be some relation between the interstitial fluid and the symptom of cough so frequently reported early in pulmonary edema. On x-ray the shadows should be those of enlarged vascular markings especially at the hilum where the fluid spaces are largest. Evidence of edema in connective tissue septa would also be seen.

Up to this point, we believe it is the negative hydrostatic pressure in the tissue spaces and alveolar wall junctional network that keeps the alveoli dry (9). But if the rate of lymph drainage cannot keep up with the rate of leakage the tissue spaces must saturate; the tissue pressure rises and overflow into the alveoli occurs. I suspect from the literature that high altitude edema develops fairly slowly and that many subjects never proceed beyond the perivascular phase. If we could measure the pulmonary extravascular water volume in newly arrived subjects at high altitude, a significant increase probably would be seen in many of them. I suggest that many people have high altitude edema but it never fills alveoli, so we don't suspect it.

Figure 3. Frozen dog lung, fixed, thin section. Early stage of alveolar filling. Some alveoli normal; others completely fluid-filled.

The onset of alveolar filling begins when the tissue spaces cannot hold any more fluid. The process of alveolar filling is interesting because it occurs individually in a single alveolus or small groups of alveoli (Fig. 3). It is a type of all-or-nothing effect, that is, once an alveolus starts to fill it proceeds rapidly to completion. Alveolar filling proceeds in an orderly manner as long as the animal does not hyperventilate (Fig. 4). I am told that humans hyperventilate even with minimal edema and, of course, they are already hyperventilating due to the hypoxic drive at high altitude. This is bad because the mixing of air with fluid makes very stable bubbles. In our experience, quietly-breathing, morphine-chloralose-anesthetized dogs do not have rales even with considerable alveolar edema. Terminally, it is the obstruction of airways even to normal parts of the lung by bubbles that makes gas exchange so difficult.

To summarize thus far, the sequence of fluid accumulation in the lungs appears to be the same in the two major classes of edema. The pathology reported in high altitude edema is consistent with this pattern. The finding of blood in high altitude edema fluid suggests high pressure leakage, but we have no evidence that the pulmonary capillaries are congested or that capillary mean pressure is elevated in life.

II. Fluid Movement from alveolar capillaries to lymphatics

Let us examine the following question. How does the fluid leaking from alveolar wall capillaries get into the perivascular spaces and lympahtics without being detected first in the alveoli?

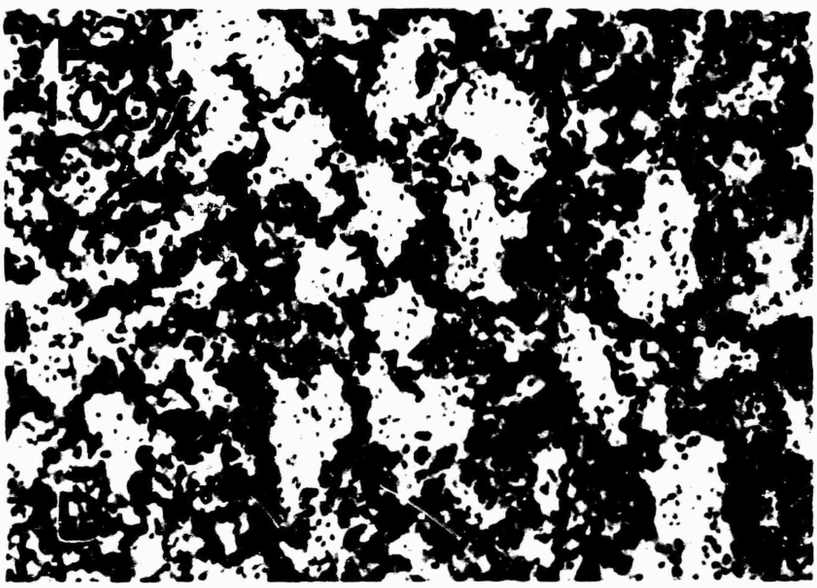

Figure 4. Frozen dog lung, fixed, thin section. All alveoli in this area are fluid-filled. No foaming or air bubbles are found unless there is hyperventilation or forced ventilation of the fluid-filled units. (From reference 11. Reproduced by permission of Journal of Applied Physiology).

Figure 5: see page 101.

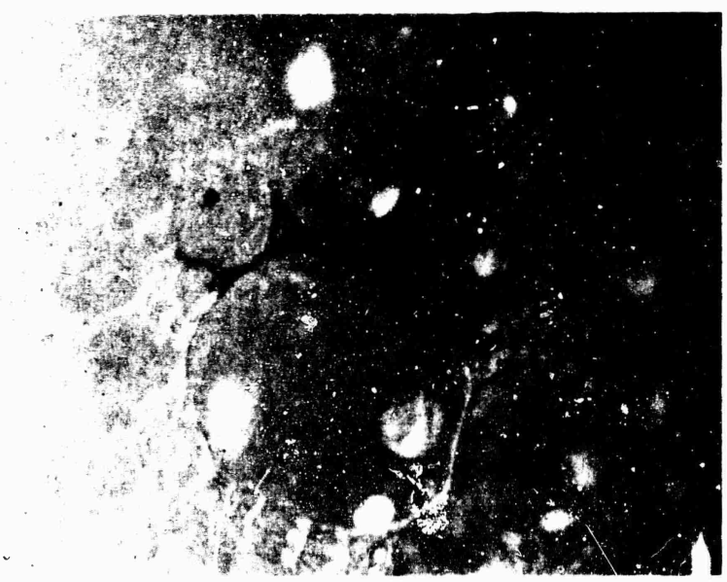

Figure 6. Injection of soap solution dyed with toluidine blue through a micropippette into a soap foam.

All the classical authorities believed that edema fluid leaks into the alveoli and flows over the alveolar walls in a blanket to the region of the respiratory bronchiole where it was absorbed into the perivascular interstitial space and lymph caps (2,6,7). But if we look at the complexity of the terminal respiratory units we question the

likelihood of such an event (Fig. 5). The path from alveolar space to respiratory bronchiole can be very long by the route described.

Recently, I have found that the phenomenon known as Plateau's border is present in the lung and satisfactorily explains the the drainage of fluid from the pericapillary space to the perivascular lymphatics. Plateau's border is the event seen in drainage of foams (Fig. 6). Fluid added at the top of a foam does not remain there or fill the bubbles. Because of the surface tension at the air-liquid interface and the sharp curvature at the bubble junctions there is a *negative* hydrostatic pressure in the junctions. These are all connected together and provide a clear, short, preferential path for fluid drainage. In the lung the alveoli are the foam and the alveolar wall junctional network is Plateau's border. Using micropipettes I have injected small amounts of a wide variety of fluids into the subplural alveoli. The fluids, both iso- and hypertonic with respect to plasma, spread rapidly from the injection site in both living and excised lungs. None of the material appears in blood nor does blood flow have any effect on the result. The dye-stained fluid passes along the alveolar wall junctional network to the small pulmonary vessels, then along the outside of the vessels into the larger, interstitial perivascular spaces and ultimately into the lymph caps (8,10). For plasma or 0.9% NaCl stained with Trypan Blue the time course is approximately as follows: Initial alveolar clearance 1-5 minutes (Fig. 7); appearance in lymphatics and perivascular spaces 15-30 min. (Fig. 8). The events occur in both static and ventilated lungs but theoretically should occur more rapidly at high lung volumes due to higher alveolar surface tension and lower perivascular hydrostatic pressures, both of which increase the pressure gradient favoring flow.

In summary, fluid leaking from alveolar capillaries moves preferentially in the alveolar wall interstitial space via the alveolar wall junctional network to the lymphatic capillaries in the perivascular interstitial spaces.

III. Site of hypoxic pulmonary vasoconstriction.

Recently, Dr. Mikio Kato (5) working in our laboratory showed conclusively that acute alveolar hypoxia with or without hypercapnea causes active constriction of the small pulmonary arteries leading into the terminal respiratory units (Fig. 9). The effect is believed due to the close relation and thus the influence of alveolar gases on PO_2 and PCO_2 within the walls of the small arteries. What Dr. Kato did not report and what we are currently developing is a method to directly measure the pulmonary capillary blood volume, Vc. From our data in dogs (Section I) we know

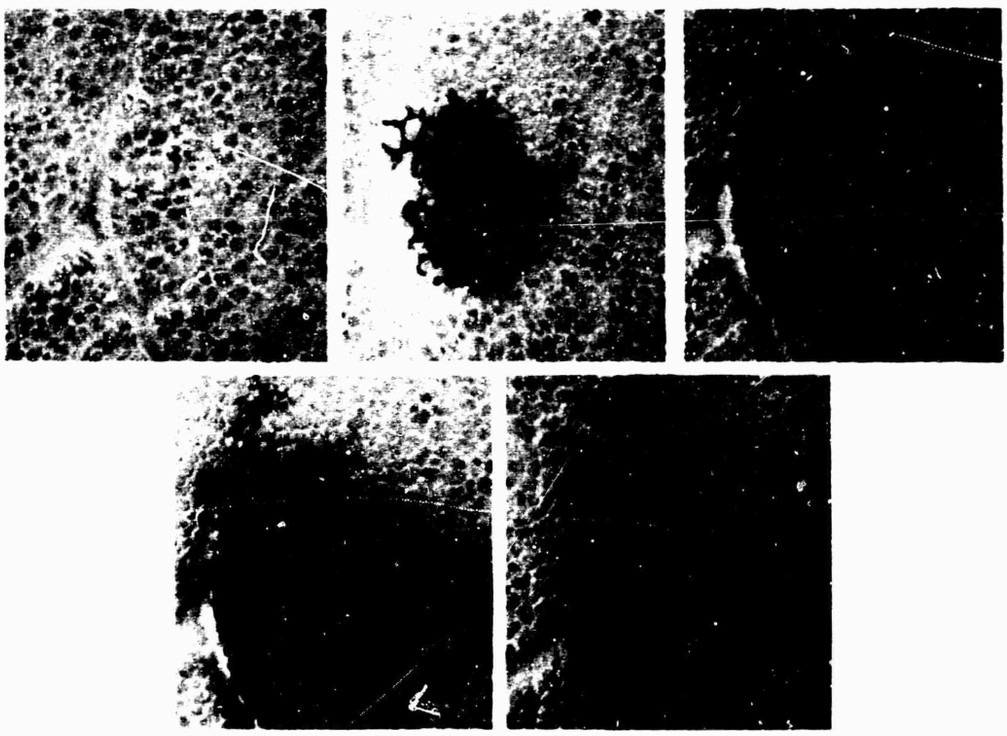

Figure 7. Isolated, air-filled cat lung lobe. Sequential photos of injection of 2 microliters of cat plasma stained with trypan blue. Upper row: left, just before injection; center, 5 sec after injection begun; right, 15 sec. Lower row: left, 30 sec; right, 120 sec. Note initial alveolar filling has almost completely cleared by 120 sec. At 5 sec there is already lateral spread of dye along the subpleural alveolar wall junctions. The small pleural vessel running vertically slightly to the left of center seems to act as a barrier to further spread in that direction.

that Vc will increase if pulmonary vascular pressure rises, particularly pulmonary venous pressure. Our new evidence, in the same animals that Kato measured, suggests that hypoxia without hypercapnea (such as occurs at high altitude) does not affect Vc significantly. Therefore hypoxic pulmonary vasoconstriction in the cat, at least, appears to be entirely due to arteriolar vasoconstriction. Edema due to elevated capillary pressure is unlikely. West's data on diffusing capacity at high altitude (12), although somewhat limited by the necessity of using simplified methods, lends support to a similar event in man, that is, no significant postcapillary vasoconstriction and no capillary congestion due to hypoxia. Postmortem reports of severe pulmonary capillary congestion in high altitude edema can, I think, be discounted as showing the end stage effect of severe asphyxial death. Such results were reported over 2,000 years ago by the Greeks in their studies on strangled animals (14).

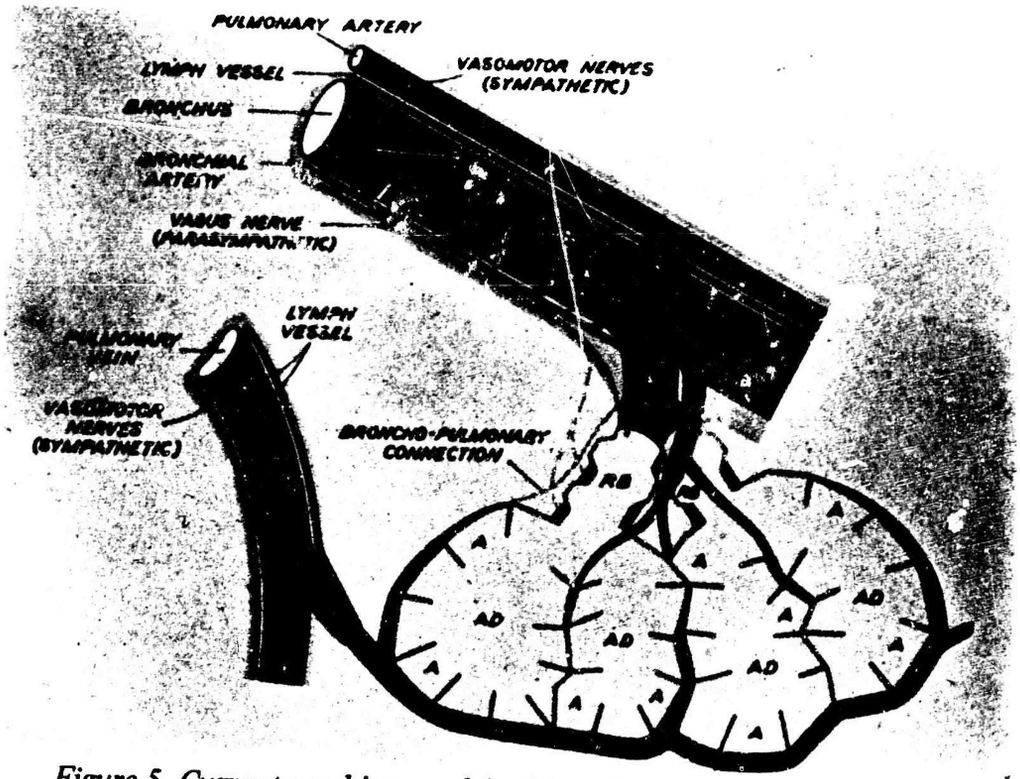

Figure 5. Current working model of lung in a realistic morphologic arrangement. The potential perivascular fluid spaces contain the lymphatic vessels. They do not extend to the alveolar walls. Note the long path that a fluid blanket flowing over the alveolar surfaces would have to take to reach the respiratory bronchioles and be absorbed into the lymphatics. TB (terminal bronchiole); RB (respiratory bronchiole); AD (alveolar duct); A (alveoli). (From reference 9. Reproduced by permission of Japanese Heart Journal).

Figure 8. Lung lobe from open thorax, anesthetized cat; 500 μ thick, frozen-dried, cleared sections. Three injections into one lobe of 1-2 microliters of 0.9% NaCl stained with alphazurine. Left, 2½ min. after injection; center, 17½ min. after; right 32½ min. after. Early phase shows only local alveolar clearance. At 17½ min. there is complete alveolar clearance and perivascular spread away from the injection site. At 32½ min. original injection site is pale. There is a large stained perivascular and peribronchiolar space.

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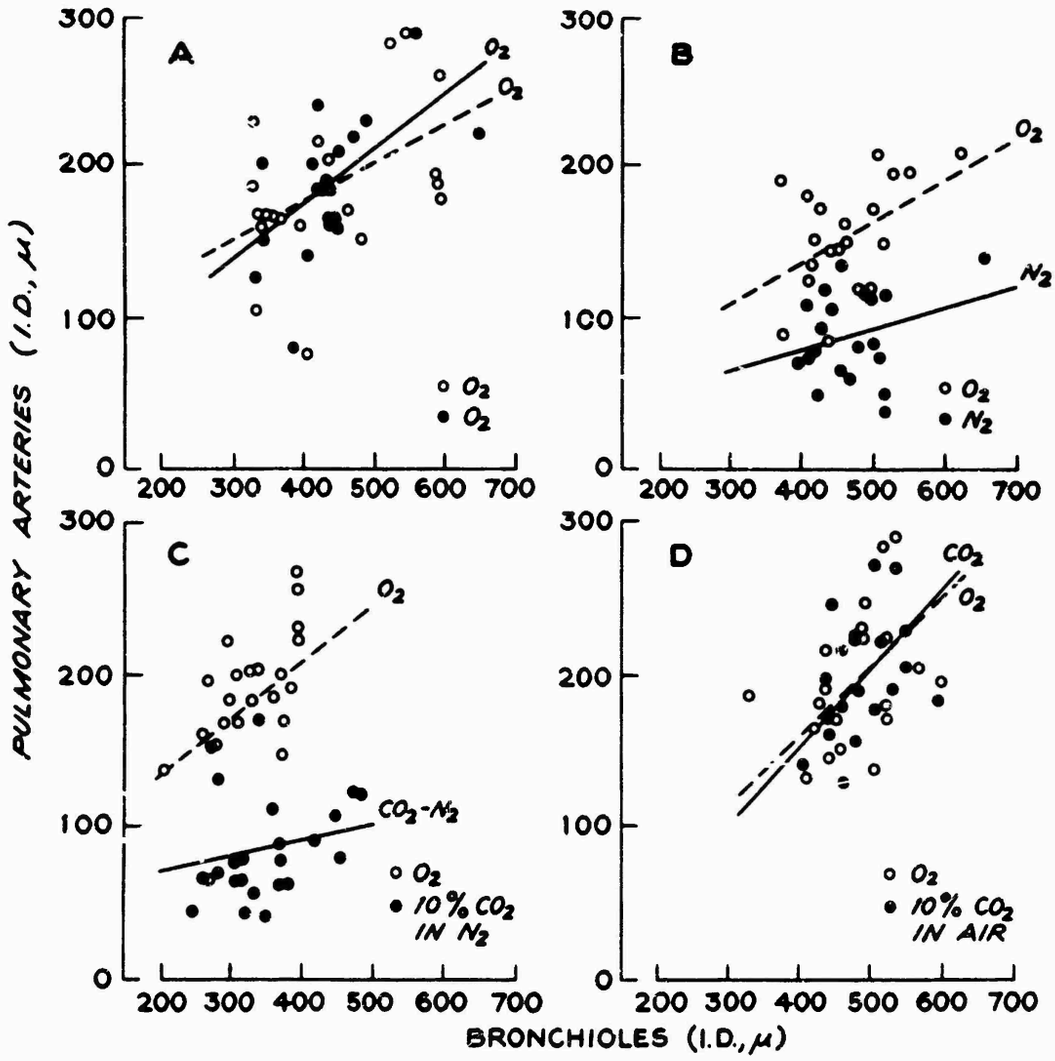

Figure 9. Representative scattergrams of small pulmonary artery diameter versus bronchiolar diameter in paired lobes in open thorax, anesthetized cats in which one lower lobe is ventilated with O_2 as a control and the other lower lobe is ventilated with (A) O_2, (B) 100% N_2, (C) 90% N_2 and 10% CO_2, (D) Air and 10% CO_2. There is active constriction of the small muscular pulmonary arteries in hypoxia with or without hypercapnia. (From reference 5. Reprinted by permission of Circulation Research).

IV. Hypothesis of Whayne and Severinghaus to Explain High Altitude Edema.

Intrigued by the above discoveries of the continuity of alveolar wall junctional space and the perivascular space and the precapillary site of vasoconstriction, Severinghaus suggested that high altitude edema might be explained if the thin-walled pulmonary arteries could leak at high transmural pressures into the peri-

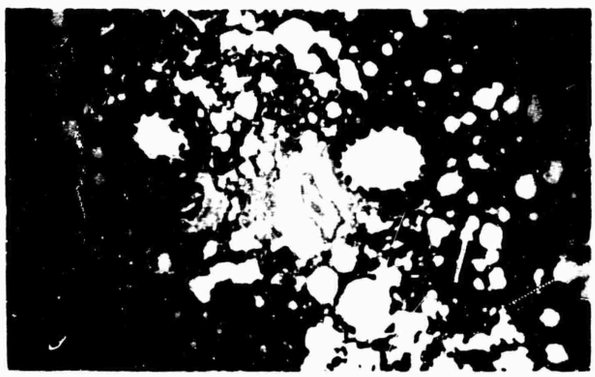

Figure 10. Routine, formalin-fixed, rat lung thin section. Animal breathed 8% O_2 in nitrogen and swam vigorously for 10 min. before being killed. Section shows extensive perivascular and slight peribronchiolar edema (arrows). There is also moderate patchy alveolar edema.

vascular space and by retrograde flow to the alveoli. Dr. Thomas Whayne attempted to test this possibility recently (13).

In rats made to swim vigorously while breathing low inspired oxygen mixtures a characteristic perivascular edema developed after about 10 minutes (Fig. 10). This was not seen in controls (Fig. 11). The fluid is not aspirated as was proven by staining the swimming water. This appears to be a real model for high altitude edema and deserves further investigation. Dr. Whayne next embolized all the pulmonary arteries of anesthetized rats with latex microspheres, 12-35 μ diameter. He perfused the pulmonary artery with blood at 100mm Hg pressure. Due to the emboli no blood went through the lungs. After 10 min. the lungs were fixed. Histologically, they showed perivascular edema in 7 of 8 experiments (Fig. 12). This is suggestive evidence but better controls are needed before it is absolutely certain that the fluid is leaking directly out of arteries.

Figure 11. Routine, formalin-fixed, rat lung, thin section. Animal breathed 8% O_2 for 20 min. at rest. No perivascular or alveolar edema found.

Figure 12. Routine, formalin-fixed, rat lung. Lung embolized by latex microspheres as seen in grossly distended vessels at lower center and left. Pulmonary artery of excised lung perfused at 100 mm Hg with blood for 10 min. Perivascular and peribronchiolar edema seen (arrows).

V. Histamine and the Hypoxic Vasoconstrictor Mechanism

After years of frustration simultaneous evidence from our own laboratory and that of Barer in England strongly implicates the local release of histamine at the alveolar level as the mediator of acute hypoxic vasoconstriction (Fig. 13). Hauge (3) and Hauge and Staub (4) showed that in isolated, perfused rats lungs or in self-perfused lung lobes in anesthetized cats that inhibition of histamine in the lung by acute depletion with 48/80 or blockade of synthesis prevented the hypoxic vasoconstrictor response (Fig. 14). In Hauge's series no other agents had any significant effect on the hypoxic response. Aviado recently reported increased pulmonary venous histamine levels in hypoxia (1).

I bring the matter up here, partially to clarify the vasoconstrictor mechanism but mainly to suggest another possible mechanism for high altitude edema. The release of histamine may alter pulmonary capillary permeability. This might be due to excessive release in some sensitive individuals or to excessive storage in high altitude natives while sojourning at lower altitudes where the hypoxic release of histamine is not active. I think some inquiry into the effects of histamine release in the lung on capillary permeability is desirable.

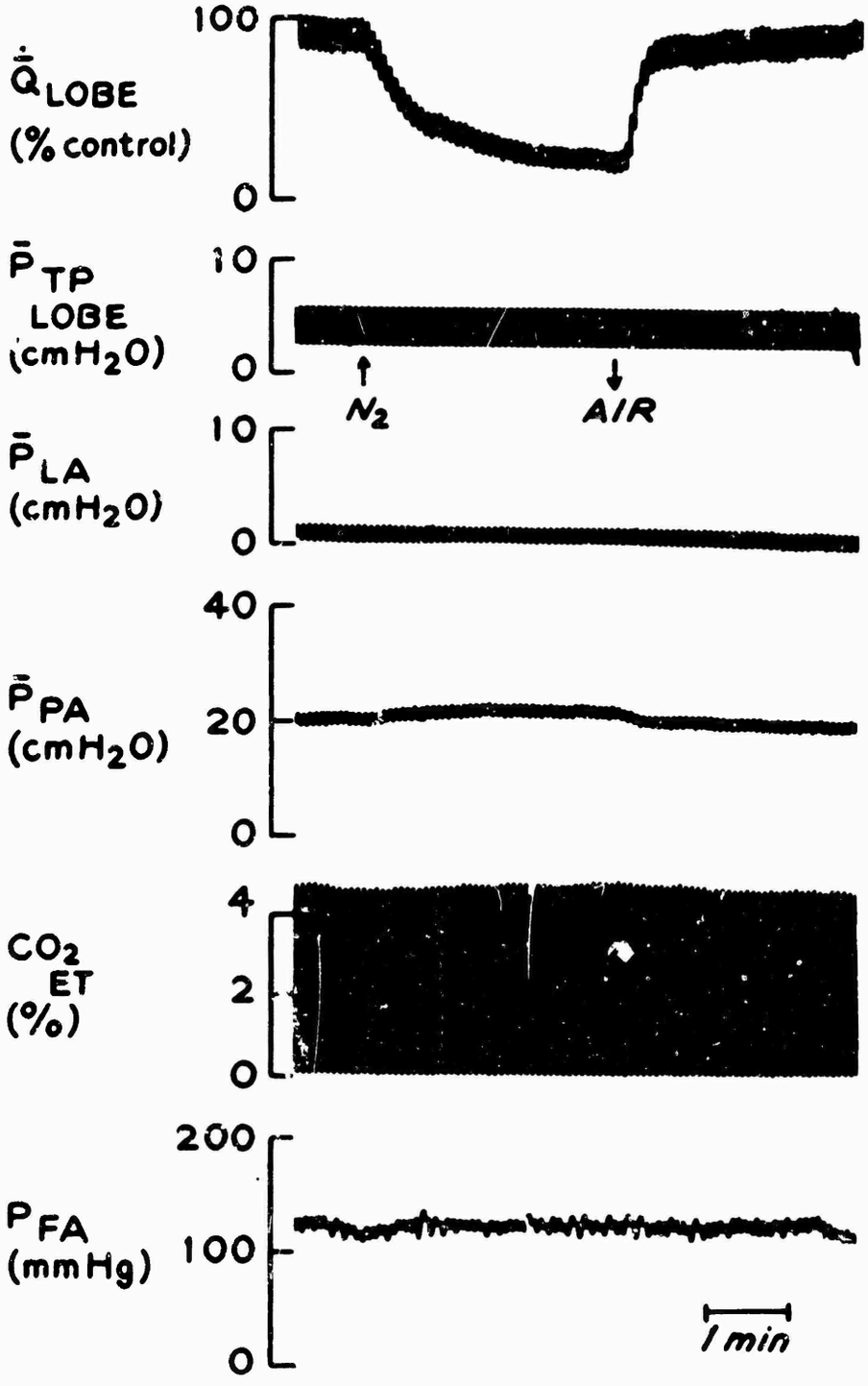

Figure 13. Open thorax, anesthetized cat. Left lower lobe ventilated separately from lung. Record shows relative lobar flow ($\bar{Q}$) via an electromagnetic flow probe on the lobar pulmonary artery, translobar air pressure ($\bar{P}_{TP}$), mean left atrial pressure ($\bar{P}_{LA}$), mean pulmonary artery pressure ($\bar{P}_{PA}$), end-tidal CO_2 from lung (CO_{2ET}) and mean femoral artery pressure (P_{FA}). Lobe flow decreases during 3 min. period of 100% N_2 ventilation while rest of lung breathed O_2.

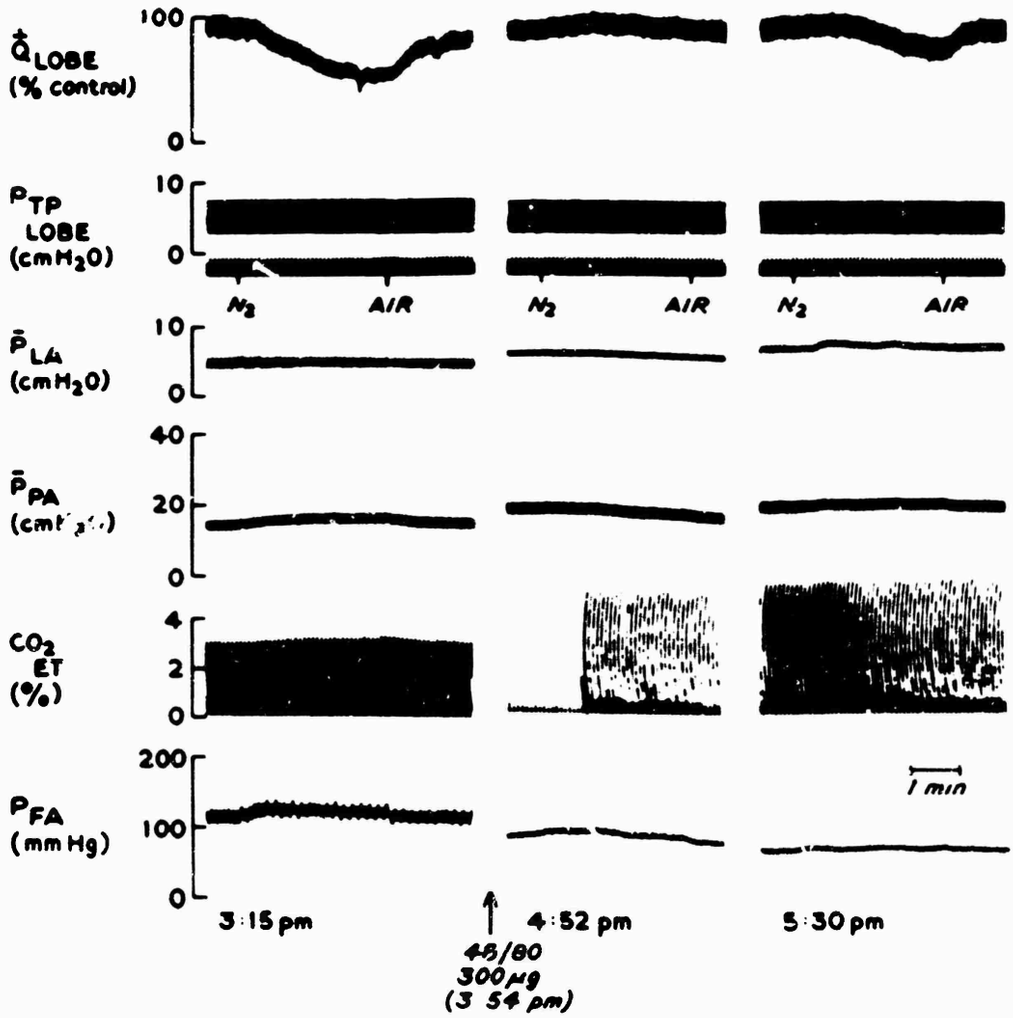

Figure 14. Open thorax, anesthetized cat. Records as in Figure 13. Three panels showing effect of acute histamine depletion. Left: active hypoxic vasoconstriction in lobe just before 48/80. Center: complete blockade of hypoxic vasoconstrictor effect 30 minutes after 48/80. Right: partial recovery of hypoxic vasoconstrictor effect after 1¾ hours.

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HIGH ALTITUDE PULMONARY EDEMA: CLINICAL , HEMODYNAMIC, AND PATHOLOGIC STUDIES

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Since our commitments in the Himalayan region in 1962, our men commonly occupy altitudes between 11,000 feet and 18,000 feet. The incidence of high altitude pulmonary edema (HAPE) in large groups of men arriving at these altitudes without acclimatization or induced diuresis varies from 23 to 155 per thousand. Our clinical experiences in the first 332 cases of HAPE have already been reported (1). Herein we outline our observations made on 562 patients with HAPE.

Predisposing Causes

Probably no age is exempt. Many of the patients previously recorded were children and young adults, and the oldest patient was 42 years of age. The Indian subjects were men between 18 and 53 years of age.

The vulnerable altitude varies from country to country and apparently depends on the snow line. It is about 8,000 feet in the Continental United States, 11,000 feet in the Himalayas and 12,000 feet in the Peruvian Andes. Details of our incidence in relation to the height are shown in Figure 1.

Rapidity of arrival from a lower to a higher altitude predisposes an individual to high altitude pulmonary edema. It is not unusual to see pulmonary edema develop in an individual who has travelled by air. A slower journey, but one associated with physical exertion, may do likewise. Physical exertion, exposure to cold, and anxiety appear to be important contributing causes.

There is a definite time lag, which varies from 6 to 96 hours, between arrival at high altitude and onset of the illness. An individual's chances of developing pulmonary edema diminish

rapidly after the fourth day of his arrival at high altitude and become remote after the tenth day (Fig. 2). Re-entrants are prone to develop it earlier than others (Fig. 3). During the time lag, antidiuresis invariably precedes high altitude pulmonary edema in both fresh inductees and re-entrants. Anti-diuresis is usually more pronounced in the former. As shown here in the second group, the incidence was much less in the fresh entrants for two possible reasons (1) they followed the inductee regulations more faithfully and (2) re-entrants probably had a higher pulmonary blood volume.

Clinical Features (Figs. 4 and 5)

Characteristically, high altitude pulmonary edema begins with progressive cough and dyspnea. Cyanosis appears on the face and extremities, and rales are heard in the chest. There is no symmetry about the rales. They first appear on one or both sides in the interscapular area and spread to the upper zones. Both pulse and respiratory rates are increased. Tacchycardia, however, is comparatively milder than dyspnea. In the early stages the lung bases are usually spared. In fulminating cases, the patient feels choked,

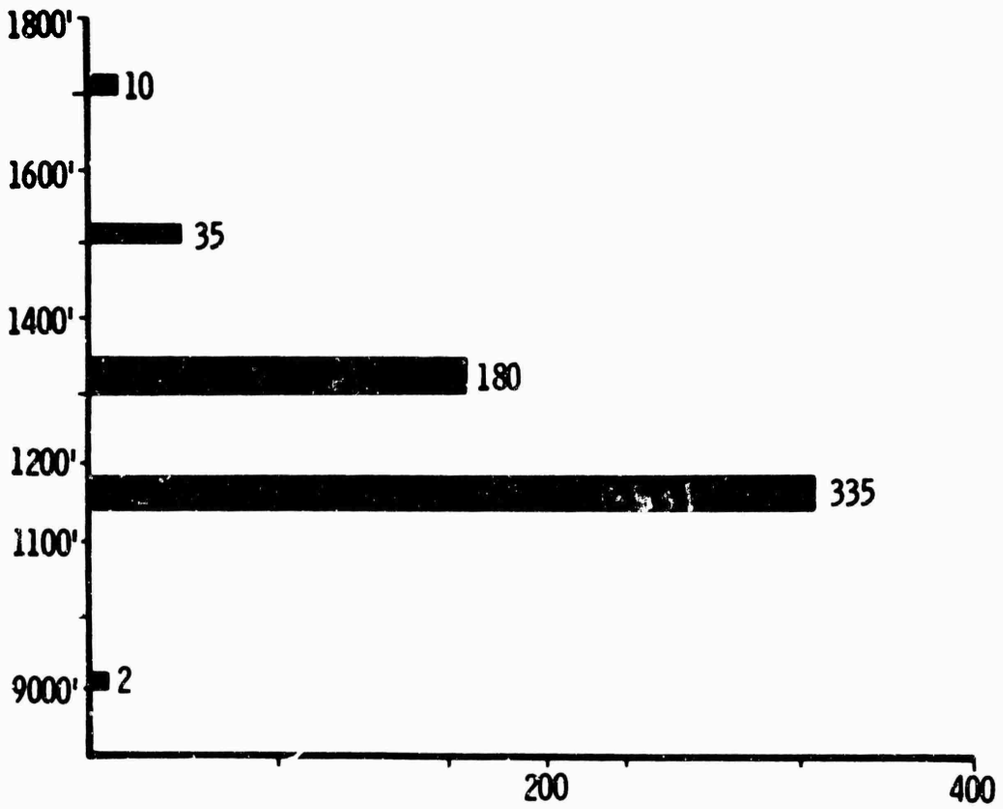

Figure 1. Relating the incidence of HAPE to the height of the altitude more than 90 per cent of the altitude edema occurred between 11,500 and 13,000 feet.

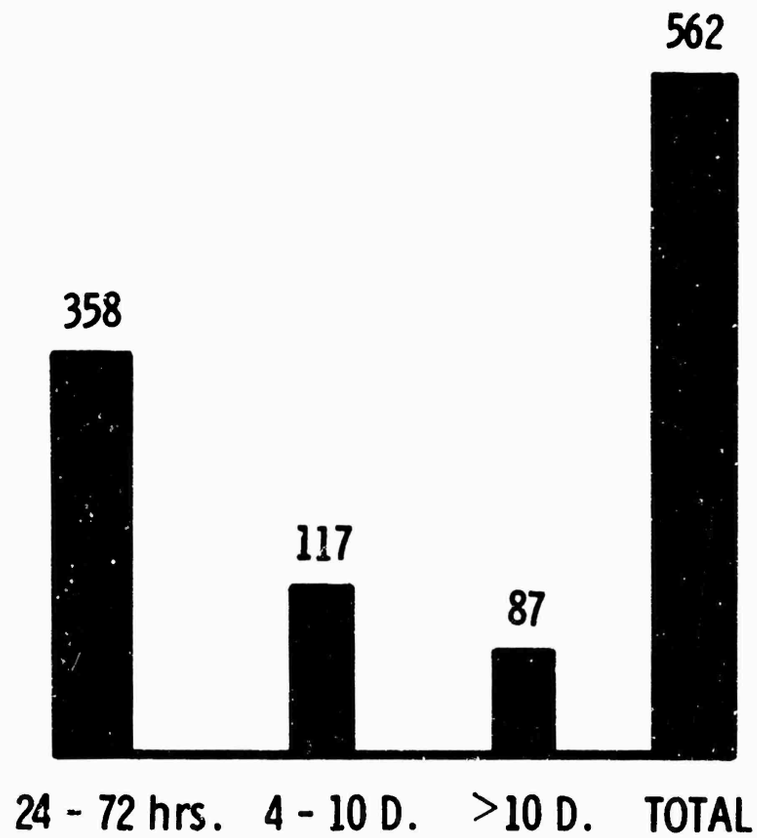

Figure 2. Highlighting the time relationship between arrival at high altitude and onset of the disease, 63 per cent of the cases occurred within the first 72 hours, and only 15 per cent after 10 days

becomes moribund, and hemorrhagic pleural effusions may occur on one or both sides before death.

As eight out of 10 subjects of HAPE are afflicted by acute mountain sickness, the onset in some of them may be less spectacular. The increasing malaise, dyspnea, or a dry cough may be the only indications of impending pulmonary edema. In some cases, premonitary malaise, weakness, cramps in the calf muscles, headache, insomnia, anxiety, and excitement are followed by dyspnea and dry cough, with or without palpitation, before a full-fledged picture of pulmonary edema becomes manifest. Dyspnea at night, at rest, on slight exertion for 1 to 3 days during which the man continues to be active, may appear to be insignificant until pulmonary edema truly sets in.

Sometimes cerebral symptoms dominate the picture. Giddiness, hallucinations, and lack of interest in surroundings lead to unconsciousness and pulmonary manifestations within a day or two. Evidence of increased cerebrospinal fluid pressure, papilledema and vitreous haemorrhages may be found in such cases.

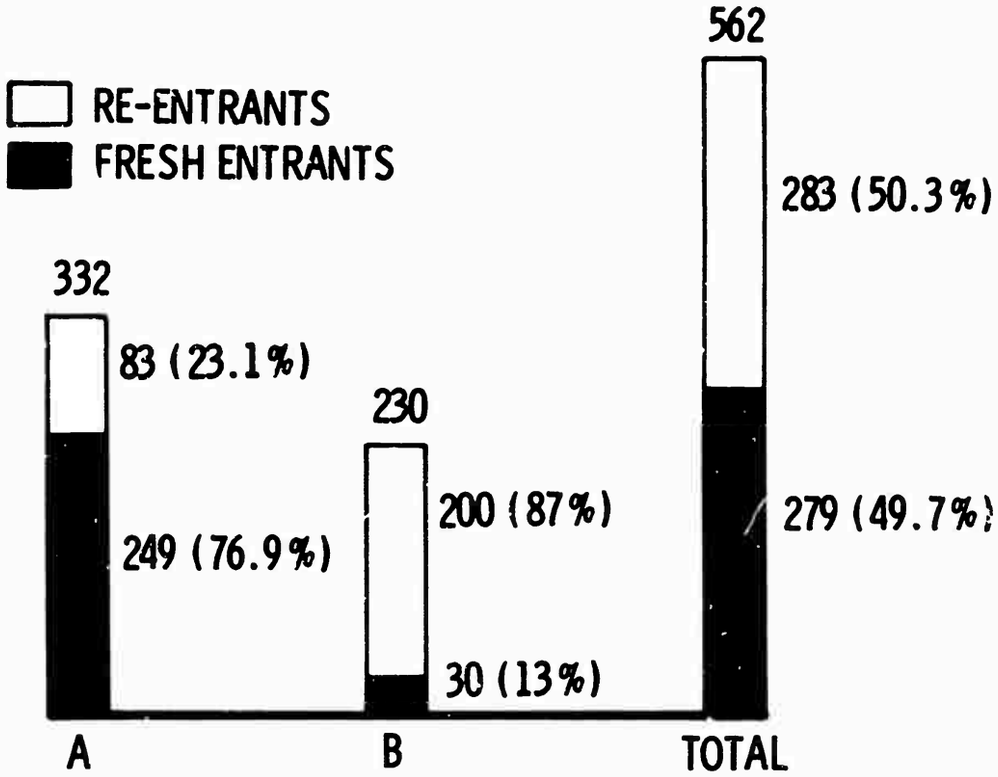

Figure 3. Outlining the differences in the incidence between the fresh and re-entrants shown in two groups – A of 332 cases (already reported) and B-230 later cases.

When the course is prolonged to 3 or 4 days or more, clinical evidence of right ventricular failure, such as distended neck veins, enlarged and tender liver, and peripheral edema may be found.

Early interscapular involvement and spread to the upper zones and absence of toxaemia distinguish pulmonary edema from infection of the lungs. High fever, marked leukocytosis, and elevated blood sedimentation rate are usually absent.

CHEST X-RAY FILMS show pulmonary densities, usually first confined to the middle and upper zones, more predominant on the right than on the left side (Fig. 6). Sometimes may involve midzone of one side and lower zone of the other – patchy distribution (Fig. 7). When of slow onset, interlobar septal lines, indicative of interstitial edema, may be seen (Fig. 8). In severe cases, especially when prolonged over 2 or 3 days, all zones may be involved, and there may be pleural effusion on one or both sides. In addition, there is fullness of the hilar blood vessels, and the pulmonary artery is often, and sometimes grossly, enlarged. The rest of the configuration of the heart is not changed, unless there is associated right ventricular failure, and in which case it becomes globular. On evacuation of the patient to sea level or upon ade-

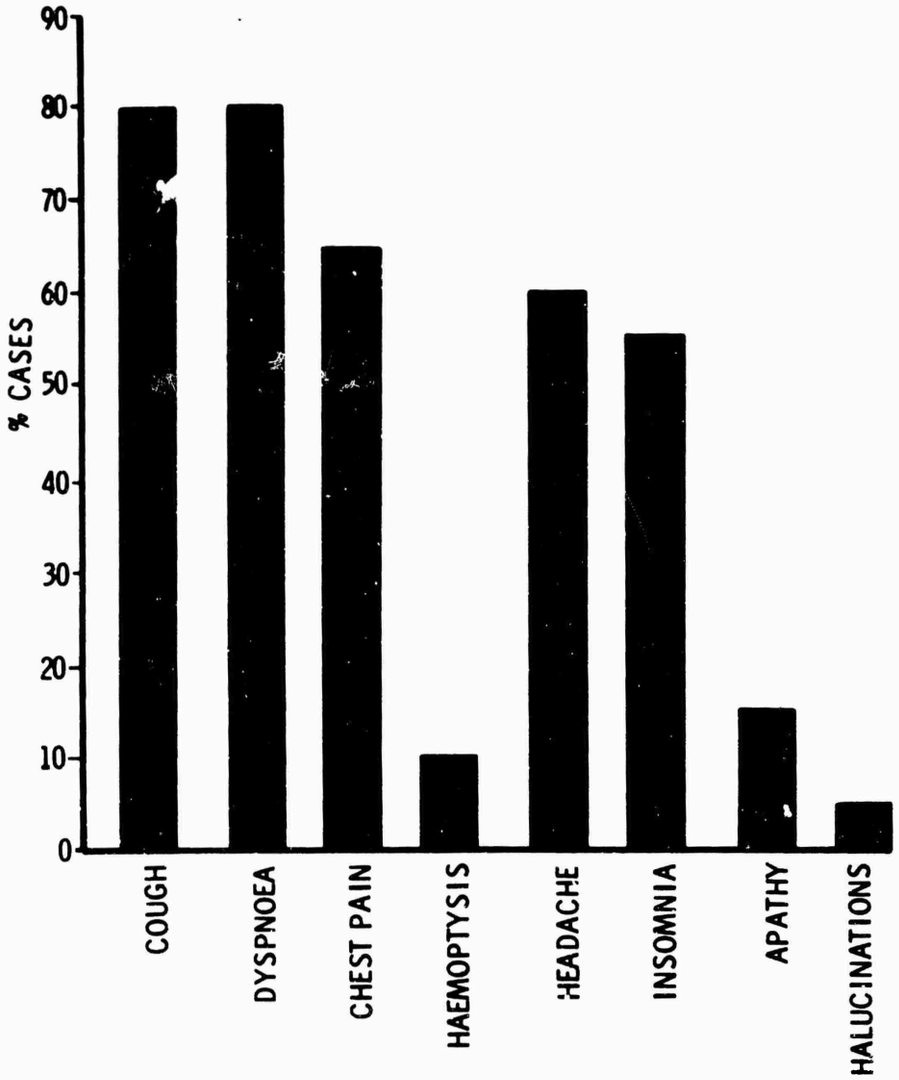

Figure 4. Depicting major symptoms in 562 cases of HAPE. It is to be noted that cough, dyspnea and chest pain were the 3 main complaints.

quate treatment, the pulmonary densities disappear in 6 to 48 hours (Fig. 9).

The electrocardiograms show evidence of right axis deviation, clockwise rotation, sharp T inversion in leads V1-V5/V7, prominent R in leads aVR, V1, and V3R/V4R, and peaked P in severe cases. One or more of these changes may be present in milder cases. Evidence of myocardial ischaemia without injury may be present in limb leads. These changes probably reflect some degree of pulmonary arterial hypertension, concomittantly present with pulmonary edema. As the inverted T waves revert, they sometimes become abnormally high in most of the V leads and remain so for some time before becoming normal.

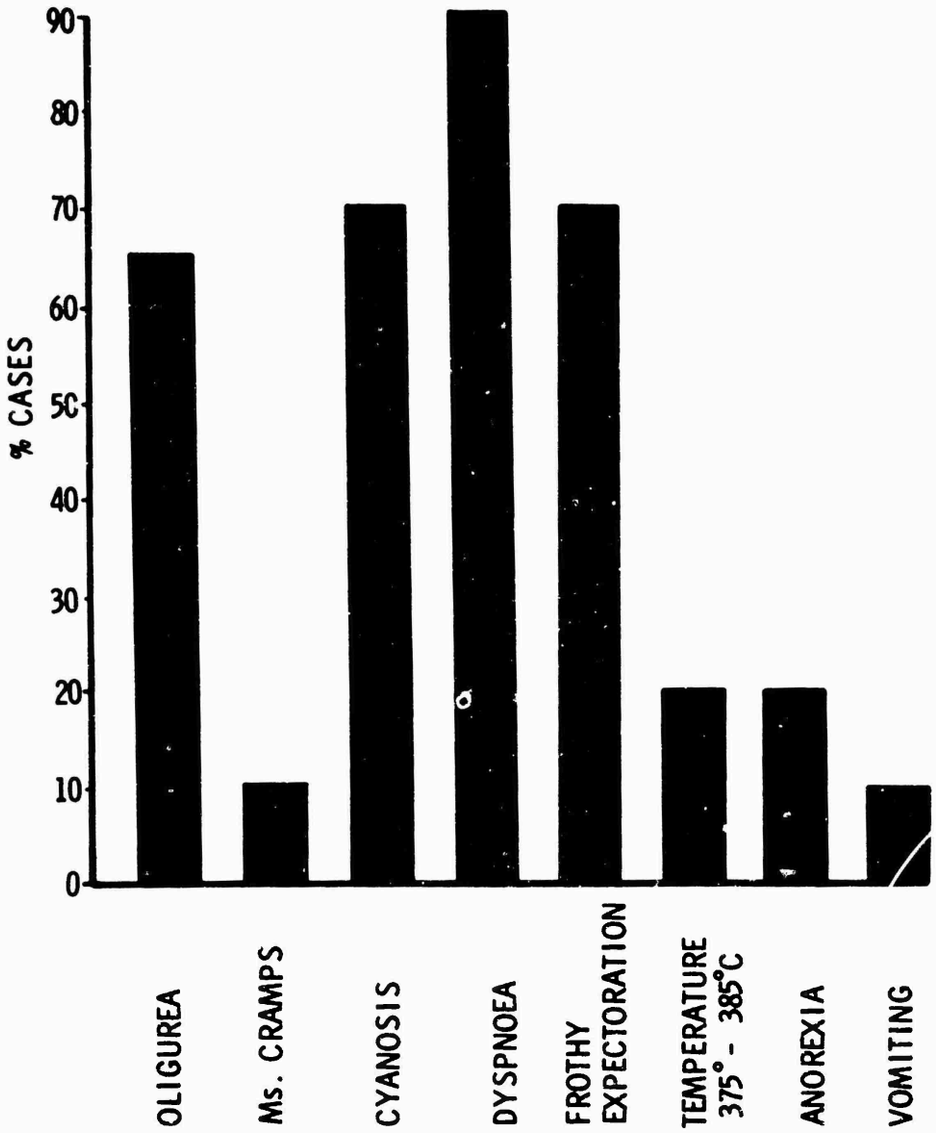

Figure 5. Major signs with cyanosis, frothy expectoration and labored breathing were the predominant features.

Hemodynamic Studies (Table 1)

Six subjects with high altitude pulmonary edema were studied within 24 hours of the onset of the illness at an altitude of 12,000 feet. The clinical histories of TB, PB and RB were identical in that they reached a high altitude post of 14,000 feet in June 1967, and were satisfactorily acclimatized on 24 August 1967. They had to move to 17,000 feet, and following exertion (digging trenches) developed pulmonary edema on 26 August. Patient Y. G. entered high altitude area (12,000 feet), rapidly ascended to 15,000 feet, exerted to precipitate the illness. P. S. is a native of Tibet, who was born and brought up at 14 to 16,000 feet. He came to India in

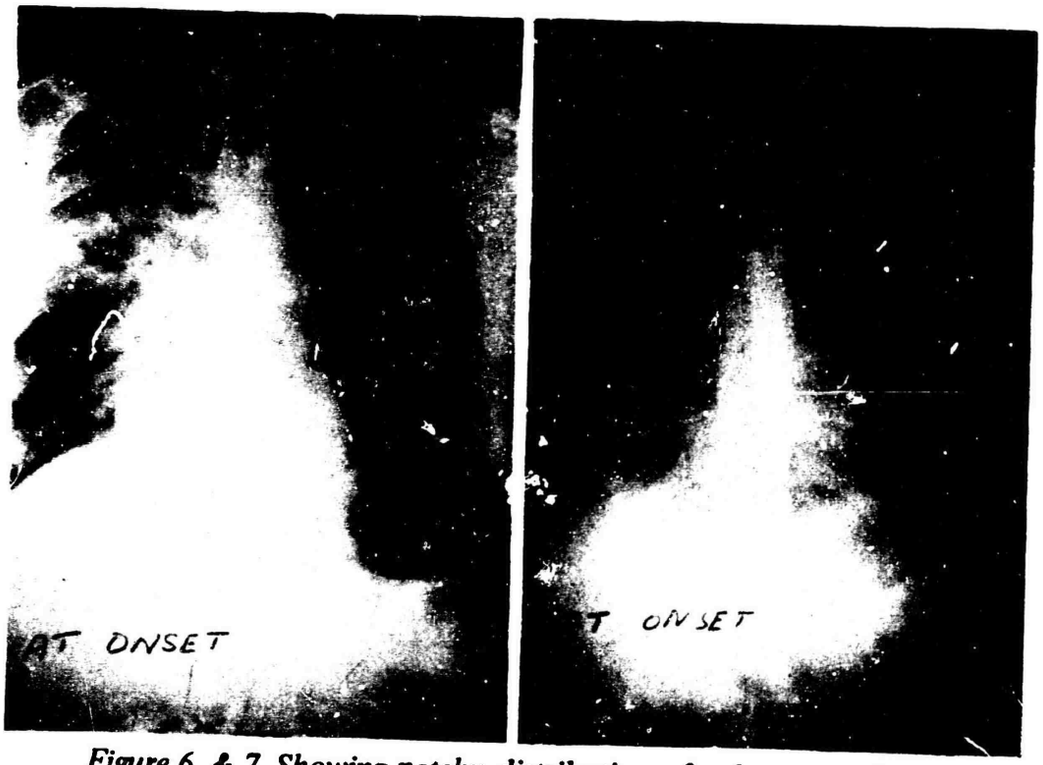

Figure 6. & 7. Showing patchy distribution of pulmonary edema. The X-ray on the left (Fig. 6) involves the right middle and upper lobes, whereas the X-ray on the right (Fig. 7) involves right base and left mid zone.

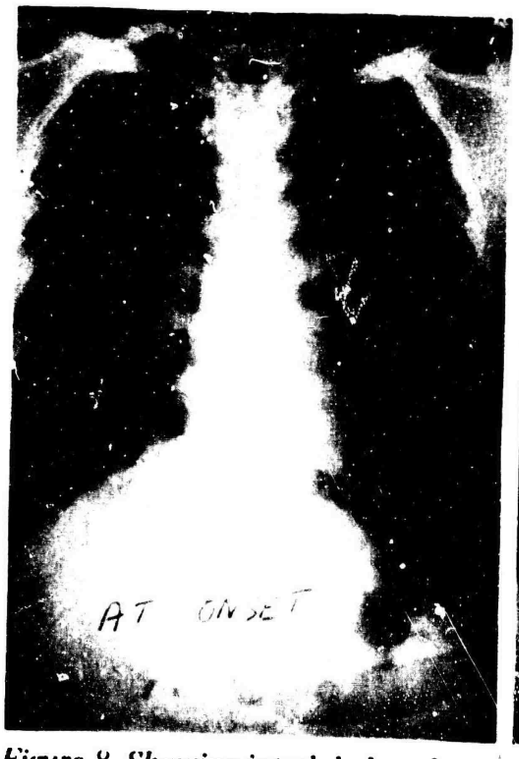

Figure 8. Showing interlobular edema.

Figure 9. 24 hours later X-rays as shown in Fig. 6 showing quick recovery.

TABLE 1. Physiologic studies in HAPE

Name	Age (yrs)	BSA m^2	Arterial blood			Heart Rate min.	RV s d ed	LA (mean)	FA s/d (m)	Cardiac Index L/min-/m^2	Blood Volume ml/m^2		
			pH	PCO_2	PO_2						Total	Central	Pulmonary
				mm Hg			mm Hg						
TB	22	1.60	7.46	24.0	52	125	50,0,5	1	120/76 (95)	2.4	3900	467	206
PB	23	1.72	7.45	29.0	42	75	54,0,3	5	128/70 (92)	4.5	4700	865	410
RB	38	1.80	7.49	26.0	40	75	34,0,5	4	130/70 (88)	3.2	3600	880	349
YJ	28	1.70	7.45	33.5	49	96	40,0,2	8	112/60 (75)	3.4	2500	648	176
PS	20	1.58	7.44	34.5	27	110	36,0,3	2	118/58 (78)	3.0	2900	440	155
CL	26	1.70	7.52	26.5	30	140	42,0,3	1	115/65 (80)	3.5	4200	518	224

s: systolic d: diastolic ed: end-diastolic m: mean

1965 where he was stationed at 6,900 feet. In May 1967, he was moved to 12,000 feet, when he developed acute pulmonary edema and was evacuated. He was reinducted to 12,000 feet on 17 August, when in 3 days he developed HAPE for the second time. C. L. is a plainsman who had HAPE in July 1966, for which he was evacuated. He was reinducted to 12,000 feet on 25 September 1967, when within 48 hours of arrival he developed HAPE for the second time. It is to be noted that all these soldiers were critically ill, had received intravenous morphine and Frusemide prior to the study, and during the procedure they were on oxygen inhalation most of the time.

The findings were consistent with previous reports (2,3) in that the cardiac index was normal, pulmonary arterial systolic pressures were elevated, and left atrial pressures were normal. What was hitherto not known was the pulmonary blood volumes during edema. We had previously reported (4) that the pulmonary blood volume estimated in the convalescents from HAPE was significantly higher than those in convalescents from high altitude pulmonary hypertension. In the present study only in two subjects, PB and RB, the values exceeded our upper limit of normal value of 311 ml/m^2 obtained by studying 25 healthy soldiers at sea level (5). There may be two explanations for these unexpected results: (1) as indicated earlier, subjects were critically ill and had received intravenous morphine and Frusemide prior to the study which had already been reported (6) to reduce the pulmonary blood volumes, and (2) the method employed to measure the pulmonary blood volume estimated only the intravascular volume, and considerable quantities of fluid that had escaped into the alveolar spaces were not accounted for. This assumption is further supported by the repeat studies in P. S. and C. L. in whom the values increased from 155 to 423 ml/m^2 and 224 to 325 ml/m^2, respectively.

Necropsy Findings

The macroscopic findings are characteristic of pulmonary edema, comparable in distribution with the clinical or radiologic findings. The right side of the heart is distended with blood, and the left side is empty. All viscera are congested.

Microscopically, there is enormous distention of the pulmonary blood vessels as far as the capillaries. Scattered foci of haemorrhages are seen in the alveoli, as well as in the pleura. A remarkable feature is the extensive plugging of alveolar capillaries with sludged red blood cells (Fig. 10). These plugs of sludged red blood cells are also seen in some of the thin-walled veins. There is

fibrinous exudate in the alveoli (Fig. 11), some of which may be lined by a hyaline membrane (Fig. 12). There are focal areas of atelectasis, and maximum capillary sludging is seen in these foci. With the phosphotungstic acid-haematoxylin stain, homogeneous or indistinctly laminated hyaline thrombi are seen in alveolar capillaries and some branches of the pulmonary artery. Similar fibrin thrombi are found in the kidney, plugging the glomerular and peritubular arteries, and in the sinusoids of the liver. The brain is edematous in severe cases.

Treatment

This consists of bed rest, warmth, and immediate administration of 100% oxygen, morphine and Frusemide. Atropine is usually combined with morphine, and aminophylline is sometimes administered to relieve bronchospasm. Betamethasone is administered to relieve cerebral edema. All drugs are initially given intravenously – morphine 15 mg, atropine 0.6 mg, Frusemide 40 mg, aminophylline 250 mg and betamethasone 4 mg. Frusemide 40 mg is repeated every 12 hours till lungs are clear, for which 3 to 4 doses generally suffice. Betamethasone, 4 mg, is administered intravenously every 8 hours as long as clinical evidence of cerebral edema is present. Subsequently betamethasone is administered orally and is gradually withdrawn over a number of days. An antibiotic is given for 4 to 5 days to prevent any supervening infection of the lung.

Very early and mild cases may benefit with only oxygen therapy without other aids. However, it has been our experience that inhalation of 100% oxygen by the BLB mask at 5 to 7 litres per minute may not correct completely the arterial haemoglobin desaturation at high altitudes even in healthy individuals. In severe cases lack of oxygen may be due either to hypoventilation or to interference in the exchange of ventilatory gases between alveoli and capillaries as a result of deposition of fibrin rich exudate.

Frusemide

On account of its potency and rapidity of action, and also its selective action on the distal tubule, Frusemide is the diuretic of choice. It is more potent than the mercurial or the chlorthiazide group of diuretics. As much as 60 per cent of the glomerular filtrate may be excreted and 47 per cent of sodium reabsorption may be blocked during Frusemide diuresis. The natruretic effect is about five times that of chlorthiazide.

When Frusemide 40 mg is injected intravenously, diuresis begins within 5 minutes, reaches its peak in 30 minutes and is

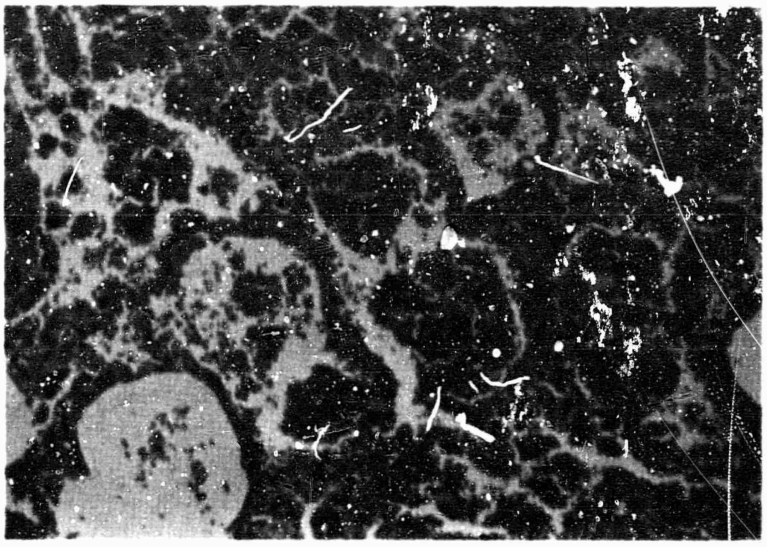

Figure 10. Showing intraalveolar haemorrhage, X180 (H&E strain)

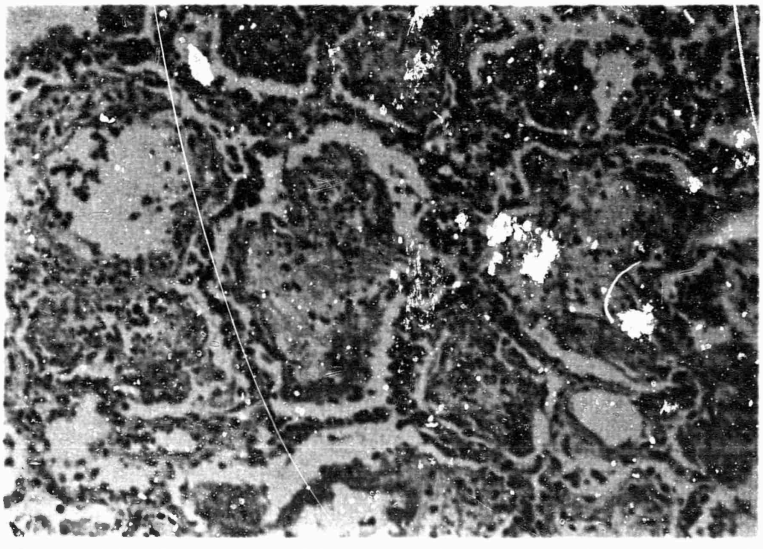

Figure 11. Organizing fibrin exudate, X180 (H&E strain)

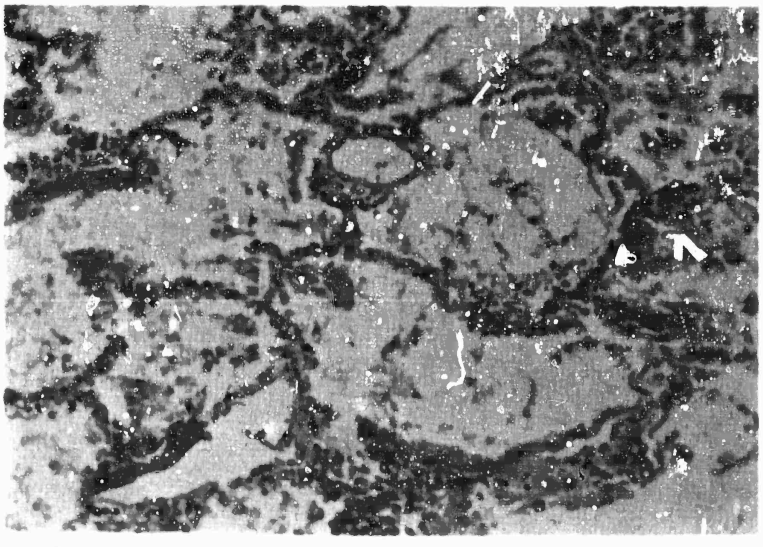

Figure 12. Hyaline membrane, X180 (H&E strain)

almost complete in 90 minutes. This coincides with the action of morphine on pulmonary blood volume, reduction of which takes place within 15 minutes. Coincident onset of action of both the drugs is probably partly responsible for a greater degree of diuresis with combined treatment (7).

Morphine

Patients suffering from pulmonary edema tolerate morphine well, and it can be used with impunity to allay anxiety and restlessness. Many patients make remarkable improvement after its use. The beneficial effect of morphine appears to be due to a redistribution of blood to the periphery. The pulmonary blood volume is thereby lowered and pulmonary edema is relieved (6).

Morphine augments Frusemide diuresis in pulmonary edema when oliguria is associated with severe anoxic stress. This effect seems to be mediated by its capacity to stimulate the release of ACTH as long as it does not cause respiratory depression and sensory impulses are intact. Conditions conducive to improvement of respiration and increased ACTH secretion are obtained when morphine 15 mg is given intravenously. Within 10 to 15 minutes of its administration, anxiety and restlessness are dramatically relieved and labored breathing is normalised, respiratory depression does not occur, and only mild sleep or drowsiness are produced.

Betamethasone

Although on exposure to acute hypoxic stress at high altitude a considerable increase in adrenal cortical activity occurs during the first 48 to 72 hours, apparently it is inadequate to promote diuresis and prevent cerebral edema.

The clinical use of betamethasone has been found to promote diuresis and relieve cerebral edema associated with high-altitude pulmonary edema.

Summary

The clinical profiles of high altitude pulmonary edema in 562 Indian soldiers are presented. The usual clinical features are (1) absence of the triad of high fever, marked leucocytosis and elevated sedimentation rate, (2) patchy distribution of edema in the lungs and (3) frequent involvement of cerebral edema. Patients generally respond satisfactorily to oxygen therapy, together with intravenous administration of morphine, Frusemide and betamethasone (when there is cerebral edema) and rapid recovery

is common. Hemodynamic studies revealed normal cardiac output, elevated pulmonary arterial pressure but normal pulmonary arterial wedge and left atrial pressures. The pulmonary blood volume measured for the first time was increased in only 2 subjects. Probable reasons for the apparent discrepancy are discussed. At autopsy the significant findings are extensive plugging of alveolar capillaries and fibrinous exudate in the alveoli, some of which may be lined with hyaline membrane. Other organs like brain, kidneys, liver may also be involved. Our experience with therapy is briefly outlined.

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GENERAL DISCUSSION

DR. BILLINGS: Dr. Roy, can you give us any incidence figures in terms of number of cases per some unit of man years of exposure?

DR. ROY: The only figure I can give you is that when a thousand soldiers are brought to the height of from 10,000 to 18,000 feet, the rate of occurrence of HAPE varied from 23 to 155 per thousand.

DR. MONCLOA: Dr. Roy, how does the ratio of fresh entrants to re-entrants for those who did not develop HAPE compare with that of those who did? I think the percentages shown will be considerably influenced by the proportion of either re-entrants or fresh entrants.

DR. ROY: After March 1964, we all had become a little wiser on two counts: 1) that soldiers cannot be brought to high altitudes suddenly and 2) that if they are so transported they should be given adequate diuretic (frusemide 80 mg stat, followed by two additional doses at 12-hour intervals), and proper rest. Incidence of HAPE in fresh inductees now is very small. Of the six patients who had HAPE, none of them were fresh inductees. Four were already stationed at high altitude and were sent on some special mission to higher altitude when they got it. The other two were re-inductees. For military reasons it is not possible for me to state the exact incidence among re-inductees.

COL. BERNSTEIN: My question has to do with predilection. I have heard that pulmonary edema occurs more readily in the young and agile group and, of course, in the military this is pretty important. Do you have any comments on that? That is, as opposed to an older age group.

DR. ROY: We do not have the older age group stationed there except that some of the officers are a little older. These 562 subjects who had HAPE, varied in age from 19 to 53. Our oldest was 53 but most of them were below the age of 30.

DR. LANDOWNE: I was quite interested, Dr. Staub, in the hypothesis, if extended to man at least, that edema would appear first in perivascular distribution. Perhaps I can add something to that although it is not very definitive. In the 43 subjects of the study which I referred to this morning, we obtained daily chest x-rays, using rather excellent portable instruments. I think no one else has yet had prospective radiograms on a group at altitude. We had no clinical pulmonary edema in this group. The subjects were examined every day and despite the directed examination no rales were heard. X-rays of one of the subjects showed the development and regression on the second and third day of a patchy, infiltrate limited to one portion of the lung which was considered to be compatible with local pulmonary edema. My prejudice has been, just as you mentioned, that a larger proportion of individuals at risk would show a sub-clinical or "forme fruste" pulmonary edema. In none of these films was there any evidence of increased perivascular markings. We do have serial films to permit the comparison in contradistinction to the clinical instances where you do not have control films, and where the secondary effects are marked.

So, the question is, would one not expect to find some roentgenographic suggestion of increased perivascular markings in our series? Secondly, increased perivascular markings certainly are not prominent in the x-ray pictures that I have seen of established pulmonary edema. Would one expect this to disappear, just as in Dr. Roy's, would there not be increased perivascular markings in some of the cool areas of the lungs that you have?

DR. STAUB: In our limited experience with dogs during acute early edema the x-rays may not show anything, but at post mortem there is considerable perivascular accumulation of fluid. This could be explained by the fact that the x-rays only show shadows, and the densities of blood and of perivascular fluid are approximately the same. If there were vascular constriction as a result of hypoxia at high altitude, the accumulation of perivascular interstitial fluid may be masked, that is, the vessels may appear about normal in size.

DR. VISSCHER: I should like to call on, first, Dr. Raphael Smith to ask if he has something to contribute to the discussion on the Pathology of High Altitude Edema.

DR. SMITH: We have studied interstitial fluid volume in trained, unanesthetized greyhounds exposed to a simulated altitude of 16,000 feet in a low pressure chamber by using simultaneously injected diffusible and nondiffusible radioactive indicators (1, 2). At this juncture our data are incomplete and the change in interstitial fluid volume has been unpredictable. Since there has not been a constant change in pulmonary interstitial volume after exposure of 24 hours we are now extending our studies to 48 hours.

DR. VISSCHER: I have also learned that Dr. Lawson has a few contributions that he would like to make.

DR. LAWSON: It is well known that lowering O_2 tension (PAO_2) increases the rate at which CO reacts with red cells, and that this increases the diffusing capacity for CO (DCO) apart from any effect which low O_2 tension may have on the pulmonary capillary bed. Forster, *et al.* (3) have shown that for PAO_2 between 600 and 60 mm Hg during 10-second breath-holding, DCO is the same for steady state and for transient changes in PAO_2 of less than 10 seconds duration, achieved by varying the O_2 concentration in the breath-holding carbon monoxide mixture. We have used a rebreathing method to measure the effects of hypoxia below PAO_2 of 60 on DCO at rest in four normal young men in the sitting position. To ascertain the effects on the capillary bed, apart from the effects of low PO_2 on the rate of reaction of CO with red cells, we made seven paired comparisons under the following two conditions:

a) transient reduction in alveolar PO_2 from ambient by rebreathing the test gas mixture (0.5% CO, 0.5% C_2H_2 and 0.3% neon) containing 2-3% O_2, and

b) quasi steady-state breathing 8.5% O_2 for 10 minutes prior to rebreathing the test gas mixture whose O_2 concentration was also 8.5%.

In either case, a or b, rebreathing did not exceed 15 seconds with 3 breaths allowed for mixing alveolar and rebreathing gas at a tidal volume exceeding 1.5 liters and greater than 60% of the rebreathing bag volume. The next 6 rebreaths were for 6 aliquot gas samples for analysis. The working assumption is that any difference in DCO at comparable PAO_2 between transient 10-15 second hypoxia and steady-state 10-minute hypoxia is due to a change in the pulmonary capillary bed, because little vascular response is likely to occur in 10-15 seconds (3). During rebreathing, functional residual volume and tidal volume were not significantly different in the paired data. Mean DCO for the transient reduction in alveolar PO_2 was 34.1 ml/min/mm Hg, S.D.±5.6,

exceeding the steady state value of 31.9, S.D.±3.6 ($p>.25$). Respective alveolar PO_2 averaged 48mm Hg, S.D.±6, and 45, S.D.±5, ($p>.3$).

These results are not in agreement with those reported earlier by Forster, *et al.* (3) who found an increase in DCO during steady-state hypoxia using a similar approach with the breath-holding method. Therefore, in nine paired measurements in two normal seated subjects we compared the effects of 10-second and steady-state hypoxia on 10-second breath-holding DCO at total lung capacity. These results tend to confirm those of Forster, *et al.* showing a significant increase in DCO from 47.5, S.D.±8.1 for transient 10-second hypoxia to 50.8, S.D.±7.3 for 3-30 minute hypoxia ($p<.02$). Average PAO_2 was lower during transient hypoxia: 40, S.D.±5 compared to 49±8, but this would tend to minimize the difference found for DCO. In a third subject who had normocytic anemia with a hemoglobin of 10 gm percent, we measured pulmonary capillary blood flow for C_2H_2 (QC) simultaneously with breath-holding DCO. These results of repeated measurements are shown in Figure 1, and reveal a nice correlation between DCO and QC. Fortunately, we had also measured rebreathing QC for C_2H_2 simultaneously with all measurements of rebreathing DCO. These results in Figure 2 reveal a significant

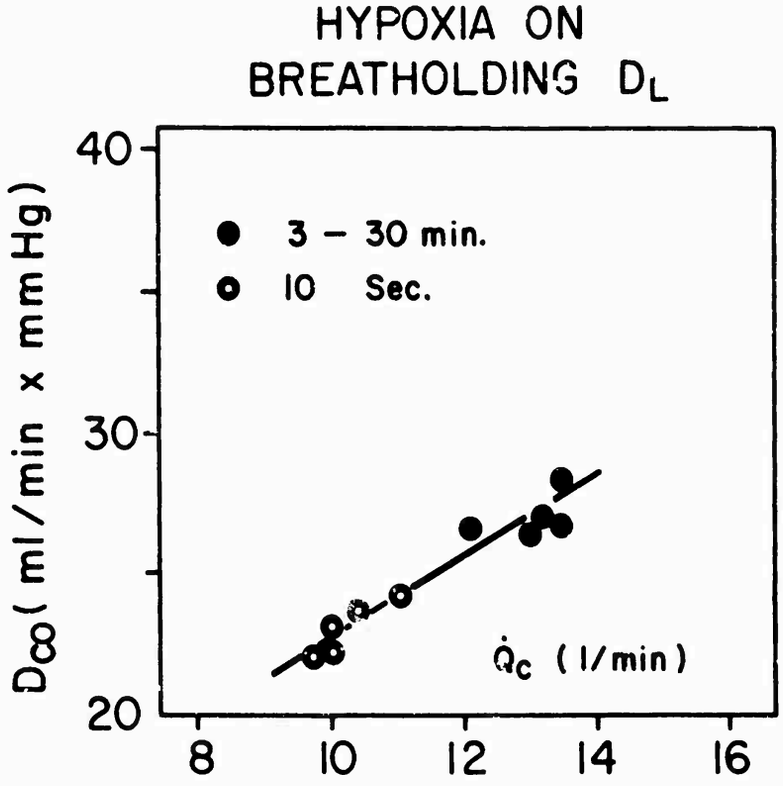

Figure 1.

correlation between DCO and QC (r = .695 $p<.01$). Unlike breath-holding, rebreathing QC during steady-state hypoxia is not significantly different from that during transient hypoxia, and this is probably because the necessary hyperpnea during rebreathing increases QC. If the data in Figures 1 and 2 are combined and replotted as change in DCO versus change in QC in l/min, the correlation is very good, DCO = -1.8 and QC = 1.66 (r = .831, $p<.001$).

These results suggest DCO increases during hypoxia if there is an associated increase in QC. The most likely mechanism is an increase in intravascular pressure acting to open unperfused capillaries in the upper lobes of the seated subject. Such a mechanism would be less likely to operate if the subject were supine with the upper lobes well perfused at normal PAO_2, and indeed Puy, *et al.* (4) found no significant change in breath-holding DCO during supine hypoxia although they found significant increases in QC averaging 30%.

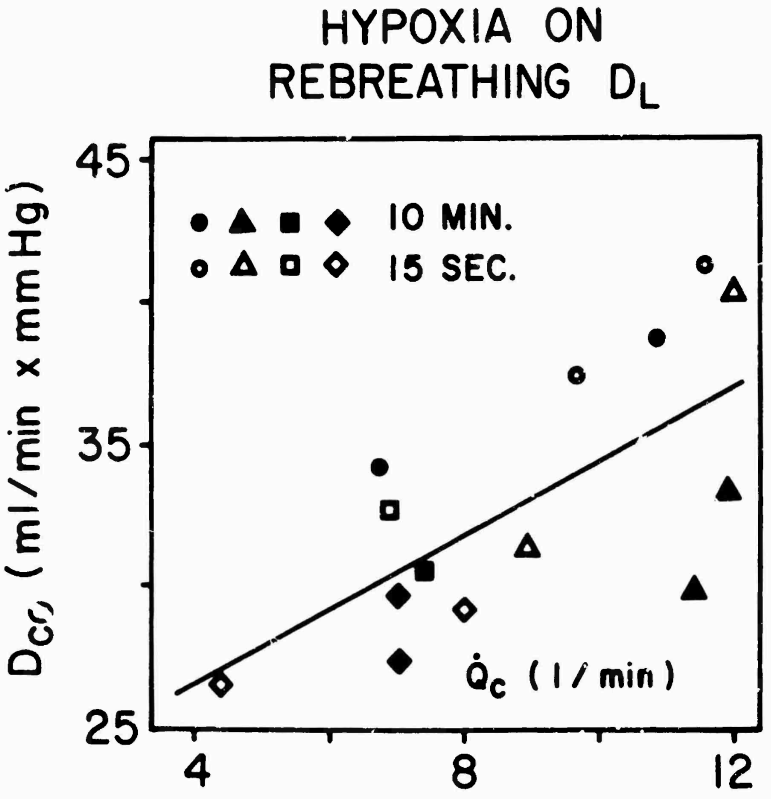

Figure 2.

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ABNORMALITIES OF THE PULMONARY AND SYSTEMATIC CIRCULATION IN CATTLE AT HIGH ALTITUDES

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This conference is concerned with problems man has encountered adjusting to oxygen deprivation of high altitude. If true adaptations have occurred they are negligible. Even temporary acclimatization is a slow difficult process which frequently ends in failure. But fragile as we may consider man to be in this regard he is vastly more competent to confront the unfriendly environment of altitude than is the bovine. The purpose of my presentation is to document this contention of a true interspecies difference in altitude tolerance by describing our experience with the effect of altitude in cattle.

About 50 years ago Glover and Newsom published a series of papers on a disease of cattle maintained on high mountain ranges in Colorado that they termed brisket disease. For many decades and continuing to the present it has been the practice in Utah for cattlemen to drive their herds up to high mountain ranges for the purpose of summer grazing. These herds comprised of cattle belonging to many farmers spend approximately 5 months of the year (June - October) at elevations of 8,000 - 10,000 feet, 5 months on farms or desert ranges during the winter at 4,000 - 7,000 feet elevation and 2 months getting between these two places. Most of the calves of a given herd are born between April and June each year, thus animals are challenged by mild chronic hypoxemia early in life. While the ranchers themselves have known for many years that they could expect to lose a certain percentage of their herd during the summer from this practice the role of hypoxia went unrecognized for decades. Veterinary investigators became interested in this problem in 1955 when they began a systematic study of the condition. Autopsies revealed the severe cardiac involvement which led to the recognition that this was

brisket disease occurring primarily in calves. In Utah mortality due to brisket disease is highest among calves under one year of age. To put it another way mortality is highest during the initial exposure of animals to high altitude. However, the mortality rate varies from year to year in the "same" herd (basically the herds consist of the same cows bred each year usually by the same bull). It also varies among the different ranges throughout the state in the same year. Calves die from causes other than brisket disease in these wild areas and the exact cause of death in calves turning up missing is rarely determined. This undoubtedly accounts for some of the variability but other factors such as genetic predisposition, temperature, availability of forage, water and salt, and exertion probably play a role.

As far as we can determine brisket disease in calves is virtually invariably fatal if untreated and it is completely preventable. The latter can be achieved by not exposing animals to elevations above 5000 feet since to our knowledge no proven case has been observed or described in herds maintained below this level. Definitive treatment consists of removing the animal to a lower elevation – and the lower, the better. Even in Salt Lake City (4,200 feet) we have observed remission resulting in cures in approximately half the cases. Others have claimed that similar cures occur even at 7,000 feet elevation, but they are rare.

We have observed the development of clinically manifest brisket disease in calves following exposure to altitude (8 - 10,000 feet) for periods as brief as 4 weeks. The average duration of exposure before clinically detectable manifestations appear however is approximately 10-12 weeks. Quite clearly this is something different from either chronic mountain sickness or acute pulmonary edema of altitude in man. In Salt Lake City, clinical and physiologic remission in survivors is complete in approximately 6-8 weeks. Clinically detectable signs of brisket disease consist of the following: The animal becomes intolerant of exercise, fails to grow, has a watery diarrhea, venous hypertension reflected in a dilated, tense external jugular vein, and tricuspid regurgitation reflected in a pulsating external jugular vein and by a loud systolic heart murmur. Swelling of the brisket (ventral region of the base of the neck between the forelegs) which is the basis for the terminology of the disease is uncommon, represents the bovine counterpart of dependent edema in man, is a late manifestation and seems to be associated with slow rather than rapid progression of the disease. The pathophysiologic hallmark of brisket disease is pulmonary hypertension. The pathologic corollary of this is spectacular dilatation and hypertrophy of the right ventricle. As many hearts

of brisket animals as I have seen either at thoracotomy in a living animal or at necropsy, I am amazed each time by the gigantic proportions of the heart. For example a 700 gm heart in a small 40 kg calf is not unusual.

The evidence that the pulmonary hypertension of brisket disease results from hypoxic pulmonary vasoconstriction is quite convincing. It is not known whether altitude exposure alone is sufficient to cause this or the additional factor of relative hypoventilation such as occurs in human chronic mountain sickness also enters in. The fact that arterial blood carbon dioxide tension in conscious afflicted animals measured under the unnatural condition of cardiac catheterization is not significantly elevated suggests that this is not the case but this may not represent the natural situation. On the other hand arterial blood hemoglobin unsaturation under this same experimental condition is not uncommon. The mechanism for the latter probably is variable and includes: right-to-left intracardiac shunting through congenital defects, ventilation-perfusion abnormalities produced by (a) atelectasis and/or occlusive vascular lesions, (b) space occupying lesions of the thorax such as large heart and pleural effusion, (c) intrapulmonary anatomic right-to-left shunts. The observation that polycythemia in the relatively (by human standards) anemic calf is unusual in brisket disease is another point of variance from chronic mountain sickness in man.

Pathologic studies especially those by Alexander have revealed a morphologic basis for excessive pulmonary vasoconstriction in the bovine. The small pulmonary arteries and arterioles of normal cattle never exposed to high altitude are endowed with a heavy muscle layer. It is incorrect to call this change medial hypertrophy since it is the normal condition. However, the vessels do appear similar to those in human pulmonary arteries associated with congenital cardiac lesions characterized by obligatory pulmonary hypertension from birth. The pulmonary arteries in brisket animals are said to show an even greater wall thickness-to-lumen ratio than in normal animals. This is interpreted to mean that the bovine pulmonary circulation has less reserve and a far greater potential for constriction. While it is not rare to find variable amounts of occlusive lesions in the pulmonary arteries at necropsy in brisket animals, this is neither an invariable nor consistent finding. It has not been determined whether these are emboli or represent in situ pulmonary thrombosis, but we have viewed such lesions as an aggravative rather than a causative factor.

A finding of interest to this panel is the presence of an unusual abundance of smooth muscle in bovine small pulmonary veins.

What role if any these play in brisket disease is difficult to say but it is possible in some animals to demonstrate a pressure gradient between the pulmonary artery "wedge" and left atrial pressure which can be interpreted to result from pulmonary venoconstriction.

With one possible exception the physiologic manifestations of heart failure in brisket disease qualitatively are no different from those which occur in man. In quantitative terms, however, they are quite different except when compared with most unusual cases of human heart disease. For example mean right atrial – venous pressures of 40 mm Hg with "V" waves of 60 - 70 mm Hg are not unusual. We have studied calves with secondary tricuspid regurgitation so severe that without catheter tip electrocardiograms or fluoroscopy it was impossible to distinguish right atrium from right ventricle just from the pressure pulse. The one exception alluded to has to do with the observation that left ventricular filling pressure usually is elevated in brisket disease despite the fact that it is primarily a form of pulmonary hypertensive heart disease. The reason for this is not entirely clear but the possibilities include exaggerated augmentation of circulating blood volume, encroachment by the enormously dilated right ventricle on left ventricular function and the syncitial nature of cardiac muscle.

As stated earlier, the interpretation that brisket disease results from hypoxic pulmonary vasoconstriction due to altitude exposure of a susceptible animal is based on powerful evidence. However, the role of susceptibility needs to be qualified because apparently it has to do with age as well as genetics. Over the past ten years we have purposely re-exposed a total of 25 animals that recovered from brisket disease to the same high altitude ranges where they developed the disease during the preceding summer. Only two of this group developed recurrent disease. Precisely what protective effect is conferred by age is not known but that it is not permanent is indicated by the fact that the disease occasionally occurs in a mature cow or bull after many sojourns to the summer range.

HIGH ALTITUDE PULMONARY EDEMA

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It is the purpose of this presentation to review our present information regarding the hemodynamic features of HAPE and to present for your consideration an experimental animal model of this unique circulatory disturbance. First, however, I would like to extend Doctor Roy's valuable comments about some of the salient clinical features of HAPE. The following characteristics have been observed in Peru and should be mentioned because they may provide valuable clues regarding causative mechanisms:

1) Pulmonary edema frequently occurs when acclimatized persons descend to sea level and return to high altitude. The minimum stay at sea level after which HAPE is likely to occur is approximately 10 days.

2) Pulmonary edema in Peru is most frequently observed in children. In persons of all ages travelling between the Peruvian highlands and the seacoast, the incidence of HAPE is 13 times higher in the age group from 1 to 20 years compared to the age group of over 20 years. It is rare before 2 years of age.

3) There is a strong tendency for HAPE to occur repeatedly in susceptible subjects, whereas other individuals exposed to high altitude an equal number of times may never have an attack.

4) Exercise clearly increases the possibility of developing HAPE. Indirect evidence of the importance of exercise has recently been obtained at the Chulee General Hospital in Peru where 11 patients with HAPE have been successfully treated at high altitude by bed rest alone. Neither oxygen or drugs were employed at any time during their hospital stay.

The essential hemodynamic features of HAPE have been obtained from cardiac catheterization studies performed during the acute illness at high altitude (1, 2). Data from 5 patients are

summarized in Table 1. These data are similar to those of 6 subjects presented by Doctor Roy. An important feature in all patients has been the presence of an elevated pulmonary artery pressure and a normal pulmonary artery wedge pressure.

In addition to studies at rest, the effect of 3 interventions upon the circulation in HAPE has been observed:

1) 100% oxygen breathing is accompanied by a prompt fall in pulmonary artery pressure (Figure 1).

2) Supine exercise is accompanied by a rise in pulmonary artery pressure without a change in pulmonary artery wedge pressure.

3) Acute hypoxia results in a striking rise in pulmonary artery pressure and again no change in wedge pressure is observed.

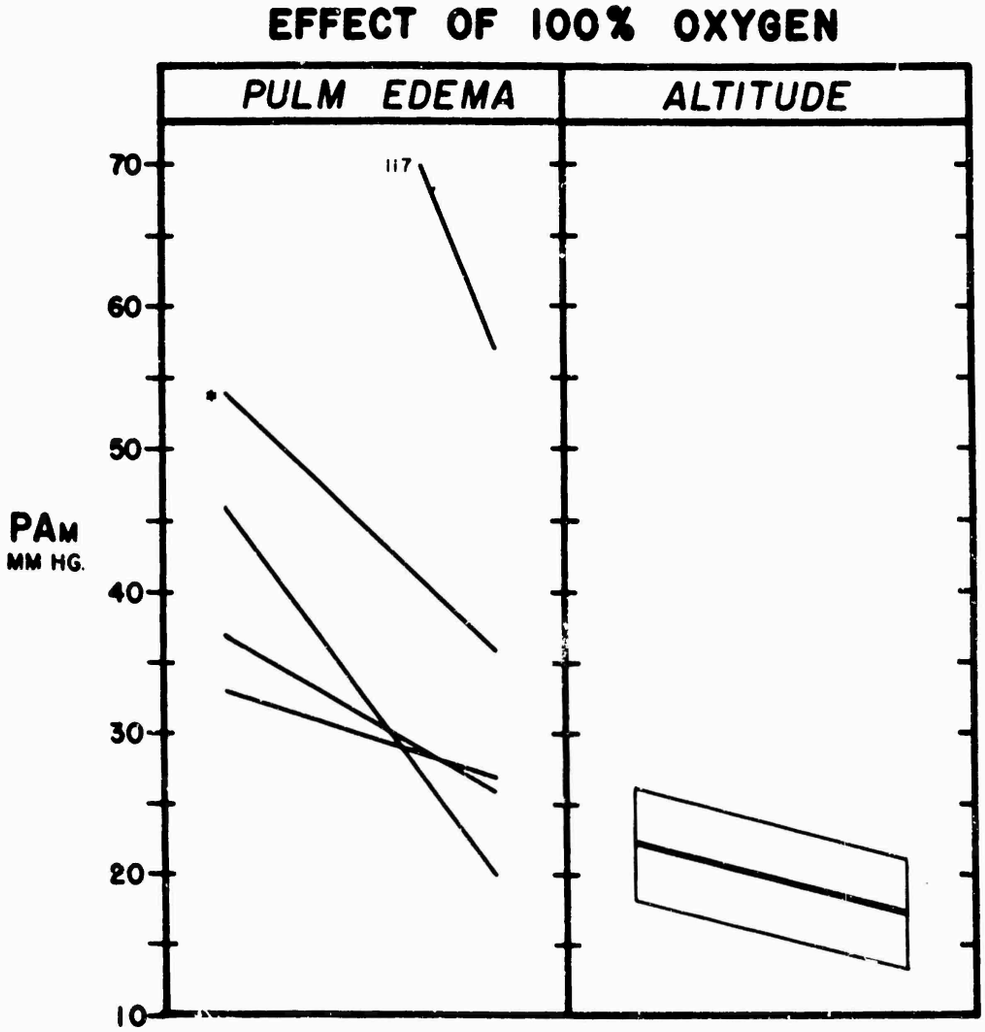

Figure 1. Effect of 100% O_2 upon the pulmonary artery mean pressure in 5 patients with acute high altitude pulmonary edema. In the right hand panel the response of normal Peruvian natives to 100% oxygen is summarized (12,200 ft.). Represented are mean values and one S.D. (1).

Table 1. Summary of hemodynamic data obtained during the acute stage of HAPE. Normal values represent those of 30 Peruvian natives living at 12,200 ft. (13).

No.	Alt.	Sex	Age Yrs.	PCV %	Art. Sat. %	PA_m	PA_w	C.I.	PAR	BA_m
1	12,200	M	8	45	76	117	4	2.6	2900	84
2	12,200	M	27	58	64	46	2	2.7	640	85
3	12,200	F	17	49		37	5			94
4	12,200	M	8			33	3			85
5*	9,000	M	48	47	76	46	6*	2.9	1104	100
Mean			21.6	49.5	72	55.8	4	2.7	1547	89.6
Normal Values for 12,200 ft.			30	54	85	22	8	3.4	224	100

***Case reported by Fred et al (2).**

These data suggest that an important feature of HAPE is pulmonary hypertension due largely to an increased pulmonary arteriolar resistance mediated by hypoxia. The normal pulmonary artery wedge pressure indicates that neither left ventricular failure nor pulmonary venous constriction are present.

Is pulmonary hypertension an important causative factor in HAPE or is it a secondary phenomenon resulting from the hypoxia produced by edema fluid in the pulmonary alveoli? If it is a causative factor, one would expect to observe a rise in pulmonary artery pressure prior to the onset of pulmonary edema in a susceptible subject. Last year this problem was investigated in collaboration with Doctor Robert Grover's high altitude group (3). Four subjects were selected who had experienced clear cut severe episodes of HAPE while climbing or skiing in the mountains. None had any evidence of cardiac or pulmonary disease. Hemodynamic studies were first performed at sea level. Each man was then transported by plane and car to 10,200 ft. (Leadville, Colorado) within 8 hours. On the next morning he carried out a 3 hour period of vigorous climbing up to 13,500 ft. and early that afternoon a repeat hemodynamic study was done. Results were compared with data from 8 sea level residents studied 10 days after arrival at 10,300 ft. ("normal").

All four subjects had normal hemodynamics and blood gases at sea level. After exposure to high altitude and following exercise, there was no evidence of pulmonary edema by chest roentgengram, auscultation or symptoms. Tachycardia was present at rest and during exercise. Mean pulmonary artery pressure at rest was markedly elevated in all subjects to 37 to 47 mmHg (normal 15) and a further rise occurred during exercise to 47 to 64 mmHg (normal 25). Pulmonary artery wedge pressures were normal (10-11 mmHg). The alveolar-arterial O_2 tension difference was abnormally wide: rest 8 to 20 mmHg (normal 4); exercise 23 to 38 mmHg (normal 15). This resulted in low arterial O_2 tensions: rest 44 to 58 mmHg (normal 56); exercise 36 to 44 mmHg (normal 53). Hyperventilation was present in all subjects. Arterial CO_2 tensions were 26 to 33 mmHg at rest and 22 to 31 mmHg with exercise. Respiratory alkalosis was present with pH values of 7.47 to 7.54 at rest and 7.44 to 7.49 during exercise.

The marked elevation of pulmonary artery pressure in the absence of any evidence of pulmonary edema strongly suggests that this is an initial abnormality in HAPE and not a phenomenon secondary to the presence of edema fluid in the alveoli. The magnitude of the rise in pulmonary artery pressure and the increased alveolar-arterial PO_2 gradient suggests the presence of a disturb-

ance in the pulmonary circulation that is not simply hypoxic arteriolar constriction. The possibility of vascular occlusion, especially in the capillaries by agglutinated red cells, platelet aggregates or micro-thrombi, should be considered since these have been observed in autopsy studies of fatal cases of HAPE (4, 5, 6).

The clinical and experimental studies described indicate that an acute elevation of pulmonary artery pressure with a normal pulmonary artery wedge pressure is an important early factor in the genesis of HAPE. How do these hemodynamic changes result in edema of the lungs? It is possible that pulmonary edema occurring in the presence of pulmonary embolism in man or in experimental preparations has a similar hemodynamic basis (7, 8). In Figure 2 (left) is a diagram of the pulmonary circulation with the normal pressure relationships indicated in the lower portion of the figure. Let us assume that 70 to 80% of the pulmonary circulation is occluded by embolism but that cardiac output is sufficient to

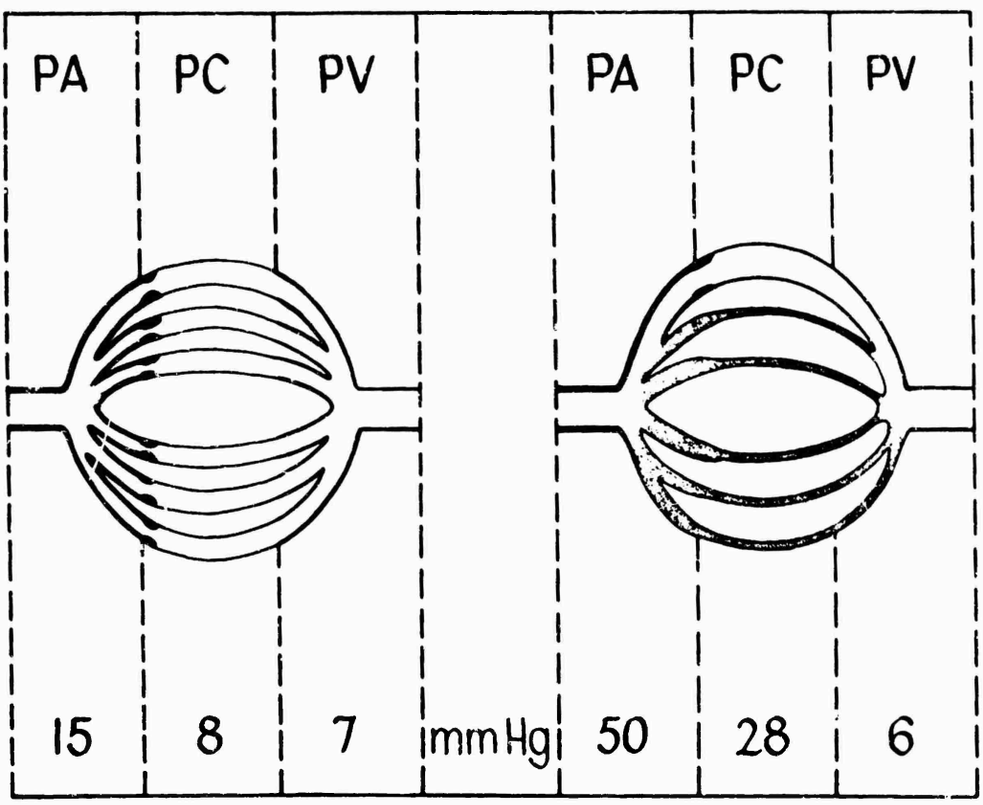

Figure 2. Diagram of the mechanism of overperfusion pulmonary edema. The normal pulmonary circulation with normal pressure values are indicated on the left. On the right 80% of the pulmonary circulation has been occluded and increased blood flow is present in the remaining portion of the pulmonary vascular bed. Pressure measurements derived from canine experiments are indicated.

allow survival. The pulmonary artery pressure will rise and flow through the unobstructed portion of the pulmonary vascular bed will be greatly increased (Fig. 2 – right). If the mean pulmonary artery pressure is raised to 50 mm Hg and the pulmonary vein pressure is unchanged, the pressure drop across the capillaries in the unobstructed pulmonary vascular bed will be 44 mm Hg. If this pressure drop is linear, the pressure at the midpoint of the capillaries will be 28 mm Hg. This is sufficient to produce pulmonary edema. One might object to this concept by pointing out that a linear pressure fall across the capillary bed would be prevented by the resistance of arterioles. However, under such conditions of high flow and pressure, the pulmonary vessels will be passively distended and arteriolar resistance may be greatly decreased. If a catheter is advanced to the wedge position in this portion of the circulation, the flow around the catheter will cease and the catheter tip will record a normal wedge pressure reflecting the normal pulmonary vein pressure. Leland and Sasahana have studied the hemodynamics of pulmonary embolism in men (9). Pulmonary artery pressure was elevated (20-80 mm Hg). The pulmonary artery wedge pressure was normal in patients without underlying cardiac disease. Cardiac output was within normal limits in 35% of patients. Thus the hemodynamic features of clinical pulmonary embolism are comparable to those encountered in HAPE. It is suggested that at high altitude pulmonary vascular obstruction occurs unevenly throughout the lung, resulting in areas of the vascular bed where essentially no blood flow occurs. Other areas may not be obstructed and in these areas high flow may be present and the pulmonary capillaries in these areas will "see" the high pulmonary artery pressure. In order to examine the hemodynamic features of this variety of pulmonary edema, an animal model has recently been prepared (10). Large mongrel dogs were used with controlled respiration. After opening the chest, the right main pulmonary artery was dissected free at its origin and ligated. Large bore polyethylene catheters were advanced to the right atrium via the femoral and external jugular veins to permit total bypass of the right ventricle. Venous blood thus collected was passed through a roller pump without oxygenation and returned via a polyethylene catheter inserted into the proximal portion of the main pulmonary artery (Fig. 3). By this method right ventricular failure could be prevented and blood flow to the lungs could be varied over a wide range of flows. After control observations had been made, the pulmonary artery branch to the left middle lobe of the lung was isolated and cannulated for blood sampling and pressure measurement. The pulmonary artery branch

to the left lower lobe was ligated. The control cardiac output was maintained by bypass pump. Under these conditions the total cardiac output passed through the pulmonary vascular bed of the left upper lobe. High pressure and high flow was obviously present in this lobe. The pulmonary artery was tense and a continuous thrill and murmur were present over the artery and the lobe. Blood gas values remained unaltered, however, and the left atrial pressure was normal. After 10 to 20 minutes the lobe gradually became more congested and less compliant and finally the sudden

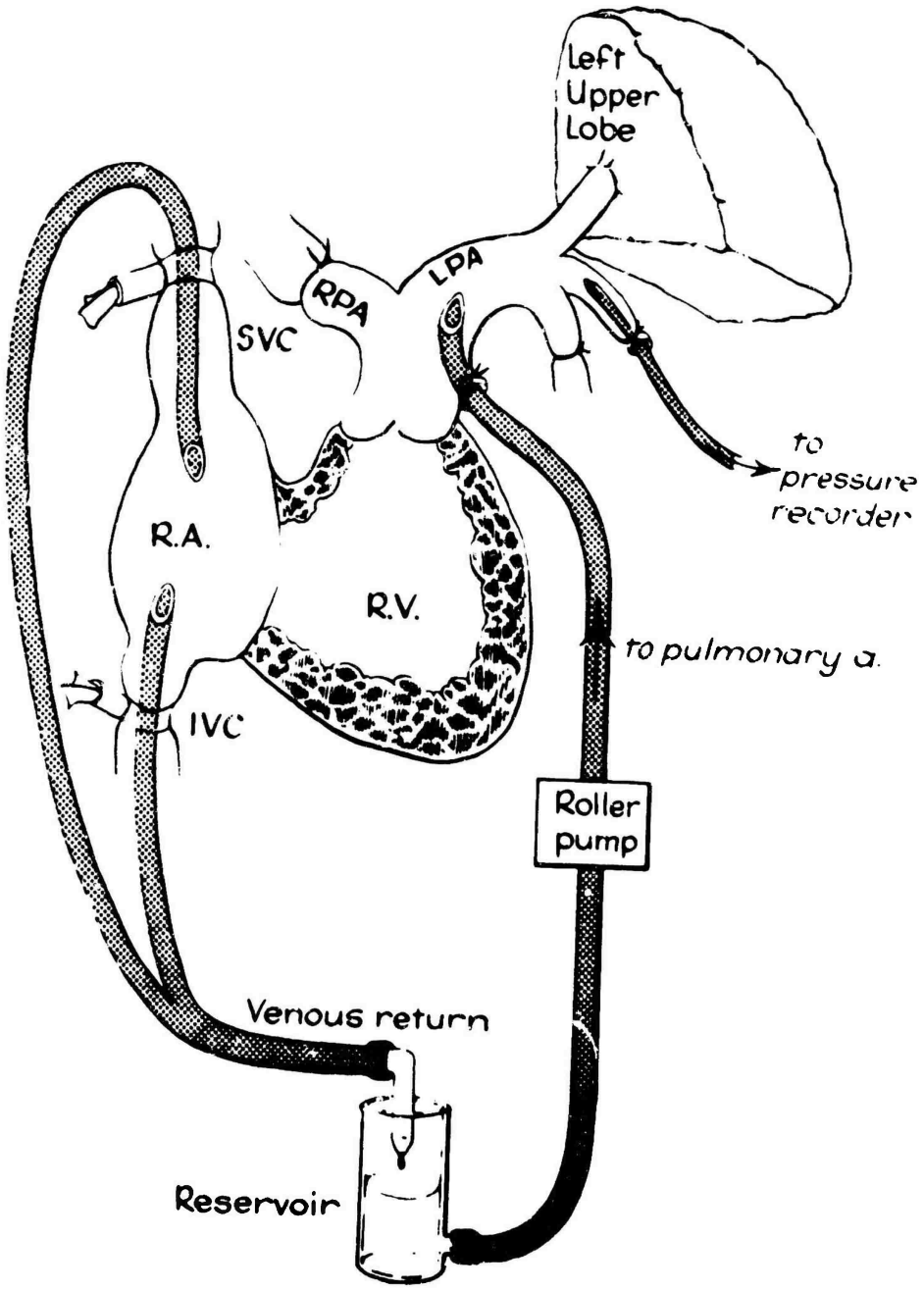

Figure 3. Diagram of experimental technique of producing pulmonary edema by increased blood flow through a single lobe of the canine lung.

appearance of pulmonary edema terminated the experiment. Cardiac failure was not present as evidenced by a normal left atrial pressure. Pulmonary artery wedge pressures in the left upper lobe were normal. The heart continued to beat for several minutes after effective gas exchange had ceased. Diffuse severe pulmonary edema was present in the overperfused lobe as evidenced by increased weight, a high specific gravity (mean 0.92, control 0.42), airlessness and the exudation of fluid from the cut surfaces. Pulmonary edema fluid filled the major airways. Histological studies demonstrated diffuse pulmonary edema and capillary congestion. Edema was never observed in the other lobes. In two experiments the pulmonary artery branch to the left upper lobe was ligated and the left lower lobe was perfused. Pulmonary edema appeared in a similar manner but a larger period of perfusion was necessary. Values of pressure and flow which were present just prior to the onset of pulmonary edema are indicated in Table 2. The relative flow through the left upper lobe was estimated to have increased from 4 to 6 times over the resting flow. It is evident from this study that occlusion of approximately 75 to 83% of the total pulmonary vascular bed with maintenance of the central cardiac output is associated with increased pressure and flow in the unoccluded portion. This has produced pulmonary edema in the presence of a normal left atrial pressure and a normal pulmonary artery wedge pressure. The mean pulmonary artery pressure was 48 mm Hg (Table 2). These values are similar to those observed in

Table 2. Hemodynamic features of overperfusion pulmonary edema. Control values were obtained after ligation of the right pulmonary artery but prior to the establishment of the right ventricular bypass. Values on the right were obtained just prior to the onset of pulmonary edema.

	Control	Pulmonary edema
PA mean	26*	48
LA mean	5	4
PA wedge	5	6
Cardiac output	2.3	2.0**
A-V difference	4.9	6.1
FA mean	131	73
Heart rate	157	135

*RPA ligated

**On bypass.

severe acute pulmonary embolism and in HAPE. The relevance of these observations to the mechanism of HAPE is clear. Pulmonary vascular obstruction in HAPE occurs as the result of hypoxic pulmonary arteriolar constriction and, possibly, by thrombotic occlusion of the capillary bed. If this process does not affect all portions of the pulmonary vascular bed to a uniform degree, there will be unobstructed areas of the lung where increased flow occurs. These areas will be the site of edema formation. Obstructed areas of the pulmonary circulation will remain clear and free of edema. What is the evidence that a non-uniform vasoconstructive response can occur in the lung?

Lehr et al (11) have subjected rabbits to various stimuli and injected India ink into the ear veins. Post-mortem examination of the lungs demonstrated an irregular distribution of India ink particles in the pulmonary vascular bed. The data suggest that in some areas vascular constriction stopped flow, thus trapping masses of particles. In other areas flow apparently was maintained, allowing the particles to pass through the capillary bed and out into the systemic circulation. Various workers have demonstrated that hypoxia exerts a local vasoconstrictive effect in the lung. In man subjected to acute hypoxia, variations in ventilation and perfusion

Figure 4. Typical roentgenographic features of high altitude pulmonary edema. Note diffuse distribution of densities, clear areas, especially at the base and absence of cardiac enlargement.

could allow vasoconstriction to be more severe in some areas of the lung than in others. Indirect evidence is available to suggest that a similar process occurs in HAPE in response to acute hypoxia. An important roentgenologic feature of HAPE is the patchy distribution of edema (12). Edematous areas and areas of clear lung are observed in close proximity to each other (Fig. 4). Diffuse edema is rarely seen except in the most severe cases. It is quite possible that the clear areas represent regions of vascular obstruction where little or no flow is occurring. Edematous areas, on the other hand, could represent regions where high flow is present resulting in pulmonary edema. This speculative concept of the mechanism of HAPE seems at this time to best fit the clinical and experimental observations that have been made in man and animals. Further studies in man of the pulmonary circulatory response to high altitude using techniques such as lung scans are necessary to further test this concept.

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GENERAL DISCUSSION

DR. VISSCHER: Dr. Hultgren, you have given us a good framework for some final discussion of the mechanism by which HAPE could possibly occur. I can confirm the observations to which you referred with respect to the ease with which one can produce pulmonary edema by restricting the area of the bed through which one makes a certain pulmonary blood flow move per unit of time. Not only is it possible to do this by ligation of the arterial supply to several of the lobules of the lung but also it is possible to do this by administration of microspheres which occlude certain fractions of the lung bed in the more general distribution.

There is just one point about which I would like to argue with you as to what happens hemodynamically. I would expect that the capillary pressure at the mid-point of the capillary would definitely be elevated if the number of capillaries that remained open after the ligation of the major pulmonary artery trunk has been carried out because, according to the Poiseuille's Law and other considerations, it would require a greater head of pressure to move, let us say, twice as much blood per unit of time along a given length of capillary than it would to move the original half as much. This is what I think we are doing when we ligate a major share of the pulmonary arteries. We are forcing twice or four times as much blood to go through the open capillaries and the pressure that is necessary to do this will be increased at the arterial end of the capillary, and although it will be falling gradually as you go the length of the capillaries, the mid-capillary pressure will be elevated.

DR. HULTGREN: I would certainly agree with that.

DR. VISSCHER: In other words, I would say if this mechanism

exists then it would be a pressure controlled phenomenon. The edema would be as a result of excessive filtration pressure.

I have been interested in the rather uniform report that there is a relationship between physical exertion and susceptibility to HAPE. It is for this reason that I have particularly asked Dr. Staub to report on the findings of the Severinghaus group with respect to the necessity, if pulmonary edema were to be produced in rats made to breath low oxygen tension, to combine this with very heavy physical exertion in swimming. Is there any dissent from the view that increased cardiac output is a factor which is predisposing to the occurrence of high altitude pulmonary edema in the human subject?

If increased cardiac output is a factor, then, of course, we are dealing with a situation in which there are elevations in capillary pressure because of the necessity for an increased pressure fall over the length of the capillary in order to move that much additional blood.

COL HANSEN: Are we certain that other variables such as anxiety or temperature changes are not important?

DR. VISSCHER: I did not mean for a moment to suggest that it was the only factor of importance. Anxiety will also increase cardiac output.

DR. STAUB: Recent evidence by Whayne and Severinghaus suggests that hypoxic rats can develop pulmonary edema at rest. It takes longer, but rats breathing 8% O_2 at sea level pressure appear to accumulate perivascular fluid after about 30-40 minutes. Unfortunately, I cannot give any more details than that.

I do not see from the data so far presented that everyone with HAPE has to have been exercising. There must be a range of sensitivities so that some people may develop the edema even at rest.

DR. HURTADO: I wonder whether an important factor, in the relationship of pulmonary edema to physical activity, is the fact that during this additional stress at high altitudes there is an accentuation in the degree of hypoxia. So, for this point of view, there is an important difference between rest and physical activity.

DR. HULTGREN: I certainly agree that it may be a very important factor. If one calculates the pulmonary vascular resistance during exercise in people who live at high altitude the resistance actually increases slightly and this may be mediated by the hypoxia of exercise.

Dr. Staub presented data which suggests that a form of edema may be created in rats; but it seems to me that this is an unusual form of edema. As I recall from the abstract, there was no statis-

tically significant increase in the weight of these lungs. In addition, I should like to inquire about the significance of this perivascular edema. Certainly, you have shown it very well by your technique of rapid freezing. But I have reviewed with Dr. Thomas the slides that we have at Stanford on fatal cases, very carefully looking for this type of perivascular edema in ordinary H & E sections. We have been unable to find it. Is this difference due to the technique used or what is its significance?

DR. STAUB: The simple wet and dry weight of the lung is not a very good way to quantify pulmonary edema. Data from our own and other laboratories indicates that lung wet and dry weights of animals with pulmonary edema do not always agree with the extravascular water volume of the lung measured by tritiated-water-indicator dilution curves. The problem is that you do not know how much of the lung water is inside and how much is outside blood vessels when you use wet-dry weights only. For example, in the acute edema due to alloxan, lung blood volume decreases and therefore one would need more extravascular water (edema) to get an increase in the wet-dry weight ratio. This may not be true of conjestive edema where the lung blood volume is increased.

As to why you have not seen perivascular edema in your routine pathology sections, I have no explanation. Our animals are always frozen with distended lungs and without any time delay. We always find perivascular edema as the first evidence of pulmonary edema.

DR. KUIDA: In the calf it is possible to have exactly the same thing happen such as you described. That is, if you put a calf on a right heart by-pass and pump-perfuse with any kind of mechanical pump, you can produce severe pulmonary hypertension. If you do it long enough, severe pulmonary edema can be produced without ligating anything. The calf shows this tremendous sensitivity to whatever it is you do when you pump-perfuse.

One observation that bears on this is that made by Dr. Will, Colorado State University, some years ago. If you just take that little bit of blood, say 10 ml or 20 ml of calf blood and hemolize it and then inject it back in to the animal, it produces severe pulmonary heart strain; whereas similar experiments carried out on a dog, cat, or any other species will do nothing. Again, there is something about traumatized blood elements that produce hemodynamic effects.

Dr. Hultgren, is it not true that some observations have been made of acute pulmonary edema at altitude developing in children who were going back up to altitude in automobiles? I am not

pretending that children are inactive in the back seat of an automobile, but certainly they are not actively exerting themselves. So, the factor of exercise is not necessarily required for the development of syndromes.

DR. HULTGREN: I agree. I do not think anyone would imply exercise is absolutely necessary to create high altitude pulmonary edema. It simply seems to be a very common additive factor.

DR. ROY: Recently we took up four subjects who had had pulmonary edema. They were under our observation in bed in the hospital. The only physical activity permitted was bathroom privilege (20 yards). One of them did develop pulmonary edema. These were susceptible cases; they already had had pulmonary edema once before. I think there are tremendous individual variations.

Whatever we may think as to the etiology of HAPE, we must remember the two different clinical pictures:

a. In large groups of people who recover (some 90 to 95 percent recover) their clinical picture changes dramatically within 24 hours, sometimes even within 12 hours. If the mechanism had something to do with the plugging of the capillaries, or something not readily reversible, one wonders how this change could take place.

b. On the other hand, in those who do not recover, some sort of capillary damage takes place, such that one gets exudation of fibrin, and hyaline membranes, and plugging and sludging of the capillaries. These are the two extremes we see with many shades between.

DR. HULTGREN: I certainly agree with Dr. Roy. I am not certain as to whether the capillary damage and obstruction represent a secondary phenomenon or an initiating phenomenon. This remains to be investigated. Certainly lysis or disappearance of pulmonary thrombi can be very rapid.

Prolonged illness may be related to the protein content of the exudate. Some patients with altitude edema are not seen by a physician until they have been ill for several days. They may have been diagnosed as cases of pneumonia and in one instance, because it was a cerebral form, the case was diagnosed as an instance of encephalitis. They may not be given oxygen initially and these patients have a very prolonged period of recovery in the hospital. Although they eventually completely recover on oxygen therapy it seemed to me that they might have had a highly proteinaceous exudate that took a long time to resorb. I am not at all sure one needs to suppose thromboses are an initiating factor, and thromboses may be occurring late in severe cases where treatment is delayed.

DR. DEXTER: Dr. Visscher, it is my understanding that one does not get up to a pH of 8 in these individuals with HAPE but they are hyperventilating and they are alkalotic. The pH may rise to about 7.6. I wonder whether or not this could be one of the factors which is contributory but not in itself the basic cause. Also, we have been discussing a lung which is "edematous". The thought has been that fluid is passing from capillary across the capillary membrane into the interstitial space and then spilling over into the alveolus. And yet, we do not seem to have very much evidence to support the thesis that fluid is going in that direction at all. Is there any possibility that this fluid is being formed in the terminal bronchioles themselves and then coming down from above into the alveolus, and that this is not pulmonary edema in the sense of a transudation of fluid from the capillary to alveolus but is more like the "bronchiolitis" of war gas origin?

DR. VISSCHER: It is a possibility that changes in pH might alter the electric charge on pores in such a way that they would allow other charged particles (i.e., plasma-proteins) to pass through them with a facility that did not occur at normal pH values. I myself have not tested it. I would think it rather unlikely, however, with the relatively small changes in pH that do occur, because in order to reverse the charge, you have to pass through the isoelectric points of the proteins that are concerned, and you would not be passing through the isoelectric point of the albumin. You would have to consider the isoelectric point of the structural protein that forms the barrier, the pore. However, I would not put it out of the realm of possibility.

In regard to your second question, Dr. Staub does have some information based on his microscopic studies that bears on this question. But, I would point out that if it is really bronchial in origin, then if one perfused only the pulmonary arteries in animals, one should not get edema as readily as though one perfused the bronchial vascular bed, which, of course, is not what we find.

Now, we do have evidence, I think, that it is water and electrolytes coming from the pulmonary vascular bed that enters into edema production. I am going to ask Dr. Staub to give a fuller answer to this question.

DR. STAUB: I cannot answer that question for high altitude edema. For other forms of acute edema that we have studied, the leakage appears to be from the pulmonary vascular bed. Our main criterion is that there is no air mixed with the alveolar fluid which we would expect if the leakage were from airway epithelium. On the other hand, we do know that in phosgene poisoning as you

mentioned, the injury is primarily a respiratory bronchiolitis, not an alveolitis. Any edema in that case appears to be leakage directly from tissues near the center of the terminal respiratory unit rather than from alveolar walls in general. There is a famous electron-micrograph by Bruno Kisch showing droplets of fluid "weeping" from the terminal airway epithelium in pulmonary edema. Apparently fluid can leak from the bronchiolar surface and flow backward into the alveoli. I have no way of knowing what happens in high altitude edema, but one thing is clear: of all the organs of the body the one that has the highest oxygen tension, regardless of the severity of hypoxia, is the lung. This is true for the airway epithelium as well as for the alveolar and pulmonary capillary epithelium. On that basis they should be *less* likely to show altered permeability due to hypoxia.

DR. ROBINSON: Dr. Roy mentioned that there is evidence of edema in the central nervous system. Has anyone made surveys of possible edema in the myocardium, the liver, the kidney, the skeletal muscle, skin, connective tissue. Dr. Kuida's brisket disease in cattle suggests that this may not be limited to the tissues that we have been discussing today.

DR. ROY: Nayak, N., et al (1) report on 13 persons who died of altitude sickness. The organs like the kidney, liver, brain, heart, and lungs were involved. We like to think of high altitude pulmonary edema as being a generalized disorder of the capillaries, where the maximum effect is seen in the lung. But there are patients who present the cerebral form which everyone has experienced. Sometimes they become unconscious for as much as 72 hours, and they do have cerebral edema.

DR. HULTGREN: It is clear that some interesting concepts have emerged here by Dr. Staub and Dr. Dexter. Both of these are certainly possible, and one cannot easily dismiss them although the lack of inflammatory change in the bronchial tree might be against Dr. Dexter's proposal and the lack of alveolar edema in the other situation might be slightly against Dr. Staub's proposal. We are limited by the facts that are available. It is clear we are not dealing with pulmonary vein constriction. We are not dealing with the left heart failure. We are observing a situation where the pulmonary artery pressure is elevated; and this is accompanied by patchy pulmonary edema. Histologic evidence of thromboses in the pulmonary and systemic vessels have been presented, but the role of these lesions in the genesis of altitude edema has not been resolved. They may represent a primary, initiating process, but on the other hand they may merely be secondary effects of severe terminal hypoxia.

DR. VISSCHER: We have not, I am sure, come to a real consensus as to all the mechanisms involved in HAPE, but we have arrived at some common ground of agreement as to what major changes in pulmonary-hemodynamics occur; and I want to thank each of you who have contributed to the discussion.

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PANEL

ACCLIMATIZATION

Chairman: Robert F. Grover

RESPIRATORY ADAPTATION TO CHRONIC HYPOXIA

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I plan to restrict my remarks this morning to summarizing what I think we know about the changes in the regulation of breathing as one acclimatizes to a high altitude such as 12,000-15,000 ft., mentioning at the end the work going on in my laboratory at present. Most of the earlier work is very well known, but perhaps a brief review here will help put the more recent work in perspective.

Hypoxia by direct action on the aortic and carotid chemoreceptors produces a small, immediate increase in breathing that is immediately reversible when the hypoxia is terminated (Fig. 1). As Nielsen and Smith (12) first showed, this represents not merely an addition to the stimuli already present but an interaction resulting in a slight steepening of the CO_2 response curve (Fig. 2). Lloyd, Jukes, and Cunningham (9) showed that the CO_2 response could be well described in most subjects by an equation of a straight line in which the slope, *S*, was increased while the intercept of the extrapolated line at the *x* axis, *B*, hardly changed. *S*, the slope, could be related to the alveolar PO_2 by a hyperbolic curve. It was subsequently shown by several investigators (2, 3, 8, 10) that the ventilatory response to inhaled CO_2 can be considered as the sum of two additive components, one related to the arterial PCO_2 *per se* and one related to the concomitant change in arterial H^+ or pH. In CO_2 inhalation, both PCO_2 and H^+ stimuli increase; but in metabolic acid-base disturbances, when the H^+ ion concentration rises and stimulates breathing, the PCO_2 secondarily falls and opposes the hyperpnea. Stimulation that correlates with the arterial PCO_2 *per se* has been explained by the effect of the highly diffusible CO_2 on the pH of the newly discovered H^+ ion recep-

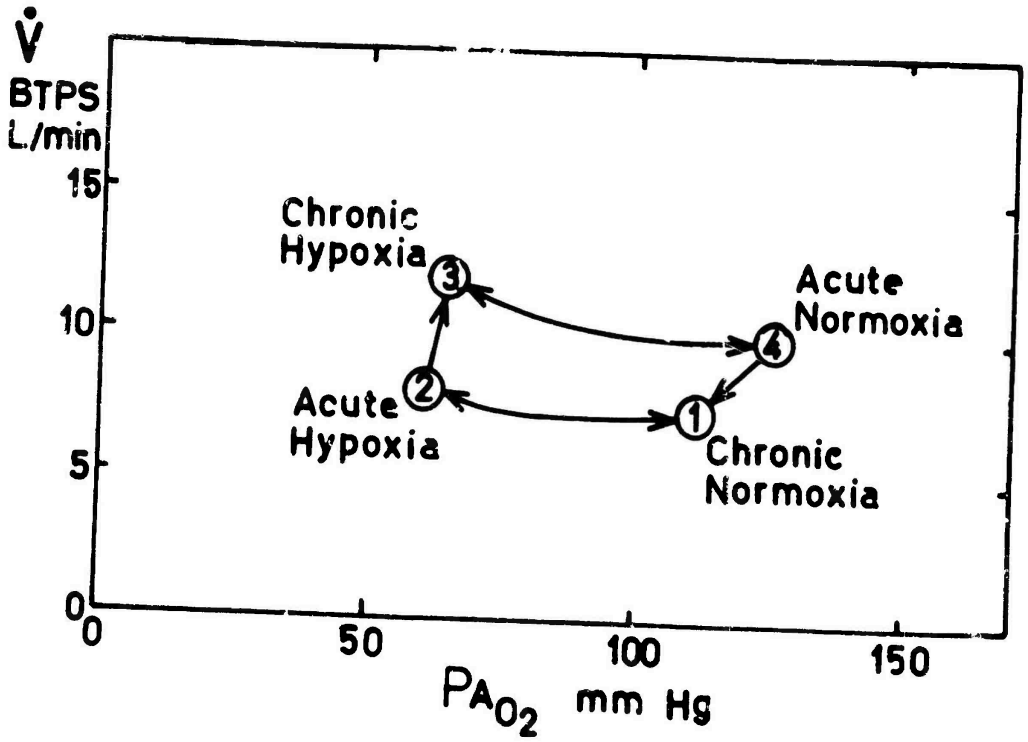

Figure 1. Schematic representation of reversible and unidirectional changes in pulmonary ventilation (V) and alveolar oxygen pressure (PAO_2) during altitude acclimatization and deacclimatization.

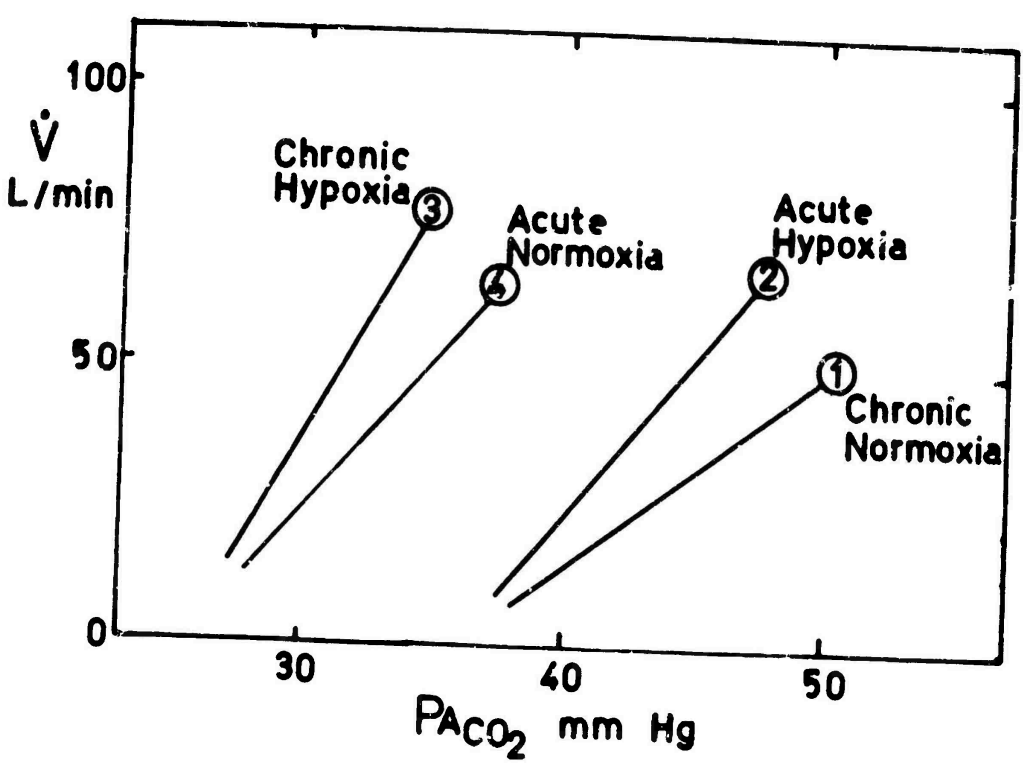

Figure 2. Schematic representation of linear CO_2 response curves corresponding to the 4 conditions shown in Figure 1.

tors located near the ventrolateral surface of the medulla oblongata (11). Thus far, I have referred solely to things that happen almost immediately, within a few seconds or a minute or two, and which are equally quickly reversed. I term these acute responses.

When one remains hypoxic for very long, however, breathing increases further, and a restoration of normoxia no longer restores the breathing to normal (Fig. 1). This slow adaptation, one that takes hours or days or longer to develop or reverse, is an early step in the process of acclimatization. It is related to a change in the CO_2 response curve, that is this time shifted greatly to the left, as well as becoming more steep (Fig. 2). This shift to the left precedes the correction of the arterial pH (7), which remains alkaline for several days or weeks, so the increase in breathing cannot be being driven by a low arterial pH. Severinghaus *et al* (15), however, have shown that there is a very rapid fall in bicarbonate concentration in the cerebrospinal fluid, which they take to be similar to the interstitial fluid bathing the medullary chemoreceptors. This lowers the PCO_2 associated with any given CSF pH and thus shifts the range of arterial PCO_2 levels that provide stimulatory H^+ ion concentrations at the medullary chemoreceptors. They feel this accounts for the shift in position of the CO_2 response curve in the first few days of altitude acclimatization, driving the breathing to keep PCO_2 low even after hypoxia has been terminated.

This raises two very important and interrelated questions: First, how is the bicarbonate concentration of CSF lowered so rapidly? Is bicarbonate pumped out by an active transport pump with a cation such as sodium, or in exchange for an anion such as chloride? Is hydrogen ion pumped into the CSF in exchange for a cation such as sodium, or along with an anion? We do not know. Second, what is the adequate stimulus and control mechanism for the transport process, whatever it may be? Is it hypoxia *per se*, or is it merely secondary to the hypocapnia that results from hyperventilation? Brown, *et al* (1) showed many years ago that passive hyperventilation for 24 hours could produce a similar shift in the CO_2 response curve.

In an attempt to investigate the second question, a group of us (4) studied the effects, in ourselves, of 8 hours of hypoxia on the position of the hyperoxic CO_2 response curve (measured with PIO_2 = 200 mm Hg) and on another day compared it with the effects of a similar period of the same hypoxia (PAO_2 = 45-50 mm Hg) during which the alveolar PCO_2 was kept at its normal resting value by addition of inspired CO_2 with continuous monitoring

(Fig. 3). We found that maintaining alveolar normocapnia during the 8 hour hypoxic acclimatization period reduced the shift in hyperoxic CO_2 response but did not abolish it (Fig. 4). Realizing that hypoxia probably dilated the blood vessels of the brain and thus lowered the brain tissue PCO_2 even when alveolar PCO_2 was held constant, we then repeated the experiments with alveolar PCO_2 held sufficiently above normal to prevent the brain tissue PCO_2 from falling (Fig. 5). (For completeness, we also held the alveolar PCO_2 constant at a low value during hypoxia for comparison with the spontaneous hypocapnia developing during ordinary hypoxia.) Prevention of brain tissue hypocapnia in this way reduced the shift in hyperoxic CO_2 response to the small amount typical of the diurnal rhythm and seen in control experiments in

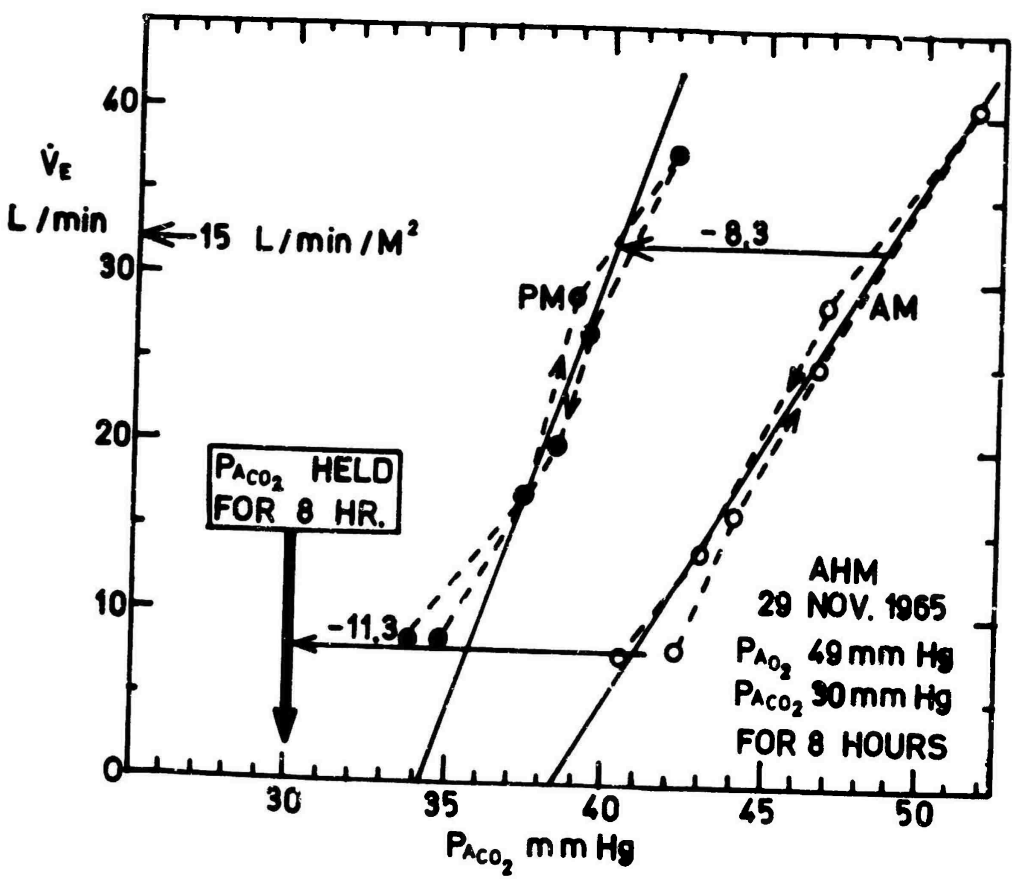

Figure 3. A typical pair hyperoxic CO_2 response curves from one subject before and after 8 hours of hypocapnic hypoxia, showing the characteristic shift to the left that occurs with this amount of acclimatization. The lines were calculated by the method of least squares from the 5 points obtained during CO_2 inhalation. The two horizontal arrows represent the degree of hypocapnia and the leftward shift of the CO_2 response, which are the coordinates of Fig. 4 (Data of Eger, et al.[4]).

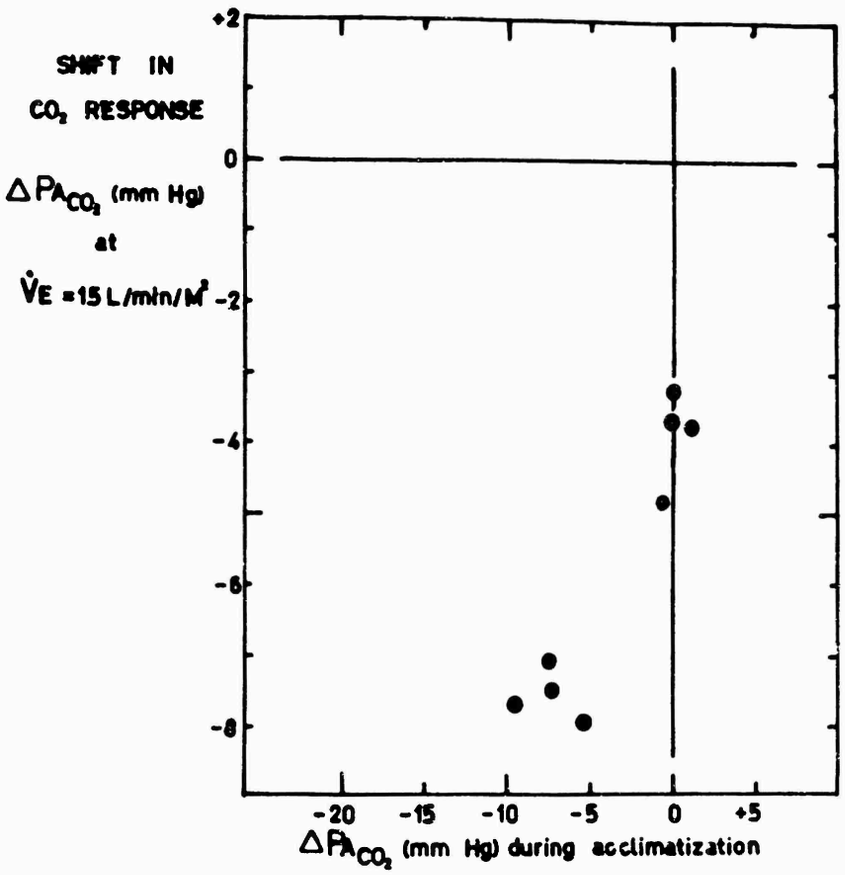

Figure 4. Shift of hyperoxic CO_2 response produced by 8 hours of hypoxia (PAO_2 = 45-50 mm Hg) with spontaneous hypocapnia ($PICO_2$ = 0) and with controlled normocapnia in each of 4 subjects. Each dot summarizes the result of an experiment similar to that shown in Figure 3. (Data of Eger et al. (4).)

which the subject merely breathed air from the apparatus with the same day's program as in hypoxia (Fig. 5).

Thus it appeared that hypocapnia was probably necessary for production of the shift in CO_2 response, but did hypoxia contribute to it in any way? To answer this question, we did a parallel series of normoxic experiments in which alveolar PCO_2 was held at various levels by mechanical or voluntary hyperventilation for 8 hours of acclimatization while hypoxia was prevented by holding the alveolar PO_2 above 100 mm Hg. The results (Fig. 6) show that graded hypocapnia alone produced a proportional shift in hyperoxic CO_2 response, but when there was hypoxia as well as hypocapnia, the shift in hyperoxic CO_2 response in 8 hours was about twice as great. Thus in some way hypoxia interacts with hypocapnia in causing the shift in position of the CO_2 response curve seen in altitude acclimatization. Since the CSF bicarbonate

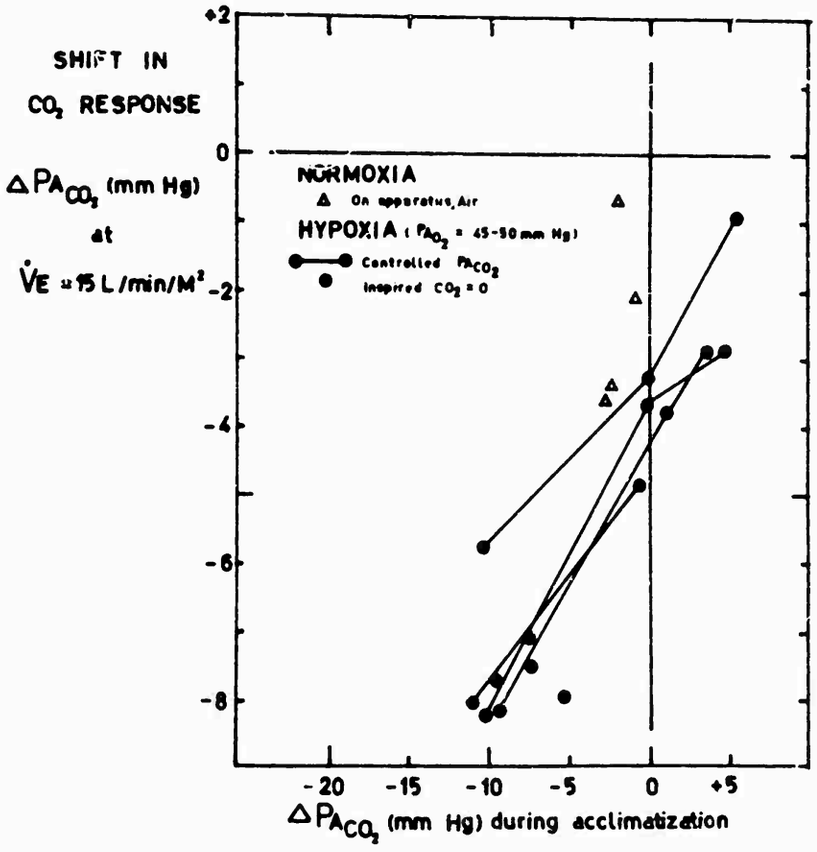

Figure 5. Shift in hyperoxic CO_2 response produced by 8 hours of hypoxia, plotted as a function of the controlled $PACO_2$ that accompanied the hypoxia in each of 4 subjects. Shown for comparison are results of 8 hours of breathing air or a hypoxic mixture on the same apparatus at the same time of day. (Data of Eger et al. (4).)

is known to fall in altitude acclimatization in an appropriate amount to account for the shift in CO_2 response, we presume that hypoxia interacts with hypocapnia in causing a rapid decrease in CSF bicarbonate concentration.

The mechanism of the fall in CSF bicarbonate concentration is still not clear. Plum and Posner (14) have reported very large increases in lactate concentration in CSF in hypocapnia, with still greater increases when there is also hypoxia. Thus one possibility is that CSF bicarbonate falls as a result of lactic acid accumulation from brain metabolism in hypoxia. The brain hypoxia would be accentuated by hypocapnia, which tends to reduce cerebral blood flow.

It seemed to me that for definitive information to be obtained, we needed an experimental animal that would provide a model of the system, for analytical experiments that could not be done on

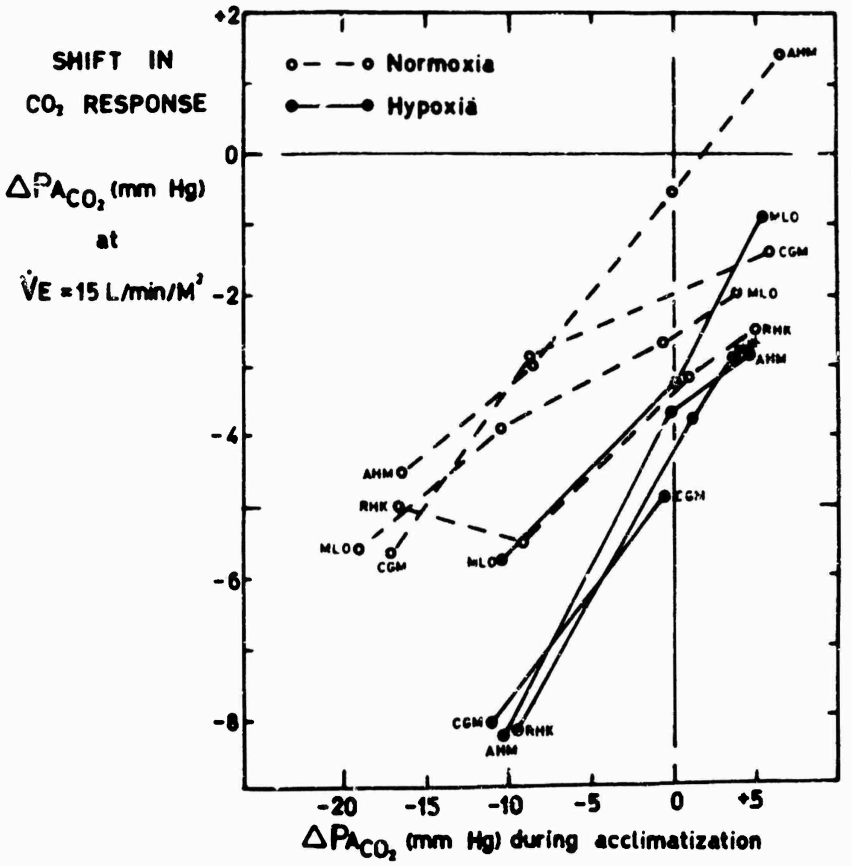

Figure 6. Shift of hyperoxic CO_2 response produced by 8 hours of controlled $PACO_2$ with and without hypoxia in each of 4 subjects. (Data of Eger et al. (4).)

man. We have therefore begun to investigate goats, which are of convenient size, docile, accustomed to standing still in a stanchion for long periods without special training, and provided with horns that constitute a natural shield for implants in the skull. We got the idea, of course, from Pappenheimer, who has been studying their CSF in relation to the regulation of breathing (13). Unlike Pappenheimer, we have used a tracheostomy so that all ventilatory measurements are carried out through an endotracheal tube, obviating any problems with potentially leaky masks or with gaseous eructation from the rumen. We have used both females and castrated males, but we prefer the latter to avoid possible progesterone effects on respiration during the sexual cycles. We have encouraging preliminary data on a number of points:

1) In normal goats, acute reduction of alveolar PO_2 to about 40 mm Hg immediately stimulates breathing and usually increases the slope of the CO_2 response curve. In this respect, our results with goats seem more like the well-known relationships in man than did the results obtained by Tenney and Brooks (16) using a mask on goats at a higher PO_2.

2) Hypoxia (alveolar PO_2 about 40 mm Hg) with varying degrees of hypocapnia shifts the CO_2 response curve about 4-10 mm Hg in 4 hours, whereas even more severe hypocapnia without hypoxia produces only a 2 to 6.5 mm Hg shift. In these experiments, the CO_2 response curve is measured with alveolar PO_2 of about 200 mm Hg to eliminate hypoxic interaction during the test and distinguish the persistent effect of acclimatization. However, unlike man, the goats do not seem to show a clear proportionality between the degree of hypocapnia and the magnitude of the shift in CO_2 response. The shift seems to be just about as great when the PCO_2 has been held within 5 mm Hg below normal as it is when the PCO_2 is held 22 mm Hg below normal. The reason for this is not clear. Perhaps hypoxia alone produces such an overwhelming effect that hypocapnia is irrelevant.

3) Two goats taken to the Barcroft Laboratory of the White Mountain Research Station (3,800 m or 12,470 ft.) for 8 weeks during the summer showed a typical shift of CO_2 response to the left with some steepening of its slope. These changes persisted all summer. Thus in this aspect of adaptation to altitude, goats seem to resemble man rather than sheep or cattle (6), which Reeves and Grover have reported to hyperventilate only transiently when taken to a similar altitude in Colorado.

I would like to emphasize once again that all these statements about goats should be considered as preliminary interpretations and working hypotheses based on only a few experiments. Thus we may have to revise our views with more experience. We have just completed what we think is our first successful implantation of a cannula for sampling CSF from the unanesthetized and undisturbed goat, and soon we will be examining the changes in CSF during experiments of the sorts that I have outlined. Thus it is premature to dwell on our conclusions or even to present quantitative data at this point. But I thought it might be worthwhile in a small conference such as this to give you some idea of the way our current work seems to be heading, and to point out the usefulness of the goat as an experimental animal in which respiratory aspects of altitude acclimatization can be studied with experimental procedures that could not be performed on man.

ACKNOWLEDGMENTS

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SOME TISSUE FACTORS IN ACCLIMATIZATION TO HIGH ALTITUDE*

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Under normal conditions at sea level, venous PO_2 is about 40 mm Hg but in the region of mitochondria it is less than 5 mm Hg, hence the "tissue PO_2 gradient" is about 35 mm Hg. It has been determined experimentally that O_2 uptake in a limb does not decrease until venous PO_2 falls below 25 mm Hg (1), but mitochondria, studied *in vitro*, show no change in O_2 uptake until PO_2 is less than 5 mm Hg (2). Clearly, the essence of the metabolic problem, when viewed in this direct way, is in the diffusion resistance of the tissue. The normal PO_2 gradient is sufficient to assure adequate flow of O_2, but below some critical value, probably about 20 mm Hg, the resistance is too high for that pressure head, and O_2 conductance falls. The immediate consequence is inadequate O_2 in the vicinity of aerobic enzymes at the mitochondria and rate of O_2 consumption is observed to decrease.

At least in man, basal oxygen consumption at high altitude proceeds at the same rate that it does at sea level (3). Since, even under normal sea level conditions, the PO_2 in the region of mitochondria is very nearly zero, there is almost no room for compromise at the site of oxidative enzymes. Further, in spite of a number of effective regulatory processes at high altitude, serving to diminish each of the series of decrements in PO_2 which occur between mouth and venous blood, the fully acclimatized individual, even under resting conditions, still carries a venous PO_2 about 10 mm Hg below that at sea level. Hence, even though tissues at altitude are always exposed to oxygen at a low pressure head, they still manage to maintain normal oxygen uptake. Since extra-

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vascular oxygen flux is principally diffusional, and given the above conditions, some adaptation(s) is required. There are three possibilities. 1) Increase capillary density (number of capillaries per unit of tissue mass) and thereby shorten diffusion distance between source and sink. 2) Increase cellular aerobic capacity by increasing the amount, or affinity of enzymic terminal oxidases. 3) Alter metabolic paths, either by shifting to anaerobic paths, or to those oxidases with a lower critical PO_2.

Diffusion from Capillary to Cell and Tissue $\bar{P}O_2$

Tissue Capillarity. There is abundant morphological evidence to indicate that fully acclimatized animals have more blood-filled capillaries per unit of tissue (4-6), but there are no data on the functional capacity of the bed, nor is there information concerning such questions as extent of change as a function of altitude, time rate of change at any given altitude, or the possible mechanisms of any change observed. With these questions in mind a technique to measure the "diffusion capacity" of a tissue has been developed and employed in rats exposed to simulated altitudes in low pressure chambers. The procedure utilizes low concentrations (0.3%) of CO whose disappearance is measured in subcutaneous gas pockets. When ancillary physiological factors are controlled (age of pocket, pocket PO_2, and pocket volume), highly reproducible results are obtained.

In normal, sea level rats the exponential constant for disappearance rate is 10.4 ± 0.15, and the average half-time is 65 min. In rats exposed to one half atmosphere pressure (equivalent altitude, 5500 m) the rate constant increases somewhat erratically during the first two weeks, but after the third week it is about double sea level control value. Packed red cell volume follows a similar time course, but control experiments in which the red cell mass was changed in sea level rats, permitted an evaluation of the hemoglobin concentration effect on tissue diffusion. Similarly, blood flow and other tissue (i.e. extravascular) components were also evaluated by studying CO flux rates in exsanguinated and in recently sacrificed animals. By "correcting" the original rate constant for these contributing factors, an index of capillary surface area can be inferred, and if capillary radius is assumed not to have changed, this gives directly an index of capillary number. On these bases, it appears that the number of capillaries per unit of tissue pocket surface area increased between 20 and 30% as a result of 3 weeks of altitude (5500 m) exposure. With the Krogh-Erlang model, the effect of this change on tissue PO_2 was calculated and

compared with PO_2 measured in the pocket. The latter is known to approximate regional venous PO_2, and although this value is very likely near mean tissue PO_2, principal interest is focused on minimal tissue PO_2, i.e., at the periphery of the diffusion cylinder near the venous capillary segment. Theoretical calculations place the value at about 20 mm Hg normally (i.e., when a regional venous PO_2 = 40 mm Hg) but it would be zero at altitudes of 4500 m and above (pocket PO_2 is 15-20 mm Hg in rats acclimatized to 5500 m) if capillarity did not change. If capillarity changes to the extent inferred from the diffusion capacity measurements, minimal tissue PO_2 is estimated to be about 5 mm Hg at 5500 m.

The effect of three weeks of exposure to different simulated altitudes revealed no effect on capillarity below 3800 m. Viewed in these terms, that altitude appears to be at "threshold".

Attempts to measure maximal tissue diffusing capacity to determine whether the observed increase of capillarity was the result of newly formed capillaries, or simply the result of more filled capillaries (under resting conditions) in an unchanged total vascular bed, were equivocal. Further studies on this point are currently underway, but the tentative conclusion, based on these studies with mature animals, is that the altitudinal effect on capillarity is the result of opening a portion of the normally unfilled capillary bed, possibly a simple mechanical distention associated with the increased blood volume.

Mitochondria, Electron Transport, and Enzymic Activity in Heart Tissue of Cattle Acclimatized to 4300 m.

Mitochondria and respiratory capacity. Mitochondrial counts (expressed either per unit of wet weight, or per unit of tissue protein) in heart muscle from cattle raised at sea level and cattle raised at an altitude of 4300 m revealed a 30% increase in the high altitude tissue. Counts expressed per mg of mitochondrial protein were the same in both populations, indicating that mitochondrial size did not change. Increase in overall activity of the electron transport chain was demonstrated in both succinoxidase and DPNH oxidase activity. Differential absorption spectra (kindly obtained by Dr. L. Smith) indicated that cytochrome oxidase a_3 concentration in high altitude mitochondria was 20% increased, but no qualitative difference could be discerned. The % increase in a_3 concentration coincided with the measured increase in mitochondrial oxygen uptake rate (succinate as substrate), hence there is probably no change in the turnover number.

The physiological significance of the increase in mitochondrial number is not clear, although it is obvious that mitochondrial surface area in the cell is thereby increased, and this may be useful in shortening the intracellular diffusion distance which an oxygen molecule must travel to reach an enzyme site. The increases of [a_3] will have a predictable kinetic effect on rate of oxygen uptake, and equivalent rates can be obtained at lower PO_2 with higher [a_3]. The magnitude of conserved pressure head is about 1 mm Hg, a small value in terms of the total tissue diffusion gradient, but important in the concept of "critical PO_2" and cytochrome:O_2 association. Because of the effect of [a_3] on V_{max}, the increase of heme-protein may be especially important in exercise.

"Critical PO_2". The PO_2 at which mitochondrial oxygen uptake rate begins to decrease was found, *in vitro*, to average 0.5 mm Hg, a lower value than reported in earlier work (2), and there was no difference between sea level and high altitude preparations in this regard. The experimental value is close to that calculated for the electron transport chain, which would mean that there is no diffusion barrier in the mitochondrial membrane and the "critical" PO_2 is an inherent property of the enzyme in the transport chain.

Tissue Chemistry of Rats Acclimatized to 5500 m.

Respiratory Control Ratio and Respiratory Capacity in Liver Mitochondria. Oxygen uptake rates in rat liver mitochondrial preparations after added substrate (phase II), substrate plus ADP (phase III), and after added ADP is used up (phase IV) were compared. Although high altitude mitochondria (from rats acclimatized to 5500 m) had a higher oxygen uptake rate with added substrate, sea level and high altitude mitochondria had comparable values when ADP was also added (i.e. respiratory capacity was the same). [This contrasts with the increased electron transport system in beef heart tissue.] On the other hand, the high altitude rat liver mitochondria had a higher uptake rate after the added ADP had been completely phosphorylated. These results suggest a higher level of ADP or other endogenous substrate in high altitude mitochondria, and increased mitochondrial ATPase. The respiratory control ratios (phase III/phase II) were the same for some substrates (succinate and α-keto-glutarate) but lower for others (β-OH butyrate, glutarate, and pyruvate) in high altitude mitochondria. P:O ratios were the same in all and indicated tightly coupled preparations. The efficiency of oxidative phosphorylation in sea level and high altitude mitochondria is the same. Based on

the evidence for increased ATPase activity we infer a greater fragility of high altitude mitochondria.

Lactate dehydrogenase. The activity of this enzyme was less in high altitude rat heart than in sea level heart, but in all other tissues studied (brain, liver, kidney, thymus) no change was seen. In rats exposed to higher altitudes there is evidence for increased anaerobic glycolysis (7).

Myokinase-Adenylic Acid Kinase – Phosphonucleotide Transferase. No change in activity of these enzymes was seen except in heart muscle where myokinase activity from high altitude animals was about 50% of that measured in sea level animals. Myokinase catalyzes the reaction ADP=ATP + AMP, and its physiological significance is to furnish ATP under anaerobic conditions. The low level in heart muscle is of particular interest because of the higher aerobic capacity of acclimatized heart tissues.

Evidence for Change in Pentose-Phosphate Shunt. G-6-P dehydrogenase activity was the same for all tissues examined, but the activity of 6-G-P dehydrogenase was lower in most tissues taken from high altitude animals. From these results it appears unlikely that the pentose-phosphate shunt pathway is used in high altitude acclimatized animals to furnish ATP, a conclusion at variance with some other studies (8). In fact, since the shunt is normally the source of various precursors for synthesis of steroids, fatty acids, and polynucleotides, the synthetic capacity for these substances may be decreased in high altitude acclimatized animals.

Conclusions

In animals acclimatized to high altitude (4500-5500 m.): 1. The principal mechanism insuring adequate flow of oxygen from capillaries to cells is an increase of tissue capillarity, thus shortening diffusion distances. The "tissue diffusing capacity" is increased twofold in rats acclimatized to 5500 m. for 3 weeks. The estimated saving in pressure drop is about 10 mm Hg.

2. In the beef heart, mitochondrial number is increased, mitochondrial cytochrome oxidase [a_3] content is increased, and aerobic metabolic capacity is increased. The magnitude of effective conservation of oxygen pressure head by these changes, is less than 1 mm Hg; but the effect on "critical PO_2" and on exercise requirements may be great.

3. In rat liver, aerobic capacity is not increased and the respiratory control ratio is the same as at sea level.

4. Mitochondria may contain more ADP, have more ATPase

activity, and may be more fragile than sea level mitochondria.

5. There is no evidence for increased anaerobic activity. Myokinase activity of high altitude heart is half that of sea level heart.

6. The pentose-phosphate shunt is either unchanged or less active than at sea level. In the liver, this could mean that some synthetic processes (e.g., steroids) may be compromised in order to save energy for other more essential physiological functions.

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ROLE OF THE AUTONOMIC NERVOUS SYSTEM IN SYSTEMATIC CIRCULATORY RESPONSES TO ACUTE HYPOXIA

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Man

Acutely-induced hypoxia in man is accompanied by increase in cardiac output, heart rate, and forearm blood flow (1), by decrease in blood flow to the hand (2), and by little change in systemic arterial blood pressure. Similar changes accompany intravenous administration of epinephrine (3, 4). To evaluate the possibility that increased circulating catecholamines or increased sympathetic neural activity contribute to the circulatory responses to acute hypoxia, we observed the effects of blockade of beta-adrenergic receptors on cardiac output and rate during hypoxia; measured the concentration of catecholamines in arterial blood; and looked for modification, by local blockade of alpha and beta-adrenergic receptors, of the responses of forearm blood vessels to hypoxia induced by inhalation of 7.5% oxygen in nitrogen by healthy men (5).

The effects of beta-adrenergic blockade with pronethalol on the circulatory responses to hypoxia in 10 healthy men are shown in Fig. 1. Prior to pronethalol, hypoxia induced by breathing 7.5% oxygen in nitrogen for 10 minutes was accompanied by reduction in arterial oxygen tension from 90 to 34 mm Hg, and by 54 per cent increase in cardiac output, measured by indicator dilution, and 41 per cent increase in heart rate. During beta-adrenergic blockade induced by pronethalol 0.8 to 1.5 mg/kg intravenously, similar reduction in arterial oxygen tension was accompanied by significantly less increase in cardiac output (27%) and in heart rate (30%). Similar results were obtained in seven additional subjects after intravenous infusion of 5 mg of propranolol. The effectiveness of beta-adrenergic blockade was tested by intravenous infu-

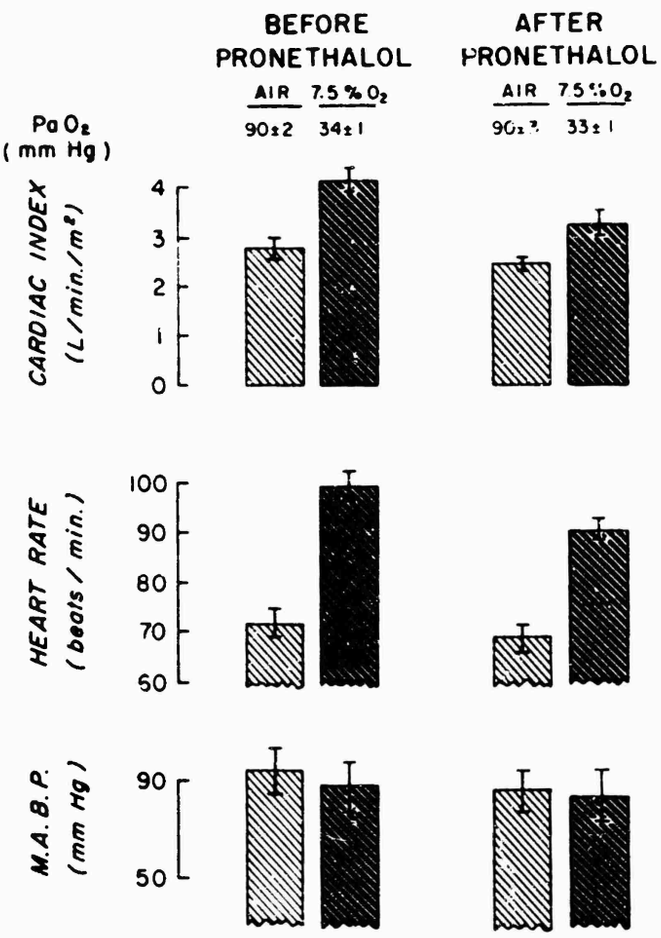

Figure 1. Modification by intravenous pronethalol of systemic circulatory responses to acute hypoxia. The bars represent the mean, and the line above and below the top of each bar the standard error, of 10 experiments in 10 healthy men.

sion of epinephrine 10 µg/min, which produced bradycardia and hypertension in each subject after pronethalol and propranolol.

These results suggest that activation of sympathetic cardiac nerves or increase in the concentration of catecholamines in the blood participate in the tachycardia and increased cardiac output which accompany hypoxia in man. To determine the contribution of circulating catecholamines to these circulatory effects of hypoxia, we measured the concentration of epinephrine and norepinephrine in arterial plasma, using the trihydroxyindole acetic acid method (6). As shown in Figure 2, plasma catecholamine concentration did not increase significantly in six subjects during inhalation of 7.5% oxygen for 10 minutes. In four of these subjects, intravenous infusion of epinephrine, 10 µg/min for 10 minutes, produced five-fold increase in plasma epinephrine concentration.

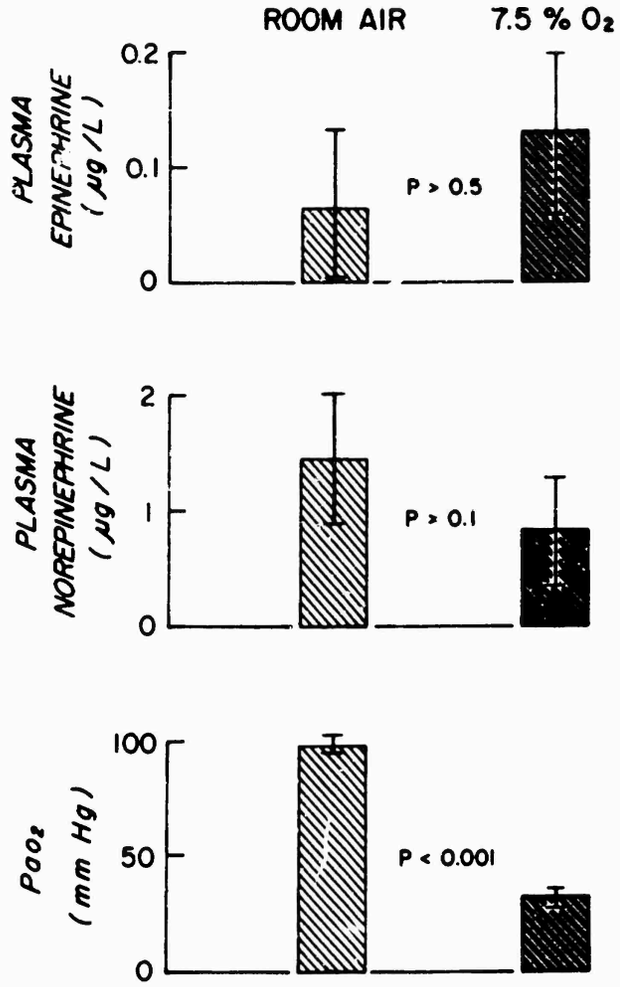

Figure 2. Effect of inhalation of 7.5% oxygen for 10 minutes on the concentrations of epinephrine and norepinephrine in arterial plasma. The figure shows the mean and standard error of the mean in 6 experiments in 6 subjects.

Because of the possibility that small increase in the concentration of catecholamines might have occurred without being observed by the method of determination, we next studied the effect of blockade of adrenergic receptors on the responses of the forearm blood vessels to hypoxia. Figure 3 shows that intra-arterial pronethalol had no effect on the increase in forearm blood flow accompanying hypoxia, although pronethalol completely blocked the increase in blood flow induced by intravenous epinephrine, 10 μg/min. Blockade of alpha-adrenergic receptors with intra-arterial phenoxybenzamine greatly enhanced the vasodilator response to intravenous epinephrine, but did not markedly affect the vasodilator response to acute hypoxia, as shown in the middle section of Figure 3. The combination of alpha and beta-adrenergic blockade with intra-arterial pronethalol and phenoxybenzamine abolished the forearm vasodilation produced by intravenous epine-

phrine, but, as shown in Figure 3, did not modify the increase in forearm blood flow accompanying hypoxia.

Hypoxia did not increase the concentration of catecholamines in arterial blood. Pharmacologic agents, which abolish or enhance

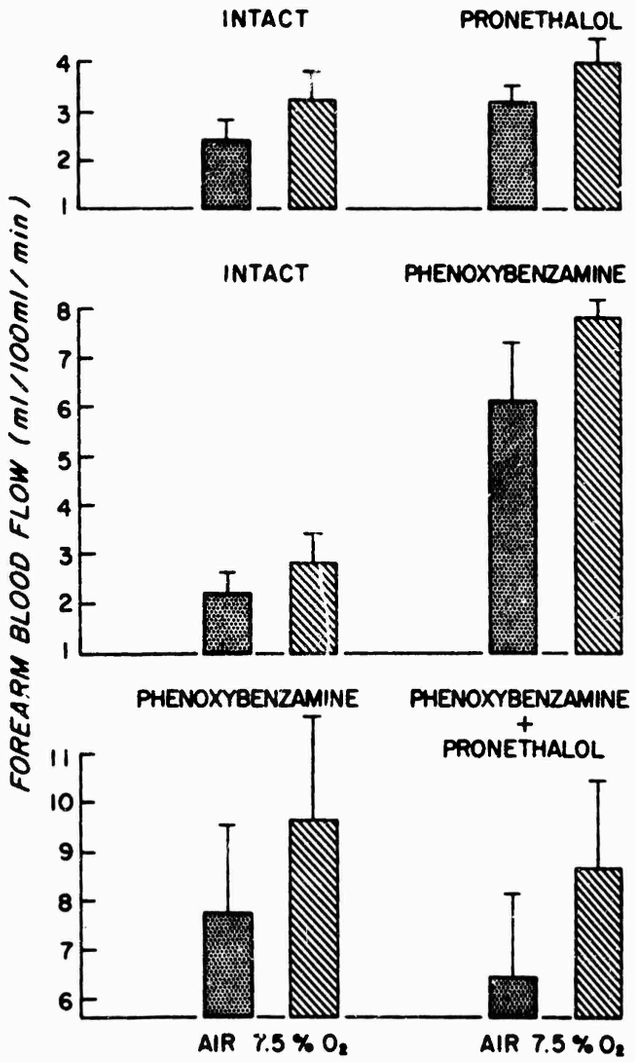

Figure 3. The effect of beta and alpha-adrenergic blockade on the change in forearm blood flow accompanying hypoxia. The four bars at the top represent mean results in 6 subjects who breathed 7.5% oxygen for 10 minutes after blockade of beta receptors in one forearm by injection of 15 mg of pronethalol into the brachial artery. The middle group of bars shows mean forearm blood flow in 6 subjects who breathed 7.5% oxygen after phenoxybenzamine 8 mg was injected intra-arterially in one arm. The four bars at the bottom represent mean forearm blood flow in 7 subjects who breathed 7.5% oxygen after 8 mg of phenoxybenzamine had been injected intra-arterially and again after 15 mg of pronethalol had been injected into the same brachial artery.

the responses of forearm vasculature to intravenously infused epinephrine, failed to modify the effects of hypoxia on forearm blood flow. These results suggest that hypoxia does not affect the human circulation by means of increase in circulating catecholamines. Since pronethalol and propranolol significantly reduced the tachycardia and increased cardiac output which accompany acute hypoxia, these circulatory alterations are probably partially mediated by activation of cardiac sympathetic nerves. Propranolol and pronethalol did not abolish completely the increase in cardiac rate and output which accompanies hypoxia, either because the doses used did not completely block the beta receptors, or because of operation of other compensatory mechanisms leading to elevation of cardiac output, such as increased venous return due to venoconstriction, or release of vagal inhibition of the heart. The possibility that we did not achieve complete blockade of beta-adrenergic receptors is supported by the recent observations of Edelman, Richards and Fishman (7) that hypoxia produced bradycardia in six patients with familial dysautonomia.

Dog

In unanesthetized, trained dogs previously fitted with an electromagnitic flowmeter on the aorta, inhalation of 7% oxygen for 7-10 minutes (Fig. 4) reduced arterial oxygen tension to 32 mm Hg, and was accompanied by increase in cardiac output, cardiac rate, and systemic arterial pressure. As shown in Figure 4, intravenous propranolol, 1 mg/kg, abolished the increase in cardiac rate and output accompanying quantitatively similar reduction in arterial oxygen tension. The dose of propranolol used was sufficient to prevent tachycardia during electrical stimulation of the stellate ganglion and to markedly diminish tachycardia during electrical stimulation of the mesencephalic central grey substance (Fig. 5).

Propranolol blocks the cardiac effects of circulating catecholamines, in addition to the cardiac effects of activation of the sympathetic nervous system. To evaluate the contribution of increased concentration of catecholamines released from the adrenals, Dr. Kontos induced hypoxia in six unanesthetized dogs before and after bilateral adrenalectomy. As shown in Figure 6, adrenalectomy did not reduce the tachycardia or the increased cardiac output associated with hypoxia.

Thus in the intact dog the observed modification by propranolol of increased cardiac output and rate during acute hypoxia was not the result of blockade of the cardiac effects of catecholamines released from the adrenal glands, and presumably resulted from

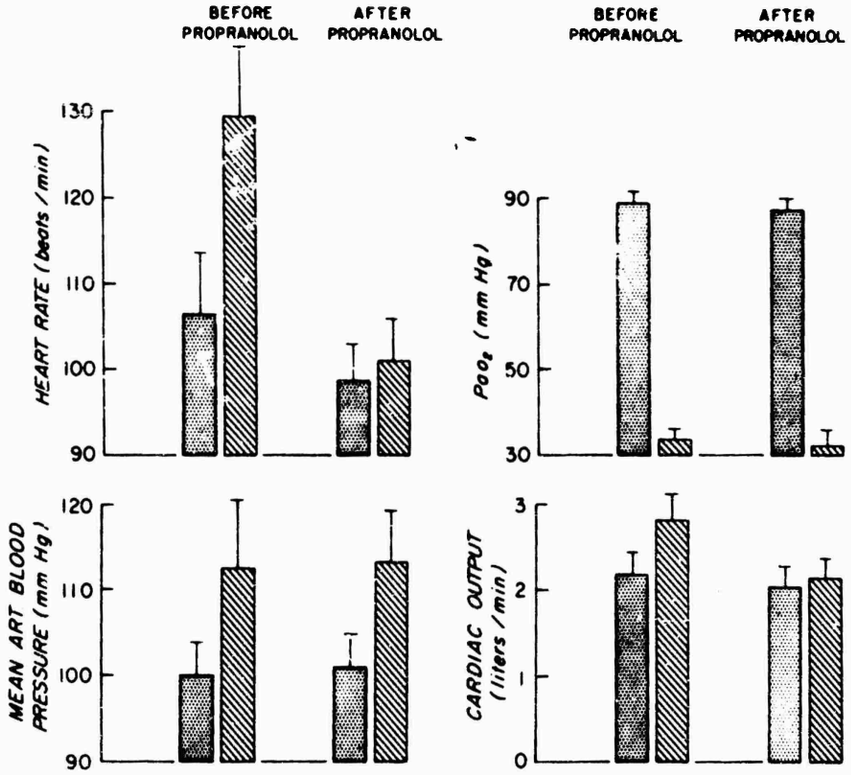

Figure 4. Effects of intravenous propranolol on systemic circulatory responses to inhalation of 7% oxygen in 11 unanesthetized dogs. Bars represent the mean value for the 11 experiments. The line above each bar represents the standard error of the mean.

blockade of the effects of hypoxic activation of cardiac sympathetic nerves.

The mechanisms by which hypoxia increases sympathetic activity are not completely understood. Stimulation of carotid chemoreceptors seems not to play an important part for the following reasons:

1) In dog (8), and cat (9), stimulation of carotid chemoreceptors with hypoxic blood when ventilation was kept constant resulted in bradycardia and decrease in cardiac output and contractile force, which were abolished by vagotomy.

2) In man, chemoreceptor stimulation with cyanide also produced bradycardia (10).

3) Removal of carotid chemoreceptors from two asthmatic patients resulted in abolition of hyperventilation, but did not alter the tachycardia produced by inhalation of 10% oxygen (11).

Downing, Mitchell, and Wallace (12) demonstrated tachycardia during perfusion of the canine brain with hypoxic blood, and Alexander (13) showed that anoxia increased the frequency of

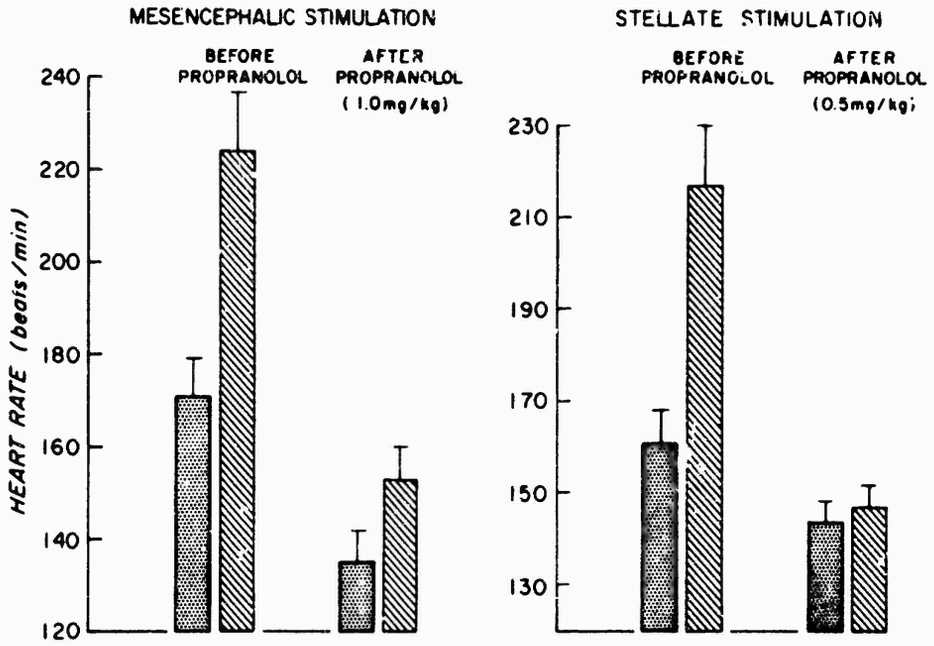

Figure 5. Effect of propranolol on the tachycardia induced by electrical stimulation of mesencephalic gray substance (left) and of stellate ganglion (right). Eleven dogs were studied during mesencephalic stimulation and 6 during stimulation of the stellate ganglion.

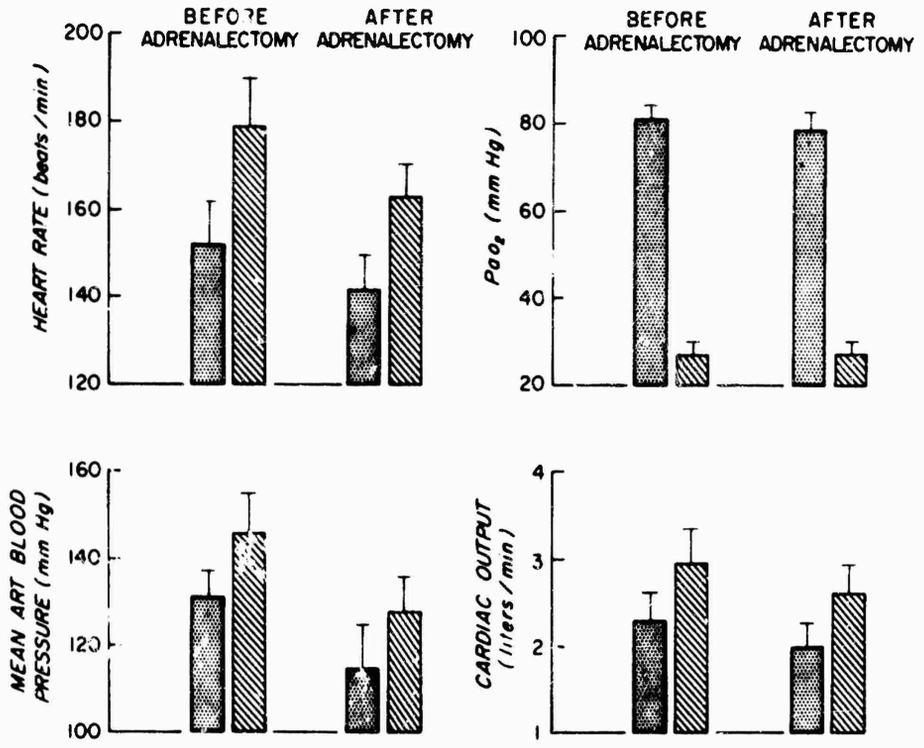

Figure 6. Change in circulatory responses to hypoxia after adrenalectomy in 6 anesthetized, spontaneously breathing dogs.

impulses in the inferior cardiac nerve despite elimination of all afferent connections to the spinal cord. Hence, it is possible that central neural hypoxia is responsible for activation of the sympathetic system.

Parasympathetic Nervous System

The vagus nerves participate in the systemic circulatory responses to hypoxia in two major respects:

A. Hypoxia was associated with tachycardia and increased cardiac output in the spontaneously breathing dog. However, hypoxia produced bradycardia without change in cardiac output in dogs whose ventilation was maintained constant, by paralysis of skeletal muscles or by opening the chest, at the level present during inhalation of room air (14). Similarly, hypoxia produced bradycardia and did not alter cardiac output in dogs whose lungs had been denervated by cutting their vagal fibers (15). Thus in the dog, afferent nerves from the lung, traveling in the vagi, stimulated by the increased ventilation which accompanied hypoxia, were necessary for normal systemic circulatory responses to hypoxia. In man, however, increased ventilation without change in arterial CO_2 tension was not accompanied by change in cardiac output or rate (16), and it seems unlikely that pulmonary stretch reflexes play a role in the human circulatory response to hypoxia.

B. The bradycardia which accompanied hypoxia in dogs whose ventilation was kept constant was converted to tachycardia by (1) prior administration of atropine, as shown in Fig. 7, and (2) previous inactivation of the carotid chemoreceptors by intracarotid injections of acetic acid, as shown in Fig. 8. Thus in the dog, hypoxia activates parasympathetic cardio-inhibitory nerves by stimulation of carotid chemoreceptors. In the spontaneously breathing animal, this effect is antagonized by a mechanism related to increased ventilation, probably a reflex whose afferent limb lies in vagal fibrs from the lungs.

In the intact dog, the systemic circulatory changes which accompany acute hypoxia depend on the balance between increased sympathetic and increased vagal activity, and on the amount by which ventilation increases. It is probable that other mechanisms not related to beta-adrenergic stimulation participate in increase in cardiac output and rate which accompany hypoxia. Among these other mechanisms may be a direct effect of hypoxia on the heart, as shown by Ng et al (17), who demonstrated increased contractile strength in the paced, isovolumetric canine left ventricle when the oxygen saturation of blood perfusing the coronary arteries was reduced to 50-70 per cent.

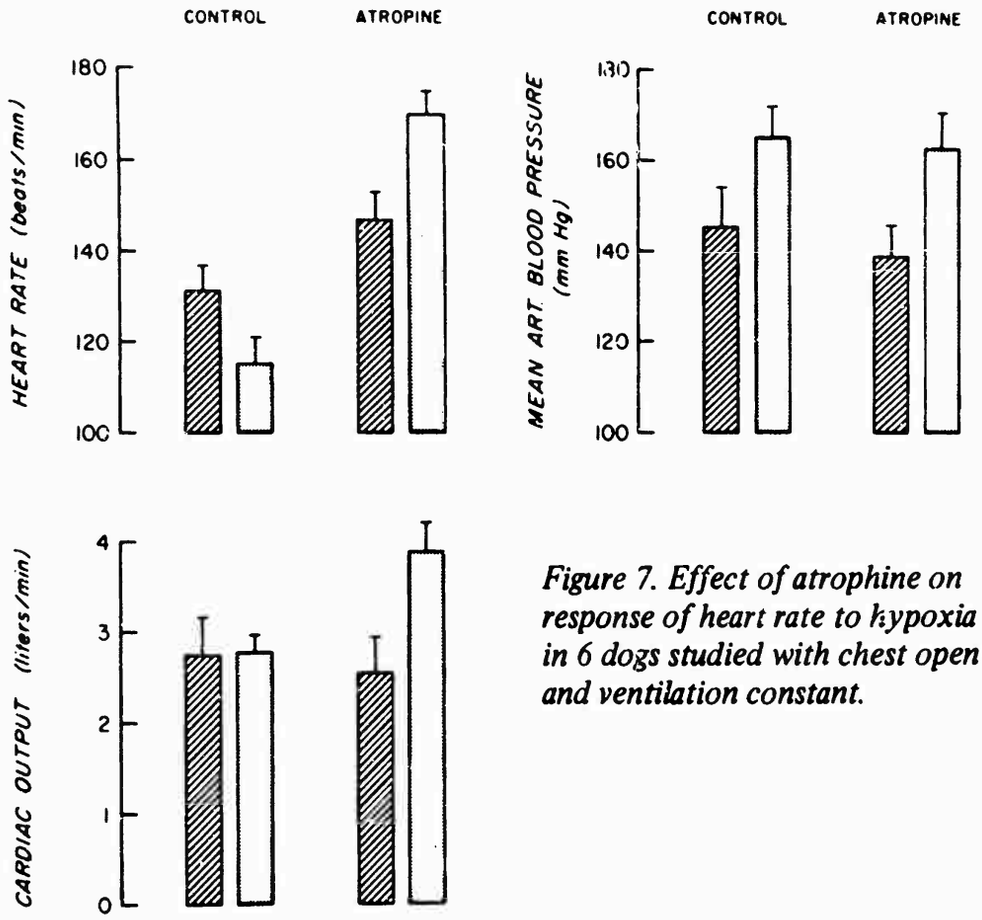

Figure 7. Effect of atrophine on response of heart rate to hypoxia in 6 dogs studied with chest open and ventilation constant.

Summary

In man, beta-adrenergic blockade with pronethalol or propranolol, in dosage sufficient to abolish tachycardia with intravenous isoproterenol, reduced, but did not abolish the tachycardia and increase in cardiac output which accompanied inhalation of 7.5% oxygen for 10 minutes. Measurement of catecholamine concentration in arterial blood during hypoxia, and pharmacologic evidence from blockade of alpha and beta receptors in the forearm suggest that the circulatory responses to hypoxia are not mediated by increase in circulating catecholamines. Thus activation of cardiac sympathetic nerves is probably responsible for part of the tachycardia and increase in cardiac output with hypoxia. The failure of pronethalol and propranolol to abolish the circulatory responses to hypoxia may result from incomplete blockade of beta-adrenergic stimulation by sympathetic nerves, or may indicate participation of other non-adrenergic mechanisms in the human circulatory responses to hypoxia.

In the intact dog, propranolol, in a dose sufficient to abolish the effects of electrical stimulation of the stellate ganglion, abolished the tachycardia and increased in cardiac output which

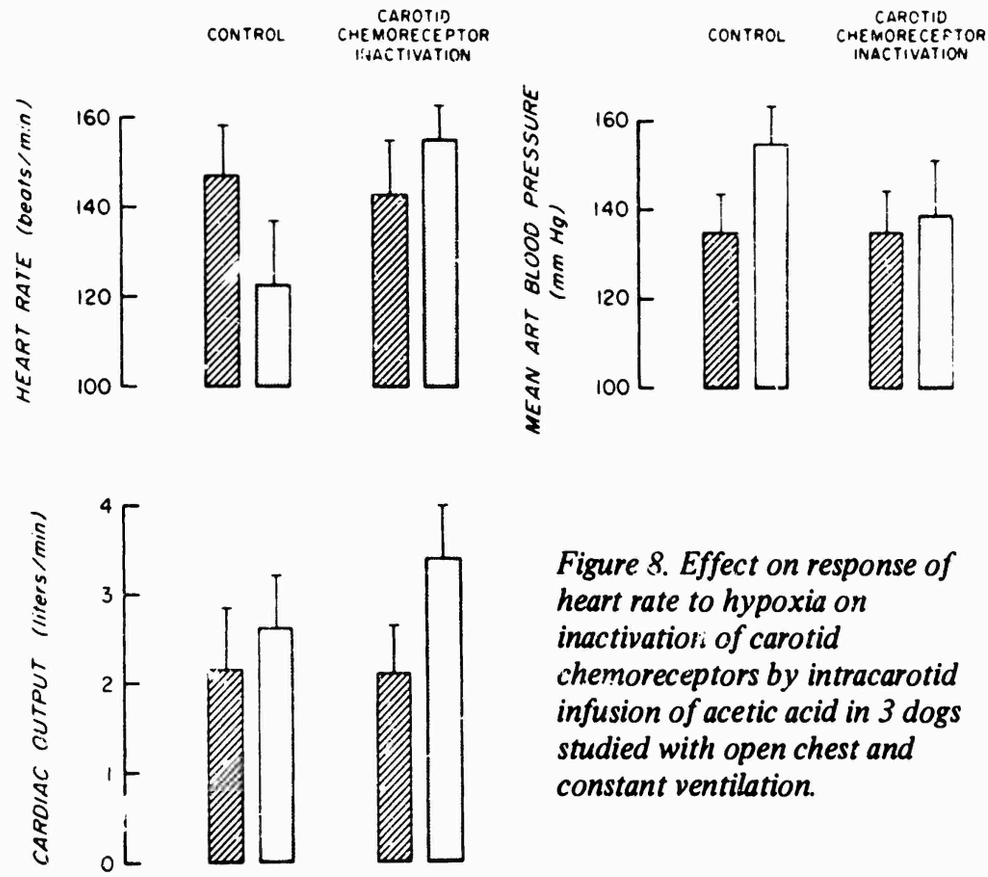

Figure 8. Effect on response of heart rate to hypoxia on inactivation of carotid chemoreceptors by intracarotid infusion of acetic acid in 3 dogs studied with open chest and constant ventilation.

accompanied hypoxia. Adrenalectomy did not alter these effects of hypoxia. Hence the increase in cardiac output and rate with hypoxia in the dog are probably mediated by activation of sympathetic nerves. Hypoxia also is accompanied by increased vagal activity in the dog. In the spontaneously breathing animal, the systemic circulatory changes during acute hypoxia depend on the balance between increased sympathetic and increased vagal activity, on the amount by which ventilation increases, and probably on other mechanisms not related to autonomic stimulation.

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GENERAL DISCUSSION

DR. LAWSON: Dr. Kellogg, would the increased amount of reduced hemoglobin during the hypoxic breathing and its associated increase in buffering capacity, lower tissue PCO_2? Could you explain part of the effect of hypoxia in the absence of hypocapnia in changing the response to ventilation?

DR. KELLOGG: At the time we measured the CO_2 responses, we had restored the oxyen and resaturated the hemoglobin. In fact, to be sure of this we routinely measured hyperoxic CO_2 response curves, holding the inspired PO_2 around 200 mm Hg. During the period of acclimatization to hypoxia, on the other hand, the blood is desaturated and the exact brain tissue PCO_2 is not clear. One can make guesses about it from what is known about blood dissociation curves, brain metabolism, and blood flow, taking into account the reduced hemoglobin. The simplest way to look at this is to consider the arterial PCO_2 and then the arteriovenous difference in PCO_2 across the brain. It quickly becomes apparent that the crucial variable in determining the venous and tissue PCO_2 at any given alveolar PCO_2 is the blood flow. Unfortunately, I do not know any really reliable data from which the blood flow in the appropriate region can be accurately predicted under our particular combinations of hypoxia and hypocapnia and with our time-course of changes.

DR. GROVER: We have made some measurements recently which indicate that in chronic polycythemia in man and in acute polycythemia in animals, the ventilatory response to CO_2, that is, the slope of the CO_2 response curve, is decreased significantly (1). I think Dr. Hurtado has reported a similar observation in men with chronic mountain sickness (2).

DR. TENNEY: If you extrapolate the problem in the other direction and study anemia, there is no change in resting ventilation and there is no change in the CO_2 response curve. There is only a change to the response to exercise.

DR. LAWSON: Dr. Tenney, if the carbon monoxide concentration which you used were very high (like three percent), the hemoglobin would be saturated before it left the pocket and the uptake of CO would be flow limited. If the concentration were lower (less than one percent), then it would be diffusion limited. Did your findings indicate that?

DR. TENNEY: The CO uptake rate as a function of the initial pocket CO concentration of course had to be done in order to standardize the method. We used, routinely, 0.12 percent CO, in which case the rate of gas uptake is diffusion limited.

DR. MONGE: Were any of the animals that you used for your mitochondrial counting experiments born in the altitude or taken up to altitude?

DR. TENNEY: The cattle on whom the heart mitochondrial counts were made were born at altitude.

DR. MONGE: Have you compared animals taken up to altitude?

DR. TENNEY: No, only in this case, rats.

DR. MONGE: Did they show mitochondrial increase too?

DR. TENNEY: I cannot tell you that. All the experiments in the rats were enzymatic and other metabolic studies. We did not do mitochondrial counts.

DR. MONGE: That would be very interesting to compare.

DR. MULVEY: Dr. Tenney, you indicated a shift in the hexosemono-phosphate pathway downward in certain of the endocrine organs. Could you indicate in which ones you saw this?

DR. TENNEY: No. I only speculated that it is possible (since one of the metabolic roles of the hexosemonophosphate shunt is to produce steroids) that one might, if there is a decrease in this metabolic path, find secondary consequence in the endocrines. We have made no such measurements.

DR. HURTADO: Dr. Kellogg, have you made any observations in cases of chronic mountain sickness about the regulation of breathing?

DR. KELLOGG: No, I have not made any at all. In fact, what I was talking about this morning is an extremely short period at the very beginning of acclimatization. The studies of Dr. Severinghaus, et al (3) suggest that people born at altitude may be quite different in their responsiveness to hypoxia from persons born at sea level and then going up to altitude as adults. I have not studied any high altitude natives at all.

DR. HURTADO: Dr. Kellogg, do you think that in cases of chronic mountain sickness there is a decrease or suppression of the ventilatory response to hypoxia, as Severinghaus and his collaborators have stated?

DR. KELLOGG: I know only the evidence that Severinghaus and his associates have presented.

DR. TENNEY: May I comment on that? The observation that Dr. Severinghaus and others have made (Dr. Lahiri has also made a comparable observation on Sherpas) that long-term residents lose, in some measure, their response to hypoxia, may have very important implications about the adaptability of man. It also would have evolutionary implications. Several important questions are raised. Is this (in man) something which has become with time a genotypic response, or is it another aspect of acclimatization – the long-term response of people exposed to altitude? Secondly, depending on which way that is answered, is it possible that the loss of hypoxic response with time is species specific, and may in other animals (perhaps better adapted to high altitude) not appear? The fundamental question is: What in the world is the "usefulness" to have lost such an important drive? Is the loss, in fact, a manifestation of "failure"? With this question in mind we have, for the last year, been studying the hypoxic response in a normal dweller at high altitudes, the llama. We have three groups of llamas. One group was born and raised at sea level, in which case one would imagine that if there is a genotypic response it would probably be held at least for several generations, in spite of the fact that the animals are living at sea level. On the other hand, if it were a rapidly developing adaptive response, it might show up on short-term acclimatization studies. So, these animals were taken to 18,000 feet for three weeks and then re-studied. And finally, if it has only to do with long-term acclimatization (as appears to be the case in man) it ought to be demonstrable in animals born and raised at high altitude, and show up in distinct difference to the first two groups. For these reasons we also studied animals born and raised at 14,000 feet. The answer to all this is that the hypoxic ventilatory response curves in all three situations are indistinguishable. If this has any relevance to the question in man, it suggests that the change in man is perhaps a species specific phenomenon, and it does raise some questions about his adaptability.

DR. RICHARDSON: Dr. Tenney, do some people lose ventilatory response to hypoxia which they had when they first went up to high altitude, or is it that some patients never have much ventilatory response to hypoxia, and are the ones who get chronic mountain sickness?

DR. TENNEY: I was not speaking about chronic mountain sickness. It certainly is true that response to hypoxia in a human population is widely variable. There are people who barely respond even when the alveolar PO_2 is dropped below 40. But, if it had some adaptive significance, then you would expect natural selection in the high altitude environment to pull this group out. That is what I meant by genotypic response. But concerning the question about mountain sickness, I do not have any idea. They seem to be a group characterized by more pronounced failure in hypoxic responsiveness – even worse off than normal residents.

DR. GROVER: I should like to comment on this briefly. It is true that at a given arterial PO_2 the high altitude native has a lesser ventilatory response to hypoxia than the man from sea level. This has led to the interpretation these people have "lost their sensitivity".

Our studies indicate that the response curve has simply been displaced to a lower range of PO_2. If you make the high altitude native sufficiently hypoxic, he will hyperventilate comparably to the sea level resident, but at a much lower arterial PO_2. So, the sensitivity is there but it is displaced into a lower range. This is somewhat analogous to the displacement of the CO_2 response curve, although in the latter it is reversible whereas the hypoxic response curve seems to be irreversible.

DR. KELLOGG: May I add a comment to that? If I understand the recent developments from Dr. Severinghaus's group, the determining factor seems to be not whether a person has spent all his adult life at altitude, but rather, what the oxygen pressure was during the critical stage of his development (4, 5). I think that it is worthwhile to go back to the old data of Miss FitzGerald (6), who studied permanent residents of the United States, and compare her figures with those obtained on Andean natives by Dr. Hurtado and his associates (7) and by Dr. Chiodi (8). According to this comparison, the European-ancestry Americans who have gone up to mining towns in Colorado and lived there for many years still continue to run lower alveolar PCO_2 levels than the Andean natives who had been born at altitude and lived there for many generations.

I think that perhaps what we really need is to study some other species, with shorter life spans, so that we can study the problem of ancestry and place of birth over several generations of animals within a reasonable length of total experiment.

DR. MONGE: In the past few weeks we have re-studied cases of natives living at high altitudes after several years, and there is a marked change in hematocrit. Hematocrit goes up as a function of

age in those who are born at and live permanently at high altitude. We have studied three groups; one at 12,000 feet, the other close to 13,000, and the last one at 15,000 feet in the Morococha Laboratories. The last group had been studied about ten years ago. We were remaking some studies when we found this tremendous change in hematocrit. I remember one had 56% ten years ago and now he has 66% hematocrit. Another one had 66 and now he has 79% hematocrit. When we pooled all the data from the two institutes we have in Lima, we found quite a good correlation with age. It seems to level off at about 30 or 40 years but we have a few cases over 60 years. So it seems to me that hematocrit is not a steady parameter and this, of course, introduces another factor – age. This may mean that ventilatory rate may be better in the very young person and that it may change according to age. I think this is a very important matter in connection with true acclimatization, because the age factor has not been taken into consideration so far.

DR. GROVER: Since red cell mass is related to arterial saturation (9), an increase in hematocrit suggests a fall in saturation with increasing age, and this could indicate a decreasing ventilatory response to hypoxia. This would certainly be worth investigating.

DR. ROBINSON: Dr. Kellogg, you did not report any arterial or CSF pH's or bicarbonates. Have these been done in connection with this change in the sensitivity?

DR. KELLOGG: Dr. Mitchell, Dr. Severinghaus, and others, going up to high altitude, studied their own cerebrospinal fluid. These data gave them the view that the major reason for the shift in CO_2 response was the rapid fall in CSF bicarbonate concentration (10). We have not been so courageous in doing lumbar punctures on ourselves. This is one reason why we think an experimental animal preparation will help us a great deal. Obviously, what is needed is controlled environmental CO_2 and oxygen to maintain desired alveolar levels, with knowledge of what is happening in the arterial blood and the cerebrospinal fluid, not only in terms of pH and bicarbonate but also in terms of lactate, which very likely might prove to be interesting (11).

DR. ROY: I think we have been mixing apples, pears, and strawberries this morning and calling them all fruit. For when we say "high altitude" we must define what we mean when we refer to high altitude natives. Obviously, the response at a height of 12,000 feet is quite different from that of 15,000 or 18,000 feet. There is also a distinct behavior pattern among subjects which depends upon whether they are indigenous, or are acclimatized residents of high altitude. These are important points.

Secondly, at whatever altitude a person may be born (say at 15,000 feet) if he is brought down to a lower level (say 6,000 feet) he loses most of the adaptive mechanisms within a matter of six weeks to six months. Tibetans are good examples of this. They are born and reared in the range of 14,000 to 16,000 feet. When they are brought down to the plains of India they lose their adaptations. One of the six HAPE subjects was a Tibetan.

Thirdly, for Dr. Kellogg. We have troops stationed at heights of 14,000 to 16,000 feet who must be supplied with fresh meat, but which cannot be air dropped. Live goats are air lifted to 12,000 feet in nonpressurized chambers flying at 18,000 to 20,000 feet for 30 to 40 minutes. Out of a shipment of 50 goats, all but one or two survive.

DR. KELLOGG: This agrees very well with our experience that to get strong hypoxic effects in goats we have to go to a lower PO_2 than we would like to use on ourselves.

DR. GROVER: Dr. Roy's comment that "high altitude" is not a single kind of fruit, but is a spectrum of altitudes, is a very important one. Dr. Hurtado has commented that it is even more than just meters above sea level. A man, when he is awake, may be living at 4,000 meters but when he goes to sleep he is, in effect, at 5,500 meters because he hypoventilates. When he exercises and his arterial PO_2 falls, he is, in effect, at a higher altitude than when he was resting. So, there is a fluctuation in physiological altitude as well as geographical altitude which should be kept in mind.

DR. TRAVIS: Dr. Tenney, what were the conditions of pH and PCO_2 in your mitochondria where you were measuring the oxygen consumption?

DR. TENNEY: The PCO_2 was 40 and the pH was 7.4.

DR. TRAVIS: Did you vary these to see what the changes would be?

DR. TENNEY: No.

DR. TRAVIS: Dr. Chaudhuri (who is now Professor of Biochemistry at New Delhi) and I have made some measurements over a wide range of PO_2 which show that as you raise the pH, or as you lower the PCO_2 over this wide range of PO_2 from 760 down to 5 or 10 mm Hg, there is an increase in oxygen consumption. If one lowers the PCO_2, say to about 25 mm Hg, this raises the oxygen consumption about 25%, and if one raises the pH from 7.4 to 7.6, again one gets about a 25% increase in oxygen consumption. So, I should just like to point out that in studies of isolated mitochondria, it is important to regulate these factors because they are almost linearly (or logarithmically) related to the values that one gets.

DR. GROVER: Dr. Richardson, I realize that your experience has been confined to acute hypoxia, but perhaps you would speculate on this point. If the tachycardia that occurs with acute hypoxia is due to stimulation of beta receptors (12), do you think that the persistence of tachycardia during residence at high altitudes, particularly during exercise, represents a persistent increase in beta sympathetic activity? Secondly, stimulation of beta receptors increases cardiac contractility and would be expected to increase stroke volume. Do you think this would be a persistent effect in chronic hypoxia?

DR. RICHARDSON: You should have warned me ahead of time. The only thing I can say is, I do not know. Yes, I would like to think that persistence of sympathetic activity accounts for the persistence of tachycardia but I just do not know whether that is true. With regard to the question about stroke volume, again, I do not know. The response of stroke volume depends so much on what has happened to heart rate that it does not seem to me to be possible to predict.

I think that increase in cardiac output may be accounted for mostly by increase in heart rate in some situations, whereas in other circumstances it may be largely the result of increase in stroke volume. To guess which actually occurs during chronic hypoxia is beyond my ability.

DR. ROY: We have enough data on the response to a given degree of exercise by fresh arrivals at high altitude, temporary residents (six months to two years), and natives. One apparent thing is that when soldiers from sea level go to high altitude, their heart rates come down after about eight months. They may then have rates of 60 to 70 per minute, which are not dissimilar to those of the natives. The difference becomes obvious when they exercise. In the natives the heart rate goes up very little as compared to the sea level soldier acclimatized for eighteen months. If in the latter the heart rate climbs to 100/min for a given level of exercise, it will increase only to about 80 in the native. A similar difference is also seen in the oxygen consumption for different controlled grades of exercise.

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ENDOCRINE ADAPTATIONS TO HIGH ALTITUDE EXPOSURE*

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Exposure to high altitude induces adaptations in many tissues to enable the organism to survive in the face of decreased oxygenation. Compared to the extensive literature which has accumulated describing changes in the cardiopulmonary and hematopoietic systems, relatively little attention has been paid to the possible role of the endocrine glands in acclimatization. The paucity of reports describing endocrine adaptations is surprising in view of the changes in endocrine function which have been described in other stressful situations. Although high altitude exposure induces many alterations in the endocrine system, the stimuli to the various glands remain unknown. Thus, tissue hypoxia, cold exposure, dehydration, psychological stress and other, as yet undefined, factors may play an important role either alone or in combination.

The current report is designed to present a limited review of changes in the activity of the adrenal and sympatho-adrenal systems in response to high altitude exposure. Also, because of recent interest in altered thyroid physiology in response to high altitude, this endocrine gland will be reviewed in greater detail. Changes in other endocrine glands during altitude exposure have been summarized elsewhere (1).

The Adrenal Cortex

Of all the endocrine system, most attention has centered on the effects of hypoxia and high altitude on adrenal cortical function. In earlier papers, which have been reviewed amply elsewhere (1), evidence for adrenal activation in his environment seems conclusive. Thus hypertrophy of the adrenal cortex occurs almost

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immediately after exposure in the rat and rabbit, as demonstrated by increases in adrenal weight and histological examination. Prolonged hypoxia may induce cellular necrosis and hemorrhage in the rat. Also, depletion of adrenal cortical ascorbic acid, lipids, and cholesterol occurs within hours after exposure. Depletion is complete after 24 hours but these moieties are restored to control levels after 7 days continuous altitude exposure.

In 1954, Koller *et al* (2) reported that an increase in glucocorticoid and 17-ketosteroid (17-KS) excretion as well as a decrease in circulating eosinophils occurred in man after ascent to 11,300 feet (Table 1). San Martin *et al* (3) and Moncloa and Pretell (4) showed that although native sea-level inhabitants and high-altitude residents had similar values, 17-hydroxycorticosteroid (17-OHCS) and 17-KS excretion were increased when sea-level subjects were exposed to 15,000 feet. Timiras, Pace, and Hwang (5) studied 6 subjects who ascended to 12,470 feet for 5 to 8 days on 3 separate occasions. Urinary 17-OHCS and 17-KS increased for the first 3 days of each exposure and then returned toward sea-level values. Plasma OHCS were also elevated. The magnitude of these changes diminished with repeated altitude exposure. In 1963, Mackinnon and coworkers (6) reported data on 4 men who ascended from 3,280 to 14,250 feet. Urinary 17-OHCS were increased for the first three days but 17-KS were not. Increases in urinary and plasma 17-OHCS have been observed even at the moderate altitude of 6,600 feet (7) and for at least 4 weeks at 20,400 feet (8). Since both plasma concentrations and urinary excretion of cortisol metabolites are increased during altitude exposure it is most probable that these changes are due to an actual increase in cortisol secretion and not to a transient augmentation in cortisol metabolism. Moderate increases in cortisol secretion rate, determined by an isotopic technique, have recently been reported by Moncloa *et al* (9).

Changes in cortisol level and urinary steroid excretion, usually transient at moderate altitudes (10,000 to 14,000 feet), can be prolonged at very high altitudes. These changes may be assumed to result from an increase in ACTH secretion by the pituitary. In one study, both pituitary and plasma ACTH concentrations were increased in animals breathing 10% oxygen for 3 hours to 5 days (10). The stimuli responsible for the activation of the hypothalamic-pituitary-adrenal system during high altitude acclimatization are, as yet, unknown.

Sympatho-Adrenal System

The important role of the sympatho-adrenal system in the

Table 1. Summary of changes in adrenal cortical function at high altitude

AUTHOR	REF-ERENCE	NO. OF SUBJECTS	MEASUREMENT*	ALTITUDE (FT)	PERCENTAGE INCREASE	DURATION (DAYS)
Koller et al.	2	9	17 OHCS	11,300	20-70	1
Timiras et al.	5	6	17 OHCS Plasma 17 OHCS	12,470	Up to 300 Up to 115	3
Mackinnon et al.	6	4	17 OHCS	14,250	60	3
Halhuber et al.	7	5	17 OHCS	6,600	30-50	7
Klein et al.	7	-	Plasma 17 OHCS	20,400	50-90	35
Moncloa	9	10 10 10	17 OHCS 17-KGS CSR	14,100 14,100 14,100	62 75 33	7 4 3

***Abbreviations: 17 OHCS = 17, 21-dihydroxy-20 ketosteroids (Porter-Silber Chromagens)**
17-KGS = 17-ketogenic steroids (Zimmerman Reaction)
CSR = Cortisol Secretion Rate.

response to several types of environmental stress is well recognized. Early data accumulated from experimental animals showed that the secretion of the catecholamines was probably increased during acute hypoxia (1). Until recently, no studies had been performed on man. The report by Ulvedal *et al* (11), in 1963, of catecholamine excretion studies in men in a space cabin simulator is not relevant because oxygen supplementation resulted in higher than normal PO_2. It is of interest, however, that no marked changes in norepinephrine (NE) or epinephrine (E) excretion were detected in his study even with severe decompression (down to 190 mm Hg) alone. In 1964, Pace *et al* (12) described the urinary excretion rates of NE and E in 6 subjects studied at 12,000 feet (Table 2). E was unchanged throughout the study. However, there was a significant increase in NE, beginning on the 2nd altitude day and reaching maximal values on the last day (14th) of exposure. These observations were confirmed by Cunningham *et al* (13) in subjects at 15,000 feet. Plasma catecholamine concentrations were not elevated during the first 36 hours of altitude exposure (14) but increases paralleling the elevated urinary excretion of NE after the first 2 days at altitude have been observed (13).

The urinary excretion of E and NE was reinvestigated by Surks, Beckwitt and Chidsey (15) in 5 subjects before, during, and after an 8-day exposure to 14,100 feet. In agreement with previous observations, mean NE excretion rose progressively at altitude (Fig. 1), reaching maximal values on the 5th and 7th day of exposure while mean E excretion remained unchanged. No significant change in metanephrine excretion was demonstrated (Fig. 2). However, the excretion of vanilmandelic acid was significantly increased, rising from 3.33 and 2.91 mg/day to 5.01 and 5.31 after 5 and 7 days at altitude.

These studies indicate a slow but progressive increase in sympathetic activity during exposure to high altitude. The absence of significant changes in E excretion suggests that the adrenal medulla does not participate in this adaptive mechanism. The increased excretion of vanilmandelic acid, the major metabolite of the catecholamines indicates that the increased excretion of NE is due to an increase in the total synthesis and degradation of this neurohormone rather than a transient release by sympathetic nervous tissue. It is of great interest to inquire into the mechanism of the progressive activation of the sympathetic nervous system in response to high altitude exposure. On ascent, there is a reduction in plasma volume which has been attributed to a redistribution of body water in favor of the interstitial or intracellular space (16). Activation of the sympatho-adrenal system can be effected by

Table 2. Summary of changes in the sympatho-adrenal system at high altitude

AUTHOR	REFERENCE	NO. OF SUBJECTS	MEASUREMENT*	ALTITUDE	OBSERVATIONS
Pace et al.	12	6	NE	12,500	Progressive increase, 14 days
		6	E	12,500	Unchanged
Cunningham et al.	13	8	NE	15,000	Progressive increase, 12 days
		8	E	15,000	Unchanged
		8	Plasma Catecholamines	15,000	Progressive increase, 12 days
Moncloa et al.	14	6	Plasma Catecholamines	14,200	Unchanged at 36 hours
Surks et al.	15	5	NE	14,100	Progressive increase, 8 days
		5	E	14,100	Unchanged
		5	Metanephrine	14,100	Unchanged
		5	Vanilmandelic Acid	14,100	Increased day 5 and 7

***Abbreviations:** **NE = Norepinephrine**
E = Epinephrine

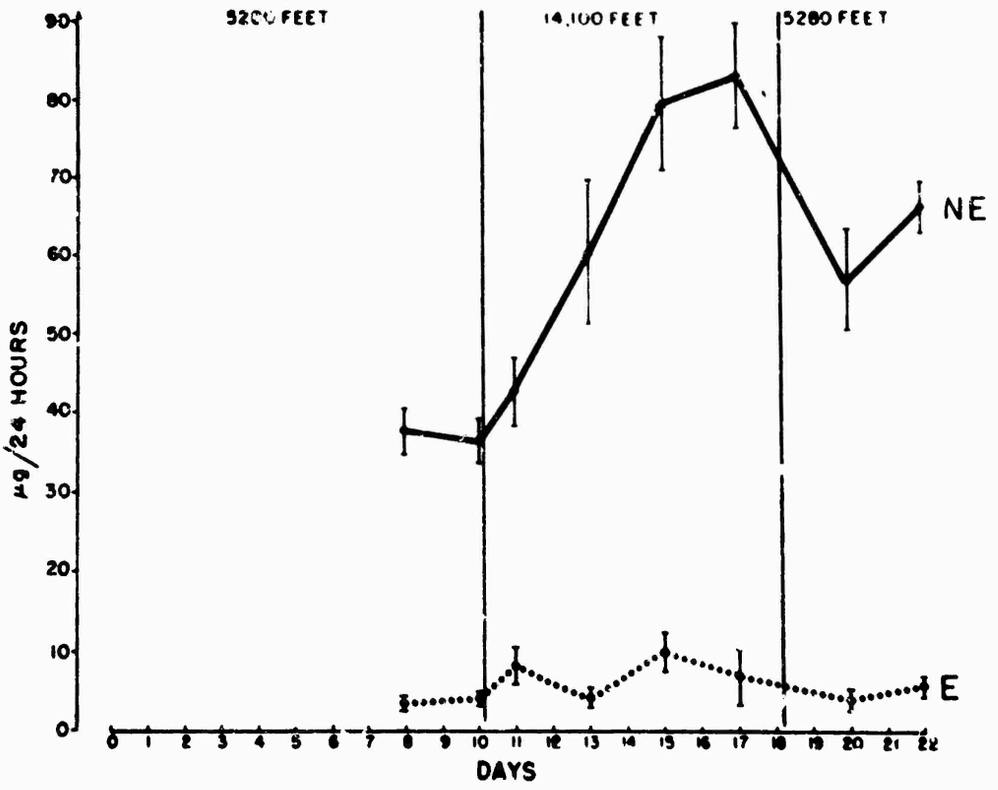

Figure 1. Urinary excretion of Epinephrine (E) and Norepinephrine (NE) during acute high altitude exposure. Each point represents the mean ± S. E. for 5 subjects.

minimal reduction of the intravascular volume as demonstrated by controlled hemorrhage (17) and it is possible that the decrease in plasma volume observed at high altitude is responsible for the stimulation of sympathetic activity. Alternatively, the administration of NE has been demonstrated to result in a diminution of the plasma volume (18) and it may be that the augmented sympathetic activity at high altitude is responsible for the reduction in plasma volume in this environment.

Thyroid Gland

In 1943, Gordon *et al.* (19) performed histologic examinations and TSH bioassays in rats exposed to 25,000 to 27,000 feet in a hypobaric chamber. Thyroid weight was increased in some exposed groups. Histological examination revealed slight lowering of the follicular epithelium and an increase in colloid. TSH bioassay showed decreased TSH activity in the serum of the exposed animals. In most experiments, however, the pituitary TSH activity was not changed.

The earliest radioiodine studies were performed by Van Middlesworth and Berry (20) in rats exposed to 27,000 feet for 36

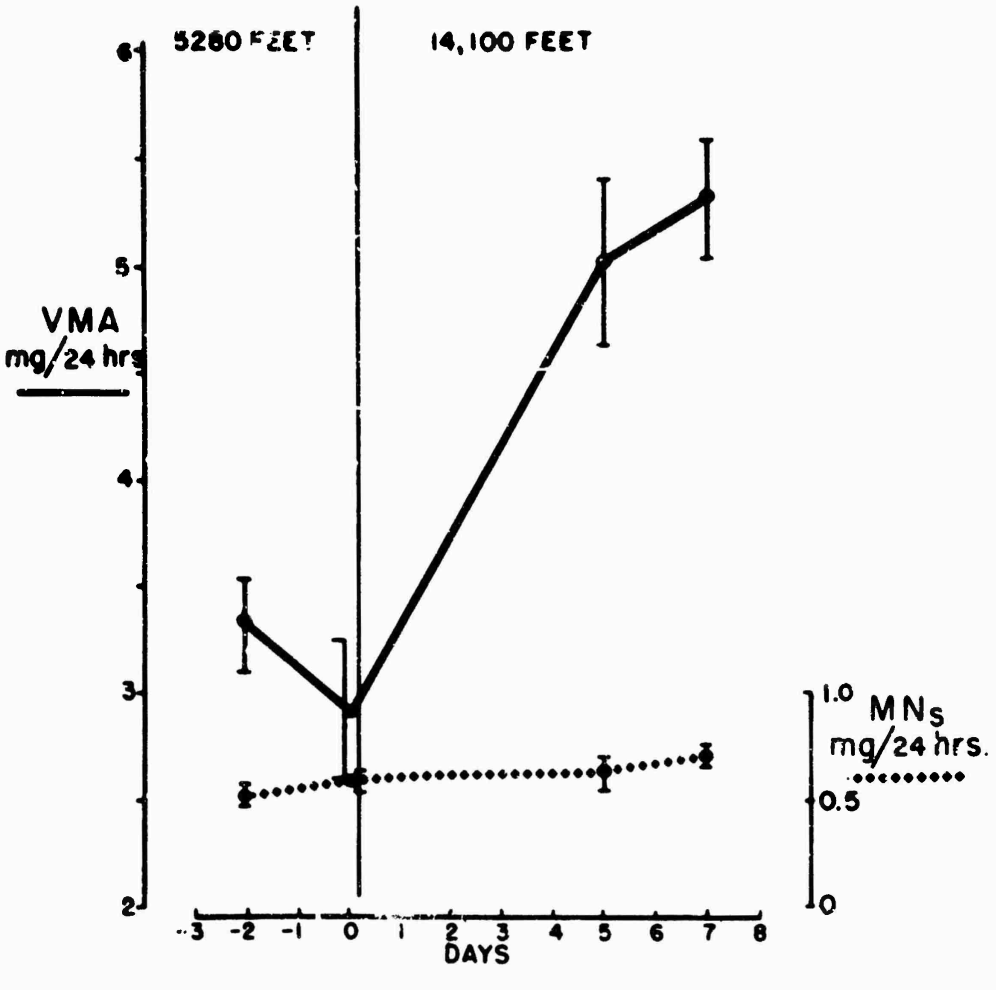

Figure 2. Urinary excretion of total Metanephrines (MNs) and Vanilmandelic Acid (VMA) during acute exposure to high altitude. Each point represents the mean ± S. E. for 5 subjects.

hours. No change in thyroid weight was apparent in their study when calculated on the basis of body weight. The 24-hr thyroidal accumulation of administered radioiodine (RAIU) in the exposed animals was 1/7 that of the controls while the plasma I^{131} concentration was 20 times greater. PBI^{131} concentration (protein-bound $iodine^{131}$), a measure of the concentration of recently synthesized thyroxine, was significantly depressed also, confirming earlier observation by the same authors (21). It should be pointed out that the RAIU represents only the fraction of injected tracer radio-iodine accumulated by the thyroid and is highly dependent on the size of the unlabeled endogenous iodide pool. Thus, primary alterations in the iodide pool may lead to changes in the observed RAIU without any change in absolute iodide uptake by the thyroid. Similarly, caution should be employed in the interpretation of PBI^{131} data in the face of large

changes in thyroidal radioiodine uptake since PBI^{131} is directly related to the specific activity of the intrathyroidal labeled iodothyronines. For example, at a low I^{131} uptake, the specific activity of intrathyroidal thyroxine (T4) is low and the PBI^{131} will be low even at a normal secretory rate for this hormone.

The observations of decreased 24-hour RAIU, PBI^{131}, and conversion ratio (PBI^{131}/total plasma I^{131}) at very high and moderate altitudes were confirmed by a number of groups. Thus, Verzar and coworkers (22) described reduced RAIU only 12 hours after rats were exposed to 25,000 feet. At an actual altitude of 11,300 feet the 24-hour RAIU was decreased as early as 5 hours after exposure and remained below control values for 8 days. Antunez and Houssay (23) studied rats at 25,000 and 14,000 feet in a hypobaric chamber and found marked reductions in these parameters as soon as 3 hours and as late as 24 hours after exposure. Fregley and Otus (24), in rats exposed to 12,000 feet for 11 weeks, and Surks (25) in rats exposed to 15,000 to 18,000 feet for 8 days both in hypoxia chambers, and Mulvey (26) in a hypobaric chamber have all made similar observations although the latter author did not detect differences from the control animals in 24-hour RAIU.

The only radioiodine studies performed in human beings were reported by Moncloa *et al* (27) who investigated ten sea-level subjects for 14 days at 14,000 feet. Iodine^{131} uptake and release measured by repeated counting of the thyroid were increased at high altitude. Once again, possible changes in the stable iodide pool make these data difficult to interpret. For, if the subjects at altitude were somewhat iodine deficient relative to sea-level, similar results would be obtained. The authors do report that although food was similar in both locations significant increases in urinary iodide excretion were observed at altitude.

Surks (28, 29) has made a more detailed study of the iodide trap in hypoxia in intact animals and *in vitro*. When the thyroid: serum iodide concentration ratio (T/S) was measured in animals on an adequate iodine and low iodine intake, significant decreases were observed for the hypoxic groups (18,000 feet) (Table 4, Experiments I and II). The T/S ratio is considered an instantaneous evaluation of the iodide trap in the thiouracil blocked thyroid and should be independent of alterations in unlabeled iodide pool. In an *in vitro* study, in which both entrance and exit rate constants for iodide could be measured independently in incubated thyroid lobes by means of two isotopes of iodine, it was observed (Table 2) that although unidirectional clearance of iodide into the lobe was decreased only after marked

reduction of oxygen concentration, the exit rate constant increased after each decrement in oxygen concentration over the incubating medium. The net effect was a decrease in thyroid: medium iodide concentration ratio (T/M ratio) with decreasing oxygen concentrations.

The distribution of I^{131} among the various iodoamino-acids of the thyroid has been investigated by several groups after varying periods of altitude exposure (Table 3). Mulvey (26) and Surks (25) have found a decrease in the amount of labeled T4 with an increase in the iodotyrosines after several hours and 8 to 37 days exposure, respectively. Nelson and Anthony (30) described a decrease in T4 after 32 hours at 18,000 feet while LaRoche and Johnson (31) found only a transient decrease in labeled T4 24-hours after exposure. The latter authors have reported increases in 24-hour radioiodine uptake by the thyroid in their experimental conditions.

In contrast to most of the reports discussed above, the data from one group has been interpreted to show increased thyroid function in response to altitude exposure (32, 33). This conclusion is based, in part, on greater 24-hour RAIU and more rapid thyroidal release of I^{131} in the exposed animals. However, it is apparent that the low recovery of radioactivity in their animals' thyroid glands (from 0.2 to 0.3% of the administered dose) prevent any firm conclusions. The erythrocyte uptake of labeled triiodothyronine (T3 uptake) was also elevated. This test is more sensitive to changes in the serum thyroxine-binding proteins than to alterations in serum hormone concentration, a fact well illustrated from values in their control groups. Normal, iodine deficient, and thyroidectomized rats had average T3 uptake values of 23.1 to 25.0%, whereas the animals receiving 1000 µg T4 per day (300 times the daily secretory rate) for 4 days had a value of only 30.2%. Thus, the T3 uptake values in their study probably reflect changes in serum thyroxine-binding but not stimulation of the thyroid.

The foregoing data, therefore, suggests that most aspects of thyroidal iodide metabolism are depressed in response to high altitude. This depression may result from decreased TSH secretion by the pituitary, altered responsiveness to TSH by the gland, specific changes in intrathyroidal iodine metabolism induced by hypoxia itself or to any combination of these factors. Evidence has been presented to support the first and third of these contentions by Gordon *et al.* (19), Houssay *et al* (34) and Surks (25). The second possibility has been excluded by the latter author (Table 4, Experiments III-V who has shown that the thyroid of hypoxic

Table 3. Summary of changes in iodine metabolism at high altitude

AUTHOR	REF-ERENCE	RAI UPTAKE	T/S RATIO	PBI^{131}	C.R.	PERCENTAGE DISTRIBUTION IN		TSH
						IODOTYROSINES	IODOTHYRONINES	
Gordon et al.	19	-	-	-	-	-	-	D
Van Middlesworth et al.	20, 21	D	-	D	-	-	-	-
Verzar et al.	22	D	-	-	-	-	-	-
Antunez et al.	23	D	-	D	D	-	-	-
Fregly et al.	24	D	-	-	D	-	-	-
Surks	25, 29	D	D	D	D	I	D	-
Mulvey	26	NC	-	D	-	I	D	-
Nelson et al.	30	I	-	-	-	NC	D	-
LaRoche et al.	31	I	-	D	-	NC	D	-
DeBias et al.	32, 33	I	-	-	-	-	-	-

Abbreviations: I = Increased; D = Decreased; NC = No Change; - = Not Measured

Table 4. Radioiodine data (unpublished)

EXPT. NO.	EXPERIMENTAL ANIMALS		PO_2	24-HR I^{131} UPTAKE (%DOSE)	PBI^{131} % DOSE/10 ML PLASMA	T/S RATIO
	CONDITION	DIET				
I	I	Purina	155	6.2	0.184	17.4
	I	Purina	84	1.0	0.064	7.6
II	I	Low Iodine	155	51.2	1.984	96.3
	I	Low Iodine	84	34.1	0.949	74.4
III	H	Low Iodine	155	2.7	0.149	2.9
	H	Low Iodine	84	2.0	0.259	1.9
IV	H	Low Iodine	155	17.1	0.788	17.2
	+0.1 U TSH	Low Iodine	84	26.7	1.180	16.4
V	H	Low Iodine	155	18.2	1.022	17.6
	+0.3 U TSH	Low Iodine	84	29.5	1.730	22.1

Abbreviations: I = Intact
H = Hypophysectomized

hypophysectomized rats (18,000 feet) respond to injected TSH at least as well as their controls (29).

Only two studies of extrathyroidal thyroxine metabolism have been reported (15, 35). In the first, which was concerned only with the nature of thyroxine transport in the blood, various aspects of thyroxine-binding were studied in 8 sea-level residents before, during and after 28 days exposure to 14,100 feet. The mean plasma concentration of protein-bound iodine (PBI), total protein, and the binding capacity of thyroxine-binding globulin (TBG) increased within 3 days, reached maximal values at 9 days and returned toward control levels between 12-15 days at altitude (Fig. 3). All parameters reached pre-exposure levels by the 4th day after descending to sea level. The concentration of thyroxine-binding prealbumin did not parallel the other plasma proteins; it either remained unchanged or decreased at altitude. In spite of an increased intensity of thyroxine-binding at high altitude mean plasma free thyroxine concentration was significantly increased during the entire experimental period. Since the electrophoretic distribution of the plasma proteins was unaltered, plasma dehydration in the early phase of altitude exposure was felt to be responsible for all of these changes except the increase in plasma free thyroxine concentration.

Attempts were then made to correlate the elevated plasma thyroxine concentrations with thyroxine metabolism and oxygen consumption (15). Thyroxine-I^{125} was injected into 5 subjects and its metabolism studied for 10 days at 5,200 feet altitude. The subjects were then transported to 14,100 feet where they remained for 8 days. An increase in the rate of thyroxine degradation was observed during the first three days at altitude in all

Table 5. Effect of various 0_2 concentrations on the one-way I - clearance (C/m), exit rate constant (K_{TM}), and thyroid: medium iodide concentration ratio (T/M ratio) of incubated thyroid lobes.

$\%0_2$	K_{TM} (min^{-1})	C/m (µl/mg/min)	T/M RATIO*
100	0.0140±0.0008	0.3132±0.0114	10.8±0.3
20.9	0.0232±0.0019+	0.3377±0.0263	9.7±0.3
12	0.0241±0.0011+	0.3150±0.0215	8.4±0.3+
0	0.0368±0.0015+	0.1999±0.0035+	2.5±0.2+

*** Determined after 50 minutes incubation**

+ Significantly different from 100% O_2 group, $p<0.001$.

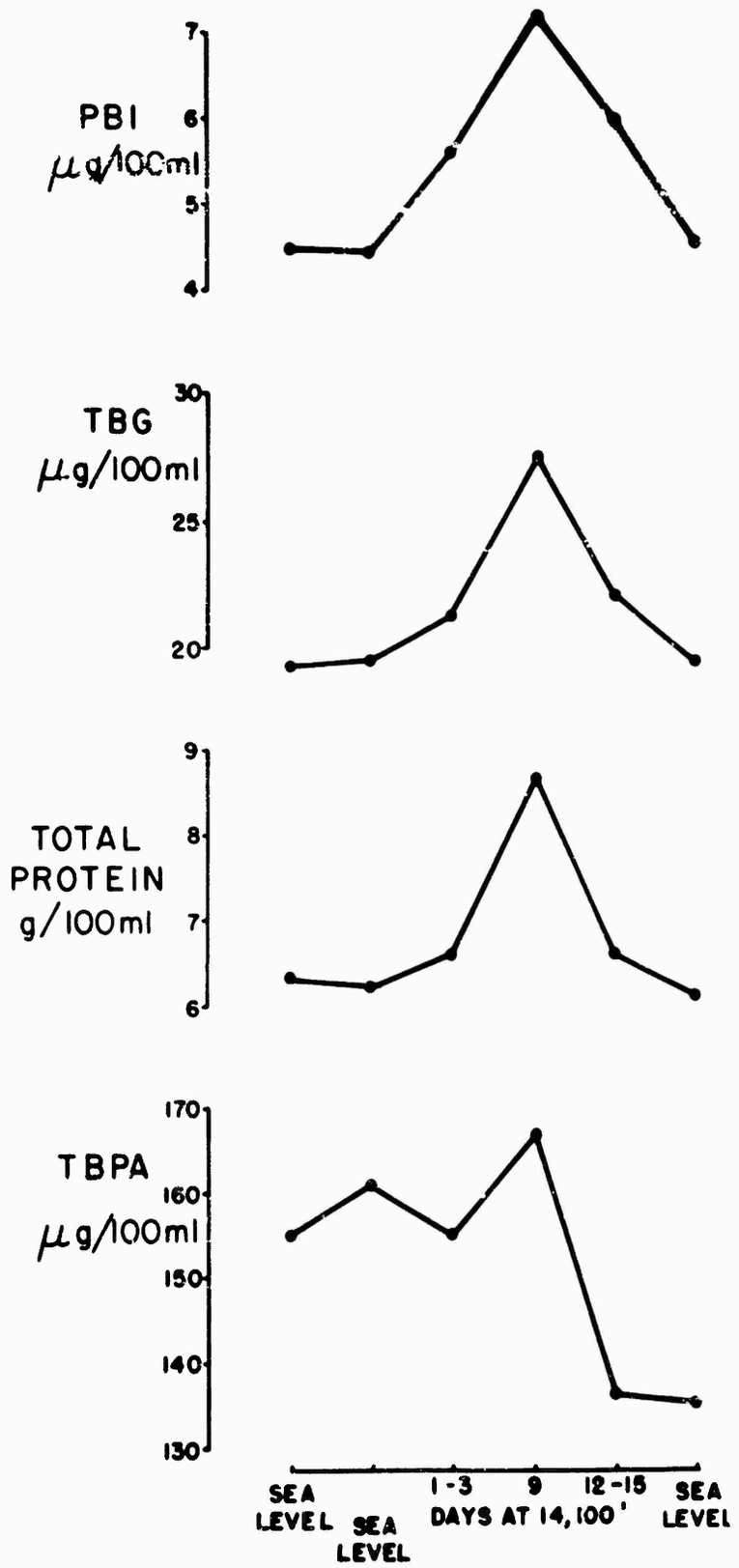

Figure 3. Effect of High Altitude on PBI and Plasma Proteins. Each point is the mean value for 8 subjects. The concentration of TBG and TBPA are given as their thyroxine-binding capacity.

subjects (Fig. 4) but these changes did not appear to correlate with later elevations (days 4-8) in PBI and plasma free thyroxine concentration. The alterations in thyroxine metabolism did, however, appear to be associated temporally with moderate increases in oxygen consumption which were demonstrated during initial exposure (Figure 5).

The studies of extrathyroidal T4 metabolism remain descriptive and afford no insight into the possible mechanisms by which the thyroid may aid in the adaptation to high altitude. This problem should be resolved by future experimentation.

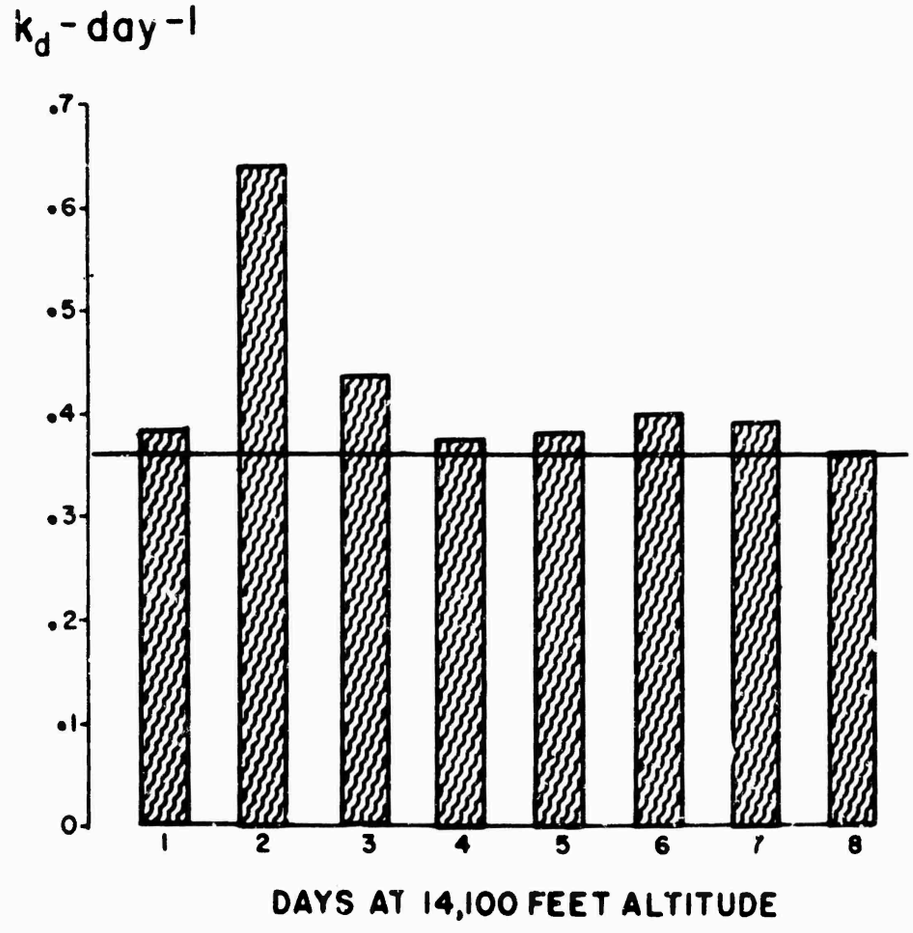

Figure 4. Mean thyroxine degradation rate in man at high altitude. Each bar represents the mean degradation rate for the plasma thyroxine pool for 5 subjects. The mean value for the control period is shown as the horizontal line. The S. E. during the control period falls within the line.

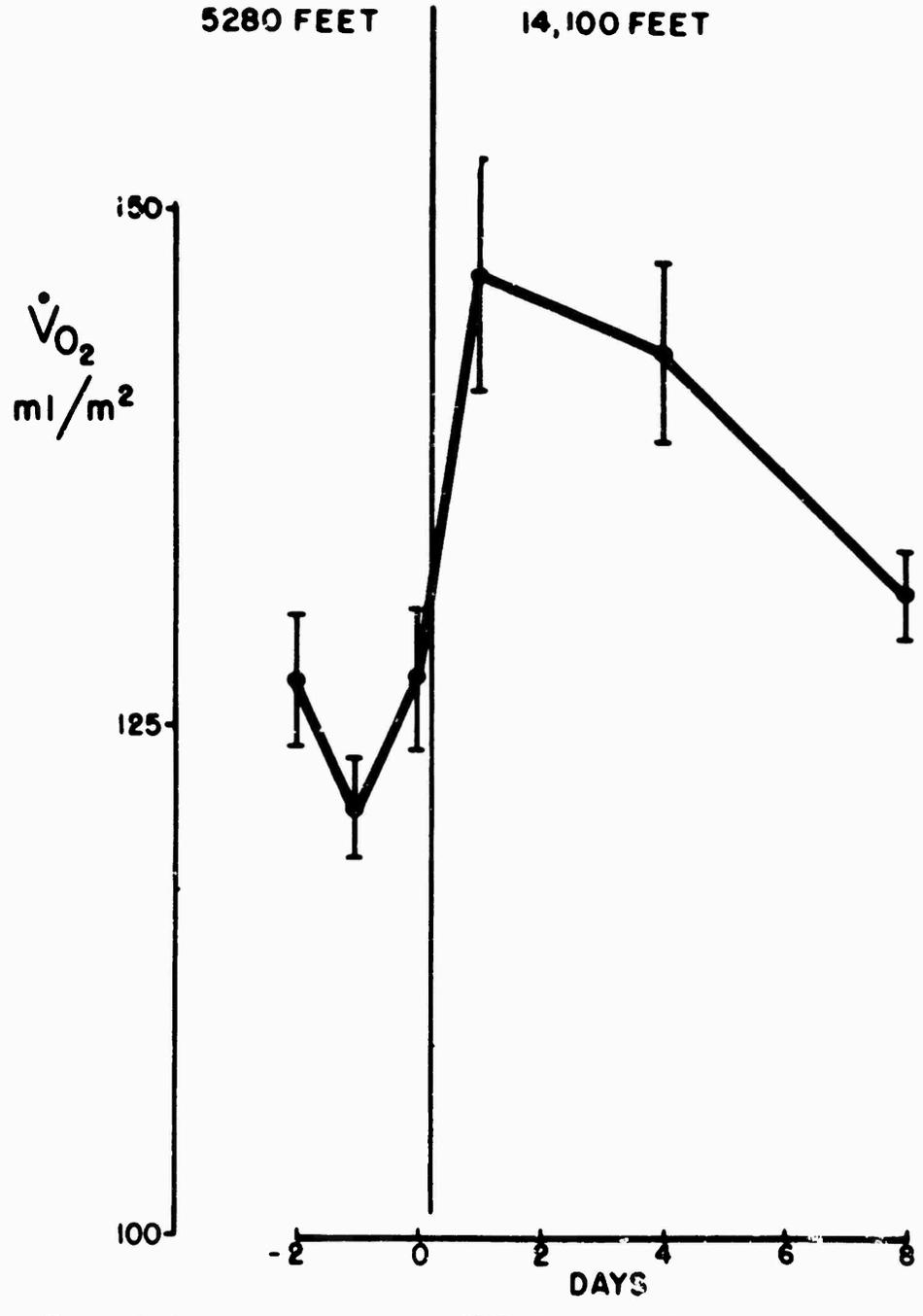

Figure 5. Oxygen Consumption (VO_2) in man during acute exposure to high altitude. The mean ± S. E. for 5 subjects are indicated.

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DECREASE IN PHYSICAL WORKING CAPACITY AT HIGH ALTITUDE

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The soldier engaged in a campaign in the mountainous areas of the world must usually work in a hypoxic environment. The well conditioned young man confronted with hypoxia, although as susceptible as others to acute mountain sickness, can usually work well within his aerobic capacity which provides him with a functional advantage over his less well conditioned colleagues or opponents.

Several studies of work capacity have been conducted at altitude over the years. In this report, data from these studies have been pooled with those from our own work to provide a more meaningful and complete picture of reduction in work capacity at altitude. My remarks are largely confined to the oxygen demands associated with maximal and submaximal work so as not to overlap with the presentations made by others at this symposium.

Maximal Work

The maximal oxygen intake is an important personal characteristic that is related to overall fitness, work capacity and actual performance. It is a measure of aerobic capacity or the capability of the combined respiratory-circulatory system to deliver oxygen to working muscle and the muscles ability to utilize oxygen. It is a useful measurement because knowing the maximal oxygen intake enables the investigator to describe the relative aerobic demands of any activity engaged in by the subject under study.

Men are uncomfortable when they work at 50% or more of their aerobic capacity. Prolonged work at 70% or more of aerobic

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capacity is carried out with considerable strain by the average man. When a newcomer has trouble at altitude it is usually because of acute mountain sickness, pulmonary hypertension and edema or because he must work close to his capacity for long periods.

Performance of tasks requiring maximal aerobic metabolism is adversely affected by reduction of the oxygen content of the ambient air. This can be shown by the decrement in running performance at altitude (Fig. 1) which is related to the decrement in maximal oxygen intake (Max $\dot{V}O_2$). The subjects in each study were well conditioned young trackmen who ran competitive distances of either one or two miles. In general, the percent decrement in Max $\dot{V}O_2$ exceeded the percent decrement in running performance (equivalent to slower running times). This is because utilization of a variable amount of anerobic energy may contribute to the running performance and the base for calculating the percentages is of different magnitude and significance for each variable.

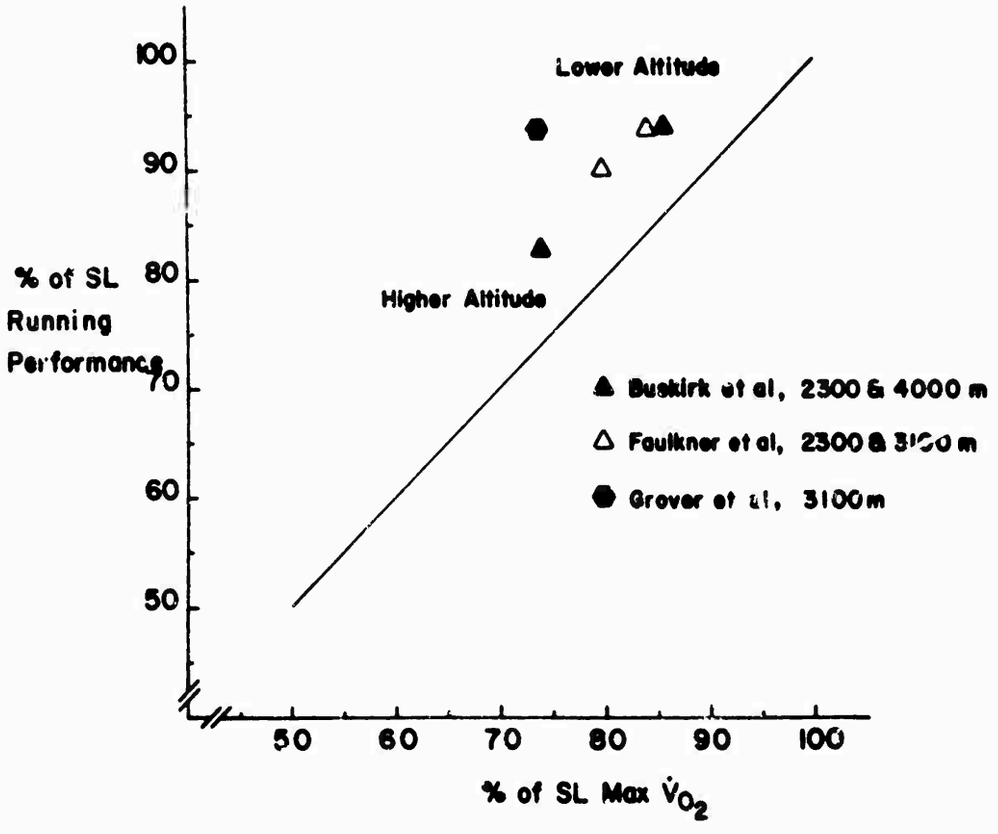

Figure 1. Relationship between the altitude induced decrement in running performance on an outdoor course and the decrement in maximal oxygen intake values expressed as a percentage of those attained by the same subjects at sea level. (7) (13) (14).

Numerous investigators have measured the reduction in Max $\dot{V}O_2$ at altitude (their observations are reported in Figure 2). The average decrement for all subjects studied was approximately 3% per 1000 feet of altitude with an intercept at 4000 to 5000 ft. If data for only well conditioned young men were considered, the decrement was approximately 2% per 1000 feet with an extrapolated intercept at sea level.

Max $\dot{V}O_2$ per kg body weight from three of the studies included in Figure 2 were replotted in Figure 3. The reduction in Max $\dot{V}O_2$ was somewhat different in the studies of Pugh (22) than in those of Buskirk *et al* (8) and Faulkner *et al* (13). The data of Pugh shows a flatter curve. The explanation is probably associated with the initial physical condition of the subjects. Those studied by Buskirk *et al* and Faulkner *et al* were well conditioned athletes in a constant state of physical condition who maintained body weight, whereas Pugh studied subjects who were initially less well conditioned and who continued to improve their condition with time at altitude. In the latter studies some body weight, presumably fat, was also

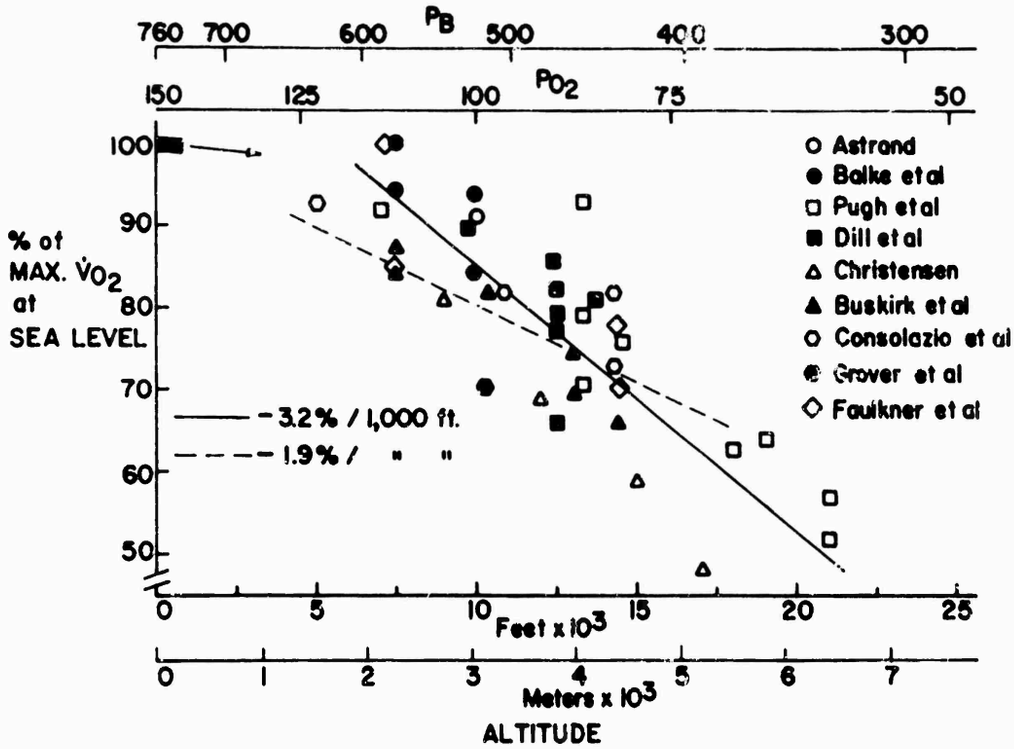

Figure 2. The decrement in maximal oxygen intake in relation to increased altitude, reduced barometric pressure, and reduced oxygen content in ambient air. Data from the literature are pooled and percentage regression lines plotted for relatively unconditioned (———) and conditioned men (- - -).

lost. Thus, the initial aerobic capacities measured by Pugh were lower than they would have been if the physical condition of his subjects had not improved and body weight had remained constant. Interpretation of Max $\dot{V}O_2$ data from studies involving conditioning, and body weight loss together with hypoxic effects is somewhat difficult to analyze for hypoxic effects alone.

The decrement in Max $\dot{V}O_2$ at altitude is significant and reproducible. Although considerable interindividual variation in aerobic capacity is evident whenever groups of subjects are studied, each individual tends to have a similar percentage reduction in aerobic capacity when exposed to hypoxic conditions. Movement from one altitude to another usually has little effect on the aerobic capacity measured at a specific altitude – although exceptions have been observed. An example of an exception is shown in figure 4 with movement of the well conditioned group of young men from 3100 back to 2300 m. Max $\dot{V}O_2$ was higher than it had been when the subjects lived at 2300 m earlier (13). No ready explanation for this rather interesting relative elevation in Max $\dot{V}O_2$ on the second occasion at 2300 m was apparent. The average

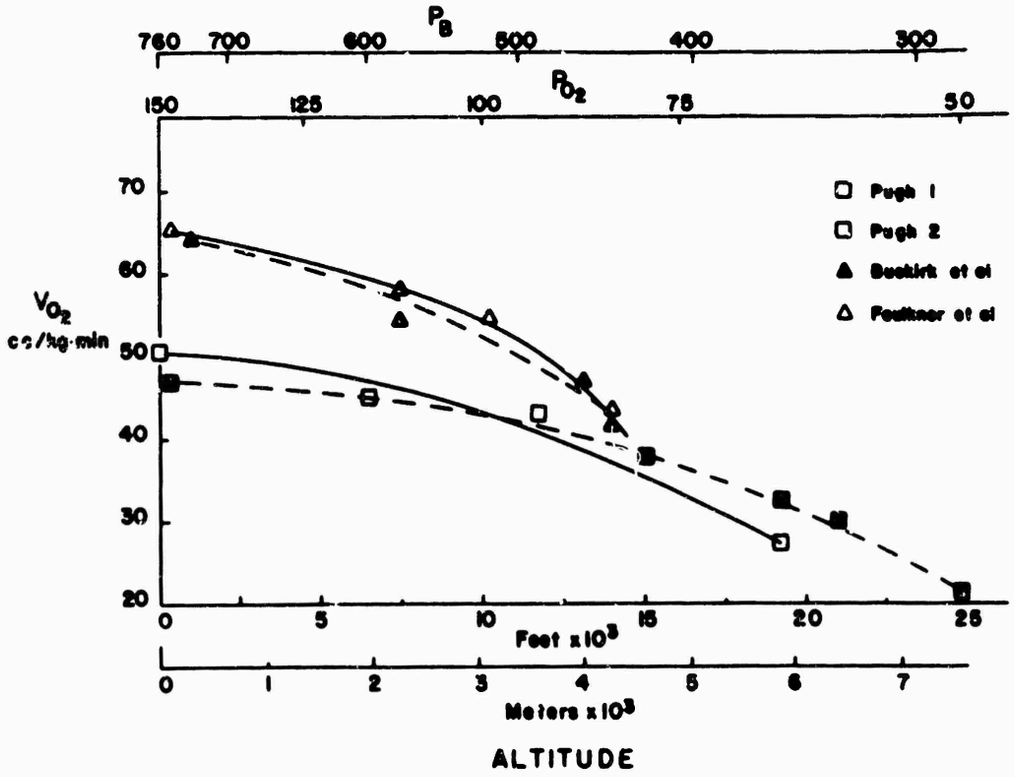

Figure 3. The decrement in maximal oxygen consumption per kg body weight in young men who became progressively conditioned (22) (23) and in men who remained well conditioned (7) (13).

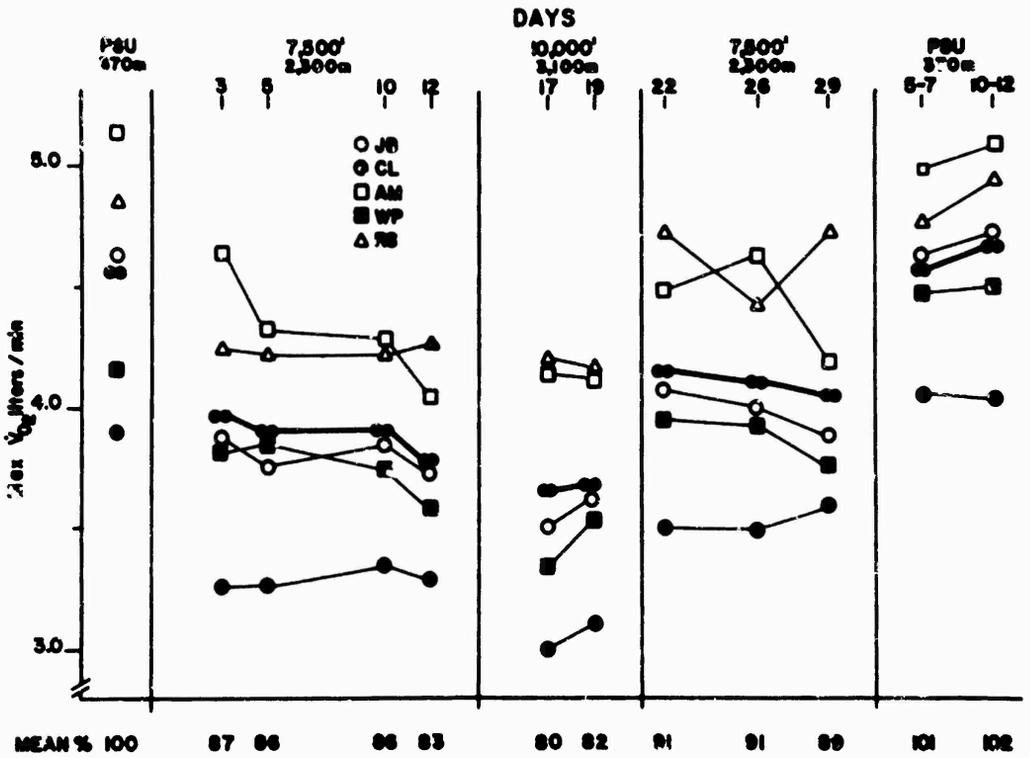

Figure 4. Changes in maximal oxygen intake with movement from one altitude to another. Subjects were well conditioned young men (23).

changes in Max $\dot{V}O_2$ in three groups of well conditioned young men who moved from one altitude to another at different times and in varying sequence are shown in figure 5. With the exception of the medium altitude group, discussed in relation to figure 4, Max $\dot{V}O_2$ at a specific altitude was similar and apparently not affected by altitude exposure history. Several variables and factors associated with aerobic capacity or the Max $\dot{V}O_2$ are shown in table 1. The subject is considered along with his exercise, his environment and various interrelated physiological factors. Aerobic capacity is an integrated measurement of systems capabilities, and not all of the variables or limiting factors have been well studied at sea level let alone altitude. Some of the possibilities are discussed below.

West (26) (27) has pointed out that a progressive fall in arterial oxygen saturation may occur in the face of a rise in alveolar oxygen tension as the exercise level increases (Fig. 6). It was suggested that this fall in saturation may point to diffusion limitations within the lung during exercise at the high altitude of 5800 m where the alveolar oxygen partial pressure was only 50 mm Hg. At an exercise level of 900 kgm/min the alveolar gas – arterial

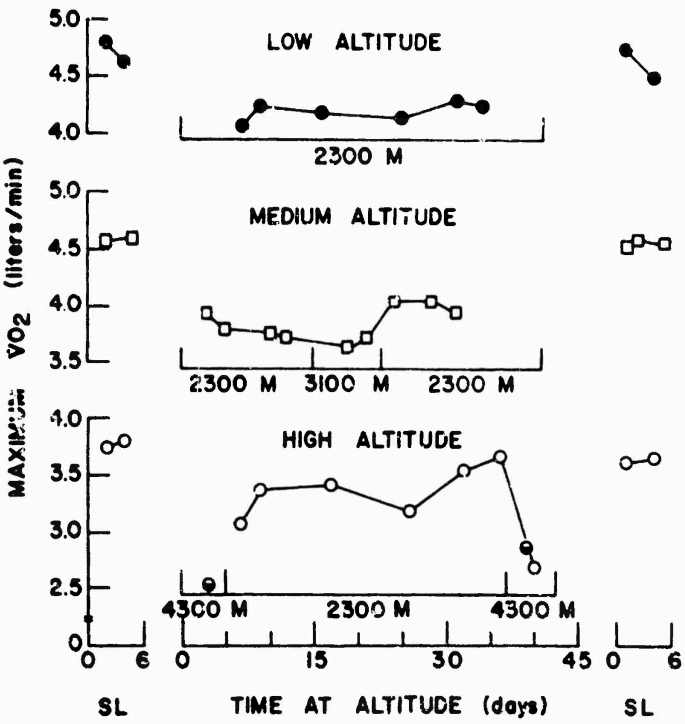

Figure 5. Mean changes in maximal oxygen intake in three groups of well conditioned young men. Each group followed a different schedule of movement from one altitude to another (13).

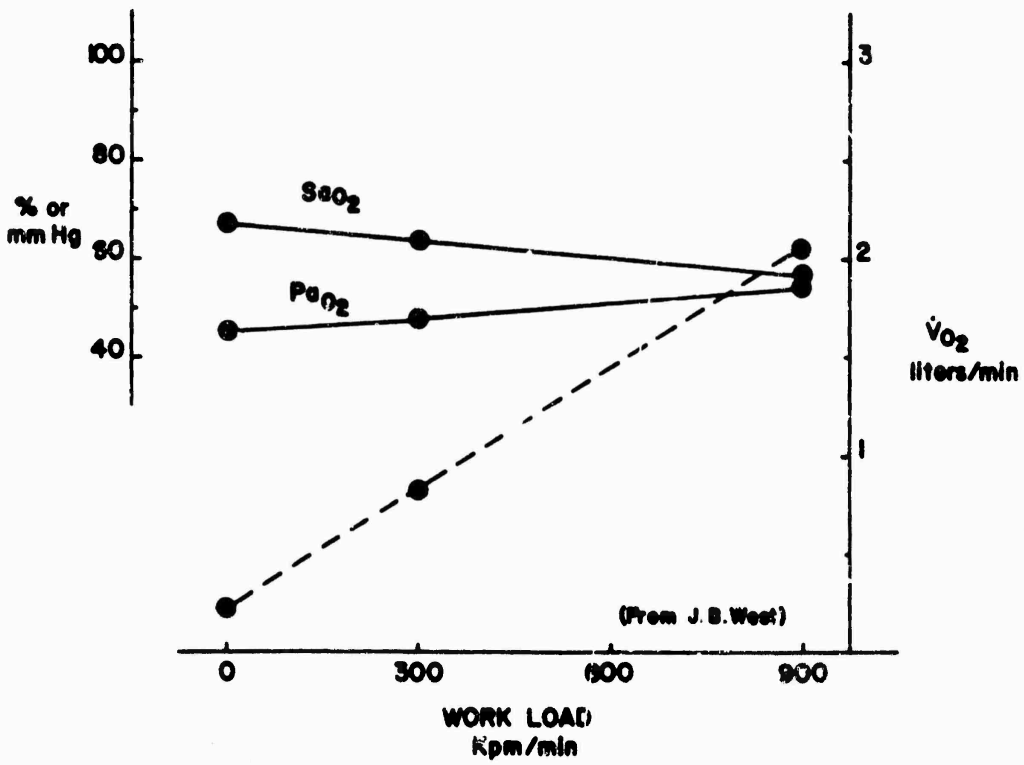

Figure 6. Arterial oxygen saturation, alveolar oxygen partial pressure, and oxygen consumption in acutely acclimatized subjects who exercised on a bicycle ergometer at 5800 m. (Redrawn from J. B. West, 26 and 27).

Table 1. Variables and factors associated with achievement of aerobic capacity

SUBJECT

Age
Sex
Body Composition
Physical Condition
Adaptation
Acclimatization

EXERCISE

Type of Exercise
Duration of Exercise
Body Position

ENVIRONMENT

P_{O_2} P_B
Temperature
Vapor Pressure

PHYSIOLOGICAL FACTORS

Pulmonary Ventilation
Pulmonary Diffusion
Pulmonary Perfusion
(A-a O_2 Gradient)
Cardiac Output
Coronary Flow
Heart Rate
Stroke Volume
Vascular Resistance
Muscular Perfusion
Muscular Diffusion
(a-vO_2 Difference)
Muscle Myoglobin
Muscle Enzymes
Quantity and Quality
Muscular Electron Transport
Metabolic Fuel Mixture
Acid-Base Balance
pH, pCO_2

blood gradient for O_2 was 26 mm Hg. Thus, approximately one-half of the oxygen in the alveolar gas never passed the blood-gas barrier.

The way in which arterial oxygen saturation falls as the work load increases, and if oxygen diffusion in the lung is limiting, is illustrated in Figure 7 for two low oxygen partial pressures in

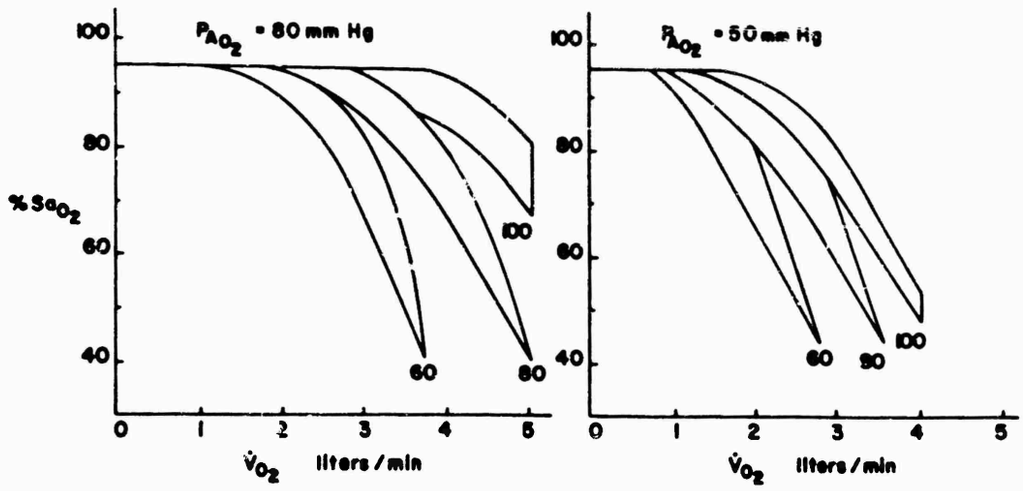

Figure 7. Decrease in arterial oxygen saturation at high levels of oxygen consumption with different diffusing capacities and values of alveolar oxygen content (Redrawn from J. B. West, 26 and 27).

alveolar gas (26). The greater the pulmonary diffusion reduction, the less the oxygen saturation in arterial blood and the less the Max $\dot{V}O_2$. It is assumed in this plot that blood pH, O_2 capacity and PAO_2 remain constant during maximal exercise, which probably is not true. If the diffusion capacity is limited to 80 ccO_2/mm Hg.·min at a PAO_2 of 50 mm Hg, a $\dot{V}O_2$ of 3 liters per minute or more is associated with a substantial reduction in arterial oxygen saturation. Thus, diffusion limitations at altitude can effectively limit performance. Even at a PAO_2 of 80 mm Hg, diffusion capacity restrictions could limit Max $\dot{V}O_2$.

Any reduction in the partial pressure of oxygen of inspired air limits diffusion because the rate of oxygen transfer across the alveolar capillary membrane is dependent on the magnitude of the A-a gradient *i.e.*, the effective partial pressure gradient. Reduction in PAO_2 may therefore limit the rate of oxygen transfer to circulating red cells in arterial blood. In well conditioned young men working up to 4300 meters, there is no current evidence for a reduction in diffusion capacity or in the membrane diffusion component (14).

Johnson (18) has plotted some theoretical limits for Max $\dot{V}O_2$ imposed by reduction in diffusion for oxygen at the alveolar capillary membrane for different altitudes (Fig. 8). These curves were estimated on the basis of assumptions and calculations too involved to present here. If maximal pulmonary blood flow was assumed to be constant at a rate of 23 liters/min, Max $\dot{V}O_2$ was established by the straight line shown. Again the reduction in

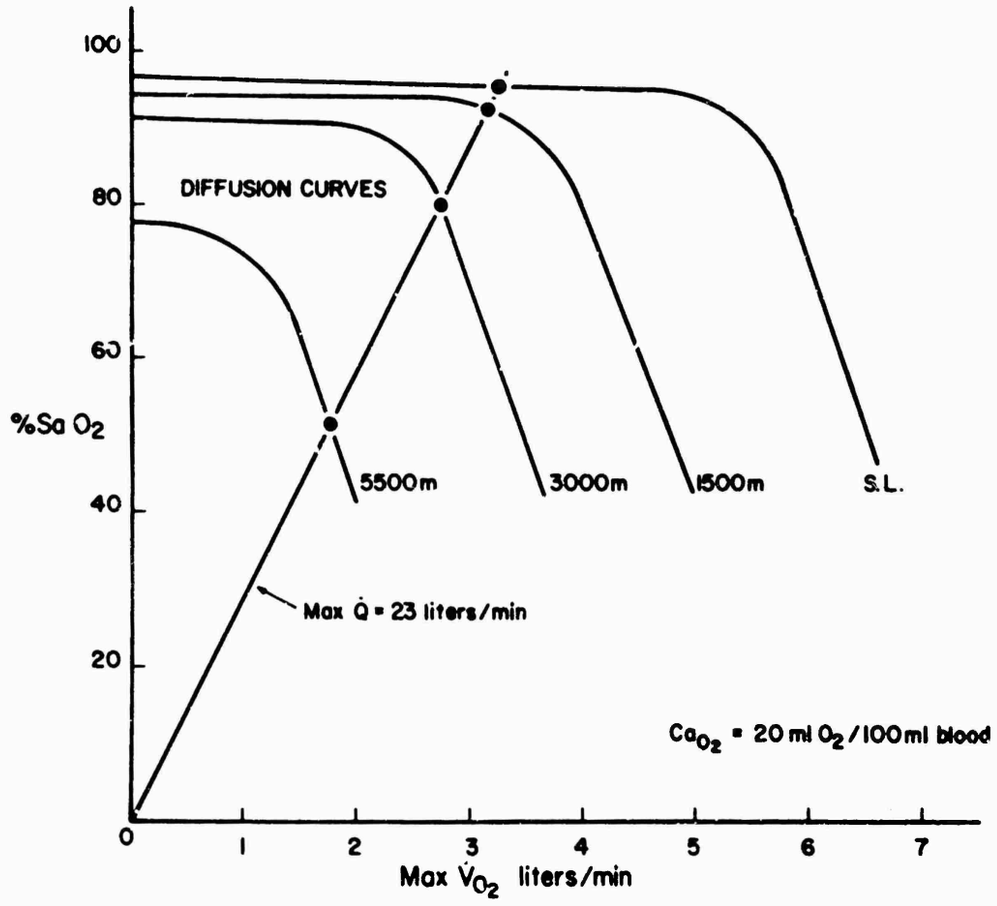

Figure 8. Upper limits for the maximal oxygen intake imposed by alveolar – arterial diffusion at an assumed maximal cardiac output of 23 liters/min. (Redrawn from R. L. Johnson, 18).

saturation of arterial blood at altitude is shown. The oxygen capacity of the blood was assumed to be 0.2 ml/ml blood or 20 volumes percent at each altitude. Johnson (18) has also predicted the effect of acclimatization on Max $\dot{V}O_2$ and increased oxygen carrying capacity of the blood (Figure 9). The arrow indicates the expected change in Max $\dot{V}O_2$ if blood oxygen carrying capacity is increased with acclimatization and a relative hyperventilation insures a relative increase in PAO_2. Only small increases in Max $\dot{V}O_2$ have been demonstrated with time spent at altitude (4) (7), although it is well known that on a per kg body weight basis natives resident to altitude have high aerobic capacities (17) (19) (Fig. 10). In the naturally acclimatized native, Max $\dot{V}O_2$ was not, however, appreciably higher than in well trained athletes who were newcomers to altitude. The comparison of the newcomer athletes with naturally acclimatized Peruvian Indians and newcomer non-athletes is shown in Figure 10.

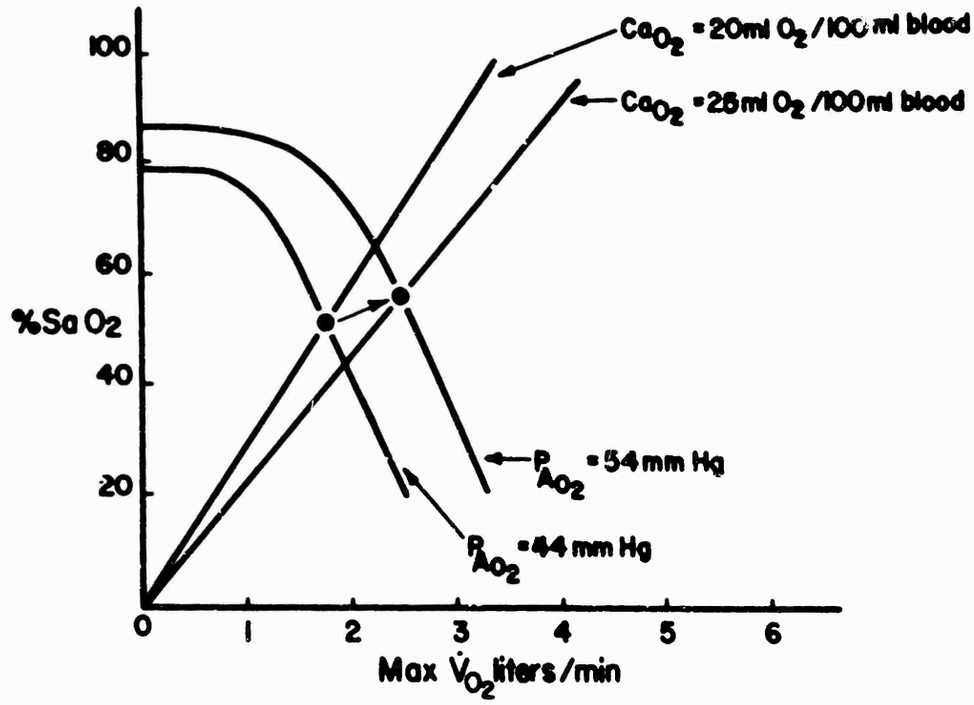

Figure 9. Increase in maximal oxygen intake with acclimatization to an altitude of 5500 m. (Redrawn from R. L. Johnson, 18).

Perhaps one reason why the acclimatization effect on Max $\dot{V}O_2$ is not as pronounced as anticipated is because there may be an optimal red cell flow through pulmonary capillaries which appears to be dependent on the hematocrit. The findings of Richardson and Guyton as discussed by Cerretelli and Debijadji (9) have shown that raising or lowering the hematocrit in dogs above or below on optimum hematocrit range of 35 to 45 reduced the number of cells available for transporting oxygen. There was an associated rise in peripheral resistance followed by a reduction in cardiac output in the polycythemic animals. The findings presented by Tenney at this symposium on CO removal rates from peripheral gas pockets oppose the view of the possible role of an optimal red cell flow in the hematocrit range of 35-45 percent.

Recavarren (24) has suggested that there may be shunting in the lung from arterioles through preterminal arterioles directly into veins in chronically acclimatized natives who have some pulmonary hypertension. This situation favors development of pulmonary edema via venous pressure elevation as well as providing an effective bypass of oxygenation and an aborting of major improvement in Max $\dot{V}O_2$ with long term acclimatization. Grover (14) (15) has indicated that a reduction in maximal heart rate, stroke volume, and cardiac output at altitude may effectively

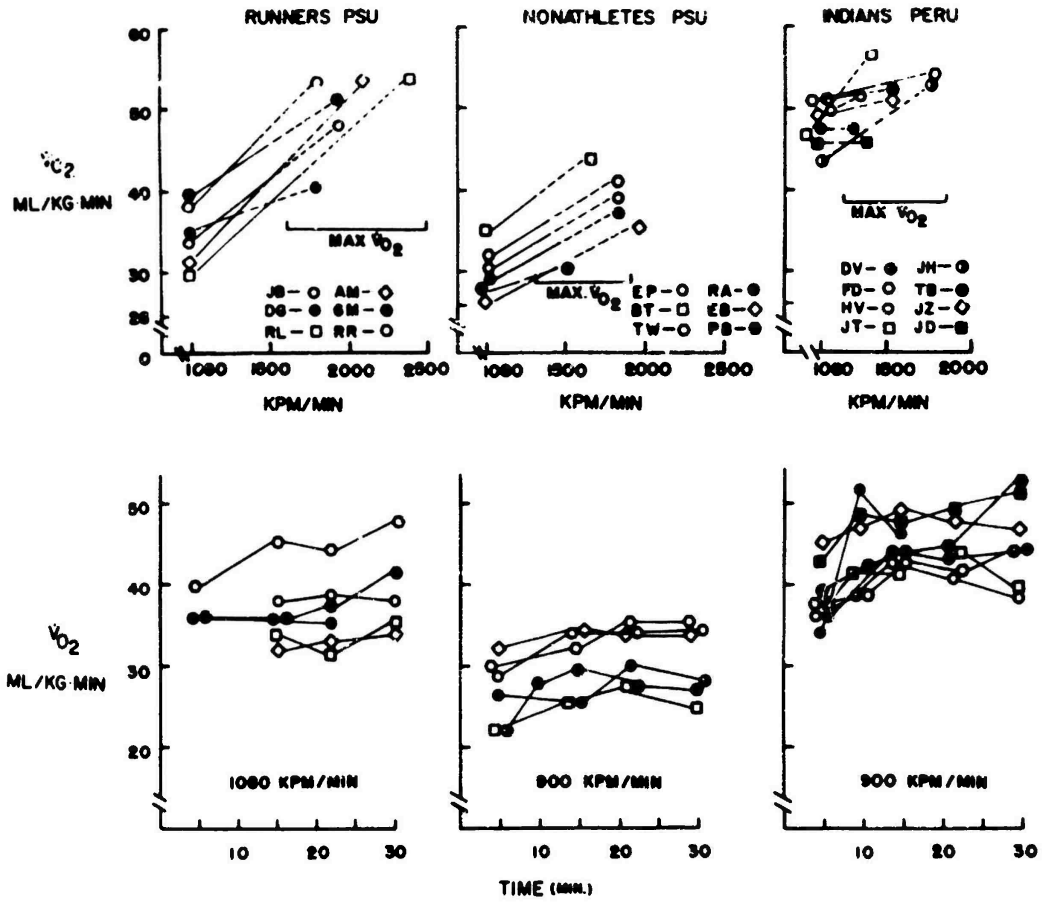

Figure 10. Oxygen consumption per kilogram of body weight in relation to the work load during submaximal and maximal work on the bicycle ergometer at 4000 m. The upper panel shows submaximal oxygen consumption obtained during a five-minute ride at 1080 kpm/min as well as the maximal oxygen intake. The lower panel shows the submaximal oxygen intake obtained during a 30-minute bicycle ride. The well conditioned runners worked at a higher work load than the nonathletes or the naturally acclimatized Indians (19).

reduce aerobic capacity and work performance. Grover has also pointed out that the possible impairment of myocardial oxygenation may be associated with decreased cardiac output at altitude. His presentation at this symposium has elaborated on these observations.

It seems apparent that major factors for limiting aerobic capacity reside in the periphery, particularly in skeletal muscle. Oxygen extraction from blood circulating through active muscle must be nearly complete to facilitate achievement of high levels of Max $\dot{V}O_2$. Very low venous oxygen contents have been found in the femoral veins of well conditioned runners performing maximal

exercise. In addition, muscle capillarity may be increased by extensive conditioning and perhaps by hypoxia. If through acclimatization, muscle myoglobin content is increased and muscle respiratory capacity enchanced, then conditions are favorable for more complete oxygen extraction from blood perfusing muscle. Reynafarje (25) has shown relatively high values for muscle myoglobin for high altitude natives together with higher than normal muscle enzymatic activity for DPNH oxidase, TPNH-cytochrome c reductase and transhydrogenase. The presentation by Tenney at this symposium has suggested the additional factor of an increased number of mitochondria in muscle exposed to hypoxic conditions at barometric pressures of 460 mm Hg or below.

Submaximal Work

The energy cost for performing submaximal work is thought to be proportional to the work load at any altitude. If the work load is well within the man's work capacity, the work can usually be accomplished aerobically and with comparable efficiency barring gross obesity or orthopedic or other disability.

A plot showing this proportionality appears in Figure 11. It is

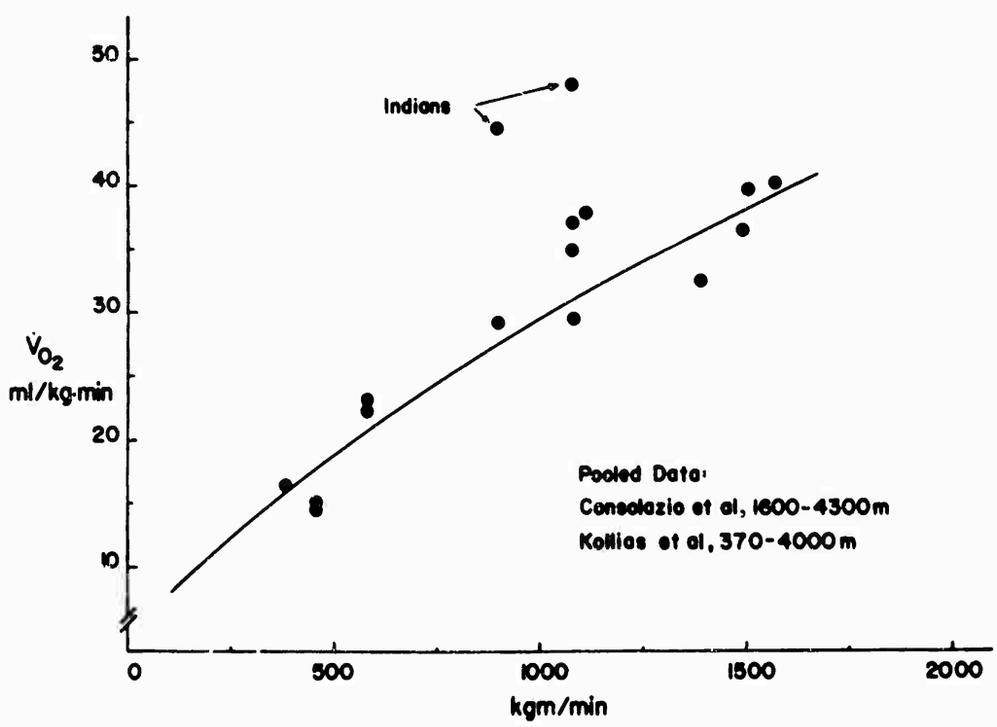

Figure 11. Oxygen consumption per kilogram body weight in young men who performed different work loads on the bicycle ergometer at several altitudes. Data for naturally acclimatized Peruvian Indians at 4000 m fall above the empirical regression line established for the newcomers to altitude. (11) (16) (19).

interesting that two points labeled Indians do not fit the curve. These data were obtained on Peruvian Indians who were working at a relatively low work load on the bicycle ergometer, but nevertheless very close to their aerobic capacity. The reason for the deviation from the regression curve is not clear, but it is suspected that the Indians, being less well trained on the bicycle ergometer, used accessory muscles to help turn the pedals as they neared their work capacity. It is also suspected that their leg strength was lower than that in the two groups of subjects to whom they were compared. The relatively low leg strength may be the reason for their possible use of accessory muscles. It is interesting that Balke (3) found that residents of Morococha at 4500 m utilized more oxygen per kg body weight during submaximal exercise than did Balke himself at the same altitude.

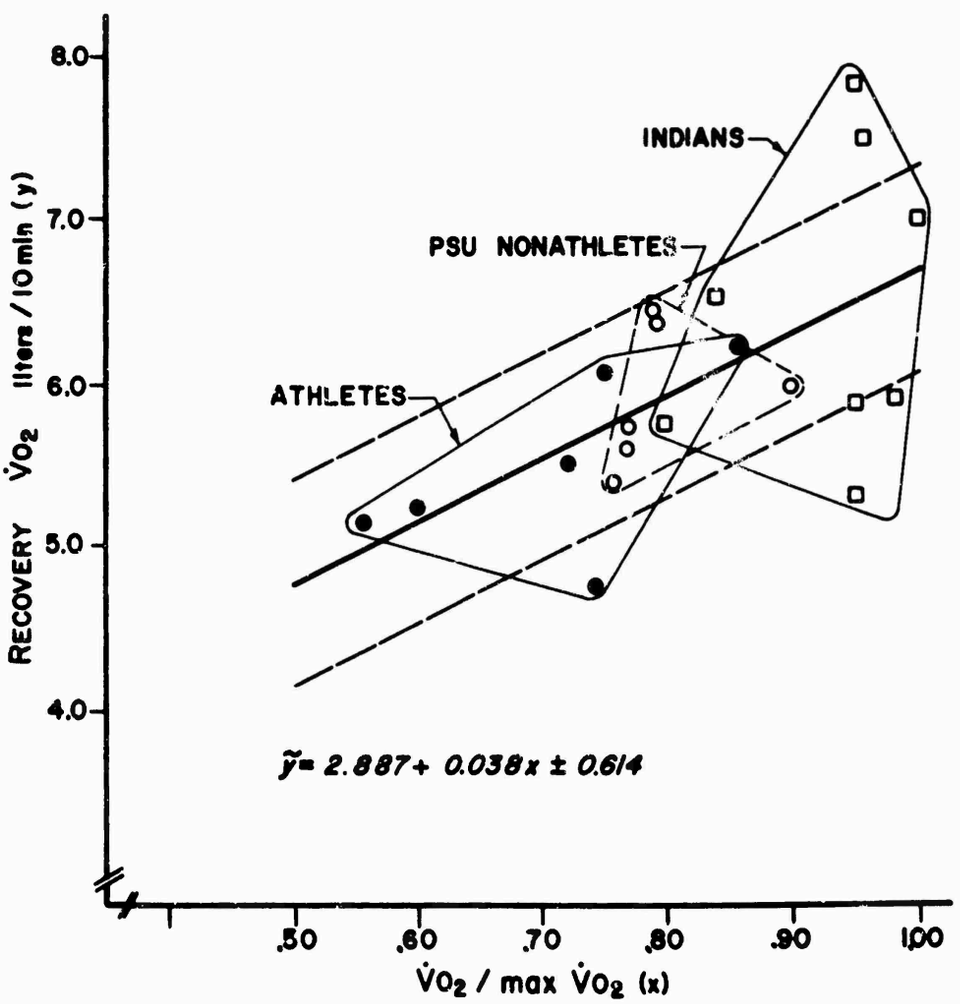

Figure 12. Recovery oxygen intake in relation to the ratio of submaximal oxygen consumption to maximal oxygen intake in the three groups of subjects referred to in Figure 10. The work load for all groups was 1080 kpm/min. (19).

Recovery oxygen consumption is compared in Figure 12 among a group of track athletes, a group of nonathletes who were newcomers to altitude, and the Peruvian Indians who resided at 4000 m. It is interesting that the naturally acclimatized natives were forced to utilize considerable anerobic metabolism to complete a 1080 kpm/min work task that the athletes in particular could easily accomplish more aerobically. The Indians worked at a greater fraction of their aerobic capacity and required a larger recovery oxygen intake. Data from this experiment are presented in a slightly different fashion in Figure 13. Total oxygen utilized per kpm of work accomplished was greater in the Indians than in the other two groups when considered in relation to the proportion of the Max $\dot{V}O_2$ utilized. In both Figure 12 and 13, relatively discrete distributions of the data are apparent. The naturally acclimatized Indian had a relatively low capacity for aerobic work on the bicycle ergometer. It should also be said that while the Indians

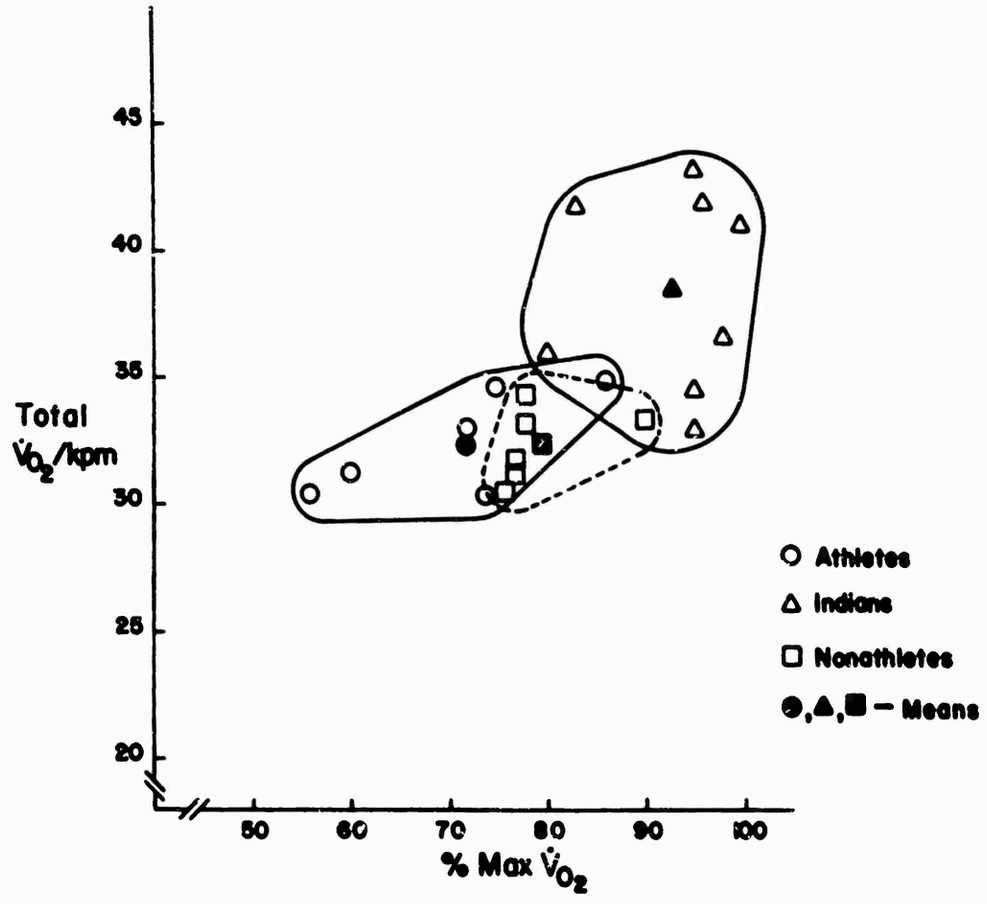

Figure 13. Total oxygen consumption during work and for ten minutes of recovery per kpm of work performed in relation to the percentage of the maximal oxygen intake attained at a work load of 1080 kpm/min. Subjects were the same as those referred to in Figures 10 and 12.

were not unfamiliar with bicycles they were not trained to cycle. Nevertheless, Max $\dot{V}O_2$'s were achieved on the bicycle by the Indians.

A second interesting finding in submaximal work has been reported by Hurtado (17). Whereas the inland natives in Peru required considerable anerobic metabolism to complete work on a bicycle ergometer, the highland Indians that Hurtado studied were able to outrun their sea level counterparts, who were athletes, when working under similar conditions on the treadmill. The highland residents accomplished more work on the treadmill and utilized anerobic mechanisms to a lesser extent (Table 2). In another experiment reported by Hurtado (17) similar data were obtained. The high altitude residents were able to run longer, farther, and more efficiently than the lowlanders. These data are presented in Table 3.

It is apparent that important differences exist between the submaximal test results in the studies of Kollias *et al* (13) and Hurtado (17). Picon-Reategui has indicated (personal communication) that he feels that there are important differences in work capabilities among Peruvian naturally acclimatized natives in different parts of his country. Kollias *et al* studied Altiplano Indians while Hurtado studied natives in the coastal highlands. It is important, however, to make work capability comparisons among different groups with a procedure well suited to the characteristics and capabilities of the subjects. It may be inappropriate to use tests suitable for European and North American subjects on the smaller

Table 2. Treadmill Work Capacity at Sea Level and Altitude (17) Work Conditions: speed 135.3 m/min 18.9% gradient

VARIABLE	ATHLETES SEA LEVEL	NATIVES 4540 m
Duration of Exercise	13′ 34″	16′ 4″
0_2 Debt cc/kg	9.4	4.6*
Blood Lactate meq/l	8.86	5.66

***Only 5 of the 12 subjects showed an oxygen debt.**
n = 12

Table 3. Treadmill Work Capacity at Sea Level and Altitude (17) Work Conditions: speed 132.4 m/min, 11% gradient

VARIABLE	SEA LEVEL	4540 m
Duration of Exercise, min	34.2	59.4*
Distance traveled, km	4.55	7.85
V_{0_2} cc/kgm	2.66	2.43
0_2 Debt litters/m^2	2.96	2.39
kcal/min. m^2	6.7	5.8
Pulse rate	183	160
V_E/V_{0_2}	27.8	36.1
0_2 Pulse	12.7	11.5
Net Efficiency, %**	19.9	22.2
Lactic Acid meq/l	6.4	3.2

All gas volumes STPD
***3 men ran over 1 hour**
****Less resting metabolism**
n = 10

Andean Indians. The treadmill used by Hurtado may be a superior ergometer for testing the highlanders although the bicycle has been widely used for testing divergent indigenous populations.

In any event, with respect to submaximal work the findings discussed diverge from the ordinary and are therefore of interest. Acceptable explanations should be sought that take into account the type of work performed, the physical condition of the subjects, their motivation, as well as their history of altitude exposure.

ACKNOWLEDGMENTS

I am indebted for the contributions of others reported in the illustrations and texts. In addition I wish to thank J. Kollias, P. Baker, E. Picon-Reategui as well as the many others who worked diligently on the contracts.

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INFLUENCE OF HIGH ALTITUDE ON CARDIAC OUTPUT RESPONSE TO EXERCISE

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The performance of aerobic work is dependent upon oxygen transport. Since man's capacity for work is diminished at high altitude, it is reasonable to postulate that this is a consequence of some compromise in the oxygen transport system. By virtue of the shape of the oxygen-hemoglobin dissociation curve combined with an increase in blood hemoglobin concentration, arterial oxygen content is relatively well maintained. It is, therefore, the cardiac output response to exercise which may be impaired at high altitude.

A number of investigators have tested this hypothesis. However, interpretation of the results is complicated by variations in absolute altitude, duration of exposure to altitude, nature of the exercise test, differences in the technique employed to measure cardiac output, and other factors.

In the present report, the limited data on this subject will be summarized. For clarity, the data have been grouped in relation to the duration of exposure to altitude. A graphic method of presentation has been selected which permits the reader to visualize cardiac output and its components, heart rate and stroke volume, in relation to absolute oxygen uptake. Most data are presented with the same format to facilitate comparison between studies. This has required interpolation of some graphic data and recalculation from some of the original reports. I trust that the authors will understand that these modifications of their presentations were necessary to achieve uniformity and hence, hopefully, greater clarity.

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First Hour At Altitude

With the use of decompression chamber, Stenberg, Ekblom and Messin (11) exposed 6 men to a simulated altitude of 4000 m. The age range of the subjects was 20 to 36 years; 3 were sedentary and 3 were well trained. Exercise was performed with the subject sitting on a bicycle ergometer. Three work loads were employed, 2 submaximal and 1 maximal, separated by periods of rest varying from 5 to 30 minutes. The duration of submaximal exercise was not stated, but maximal exercise produced exhaustion in 6 minutes. Cardiac output was determined by the dye dilution technique. Measurements at simulated altitude were made 10 to 60 minutes following decompression.

At high altitude, maximum oxygen uptake ($\dot{V}O_2$) was reduced an average of 28%, but maximum heart rate (HR) was not depressed. For a given level of submaximal $\dot{V}O_2$, HR was faster at altitude, stroke volume (SV) was decreased, while cardiac output ($\dot{Q}$) was greater (Fig. 1). At maximal $\dot{V}O_2$, HR, SV, and $\dot{Q}$ were all unchanged from their values during maximal exercise at sea level.

One to Eight Days at Altitude

Following ascent to high altitude, serial daily measurements of $\dot{Q}$ have been made in only two studies. Klausen (6) made observations on 2 young men at 3800 m (additional data from D. B. Dill introduced another significant variable, age, which will not be covered in this summary). Their ages were 32 and 34 years, and neither was in "exceptionally good physical condition." Each subject exercised at 1 or 2 submaximal work loads while sitting on a bicycle ergometer. Cardiac output was measured by the carbon dioxide rebreathing method after the subject had been exercising for 15 minutes.

The findings after 1 day at high altitude differed somewhat from the preceding data at 1 hour. For a given submaximal level of $\dot{V}O_2$, both HR and $\dot{Q}$ were increased, but Klausen found that SV was also clearly increased in subject KK (Fig. 2). On succeeding days, $\dot{Q}$ declined, primarily as a result of a decrease in SV, and eventually both SV and $\dot{Q}$ were less than the sea level values. However, the time course of these changes was much more rapid in EP (Fig. 3) than in KK (Fig. 2). Apparently there are marked individual differences in the rate of circulatory adaptation to high altitude.

Serial measurements of $\dot{Q}$ were also made by Asmussen and Consolazio (2) in 2 subjects following ascent to 4300 m. The ages of the subjects were 27 and 33 years and both were in "good

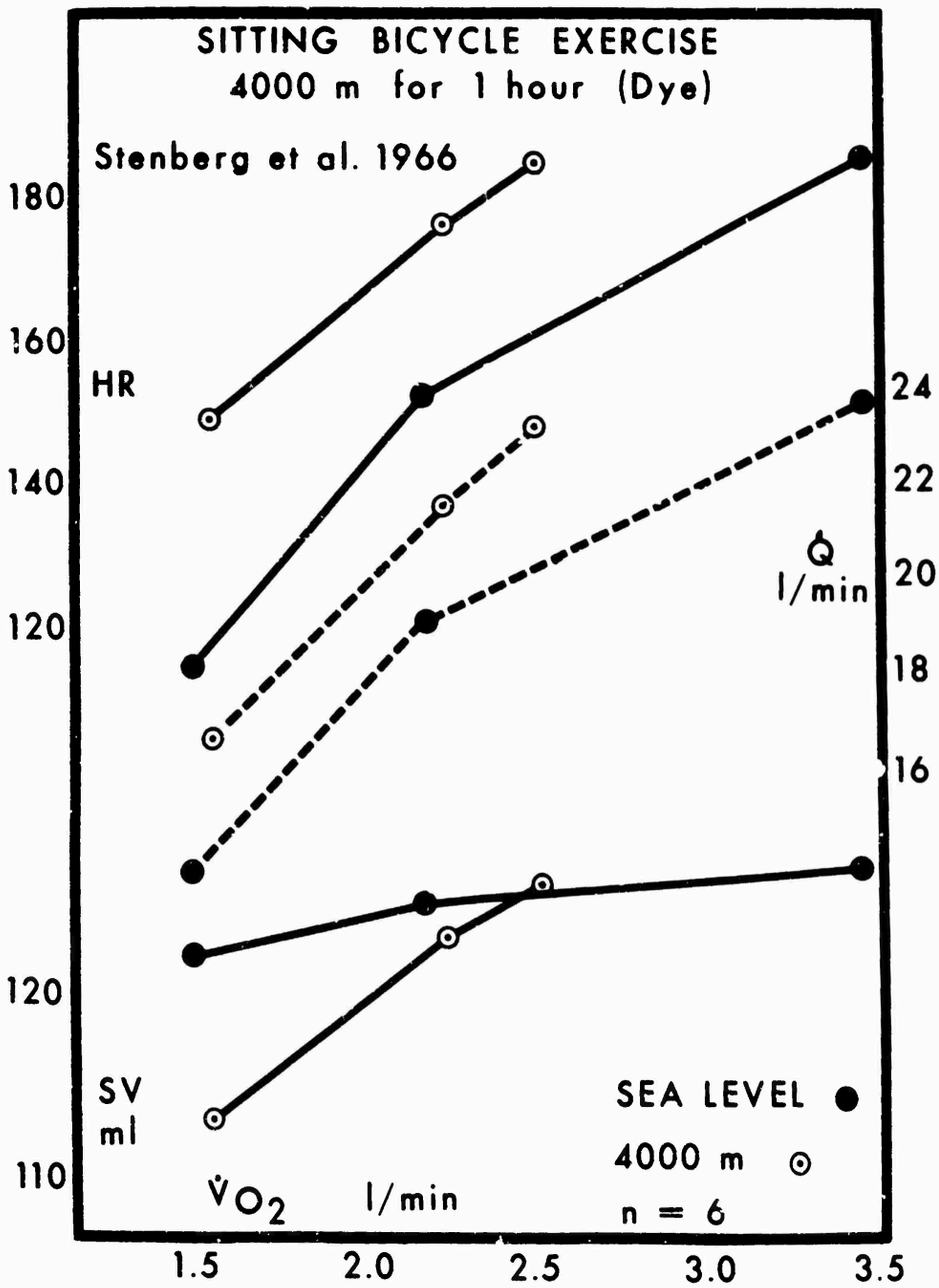

Figure 1. Cardiac output ($\dot{Q}$), heart rate (HR), and stroke volume (SV) in subjects (n=6) exercising at sea level (●) and 10 to 60 minutes after decompression to 4000 m (⊙). Reference 11.

physical condition". Each subject exercised at two submaximal work loads while sitting on a bicycle ergometer, but the durations of the exercise and the intervening rest period were not reported. The acetylene method was used to determine $\dot{Q}$.

Results were qualitatively similar to those of Klausen. No data were collected during the first two days because the subjects

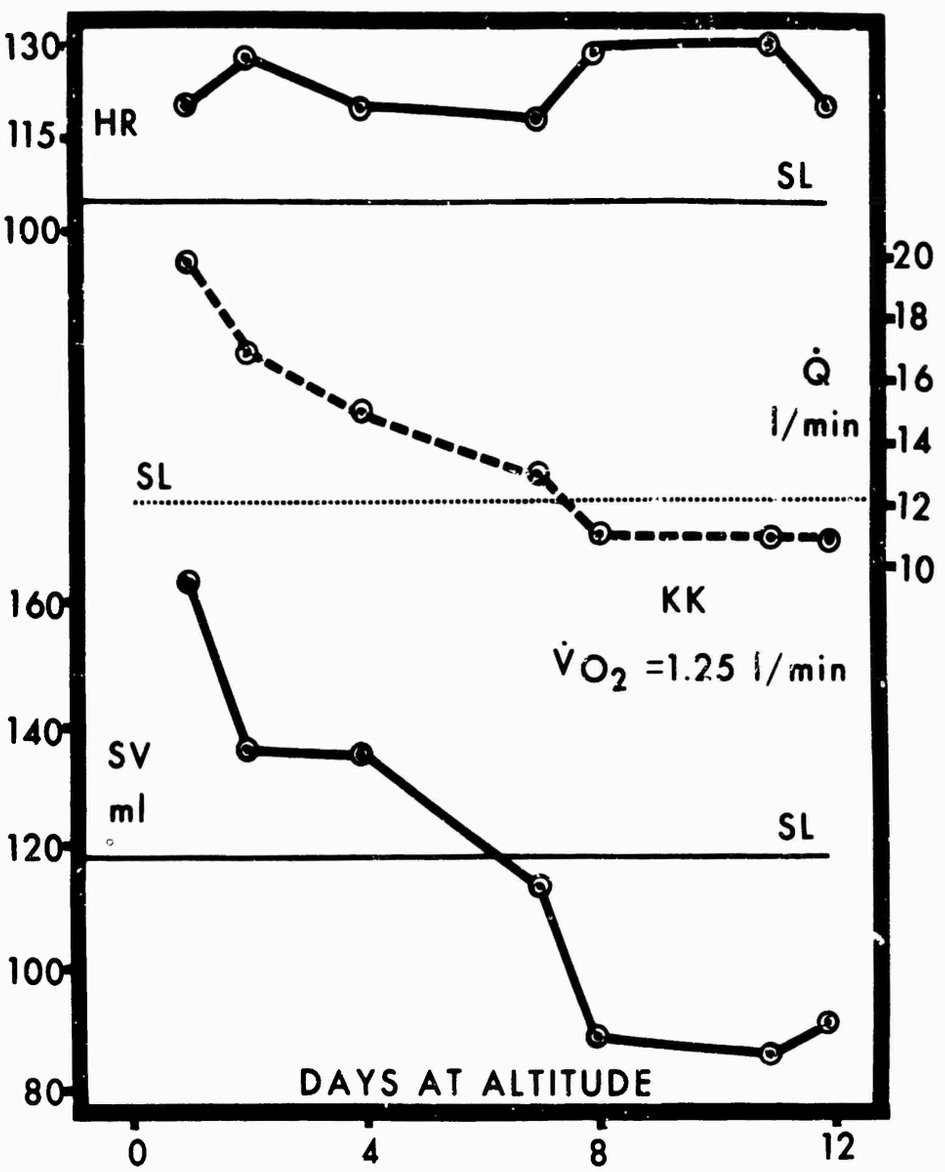

Figure 2. Cardiac output ($\dot{Q}$) and its components SV and HR in one subject, KK. exercising at a single submaximal work load requiring a $\dot{V}O_2$ of 1.25 l/min. Values at sea level (SL) are indicated by the three horizontal lines. Serial data over the first 12 days at 3800 m are plotted (Θ). Reference 6.

suffered from acute mountain sickness. By the third day, HR, SV, and $\dot{Q}$ were all greater than at sea level for the same submaximal work load (Fig. 4). Over the next 4 days, $\dot{Q}$ decreased as a result of a progressive decrease in SV, but the values remained greater than those obtained at sea level. Therefore, after both subjects had been at 4300 m for 4 to 5 days, HR, SV, and $\dot{Q}$ were greater than they had been at sea level for the two submaximal values of $\dot{V}O_2$ (Fig. 5).

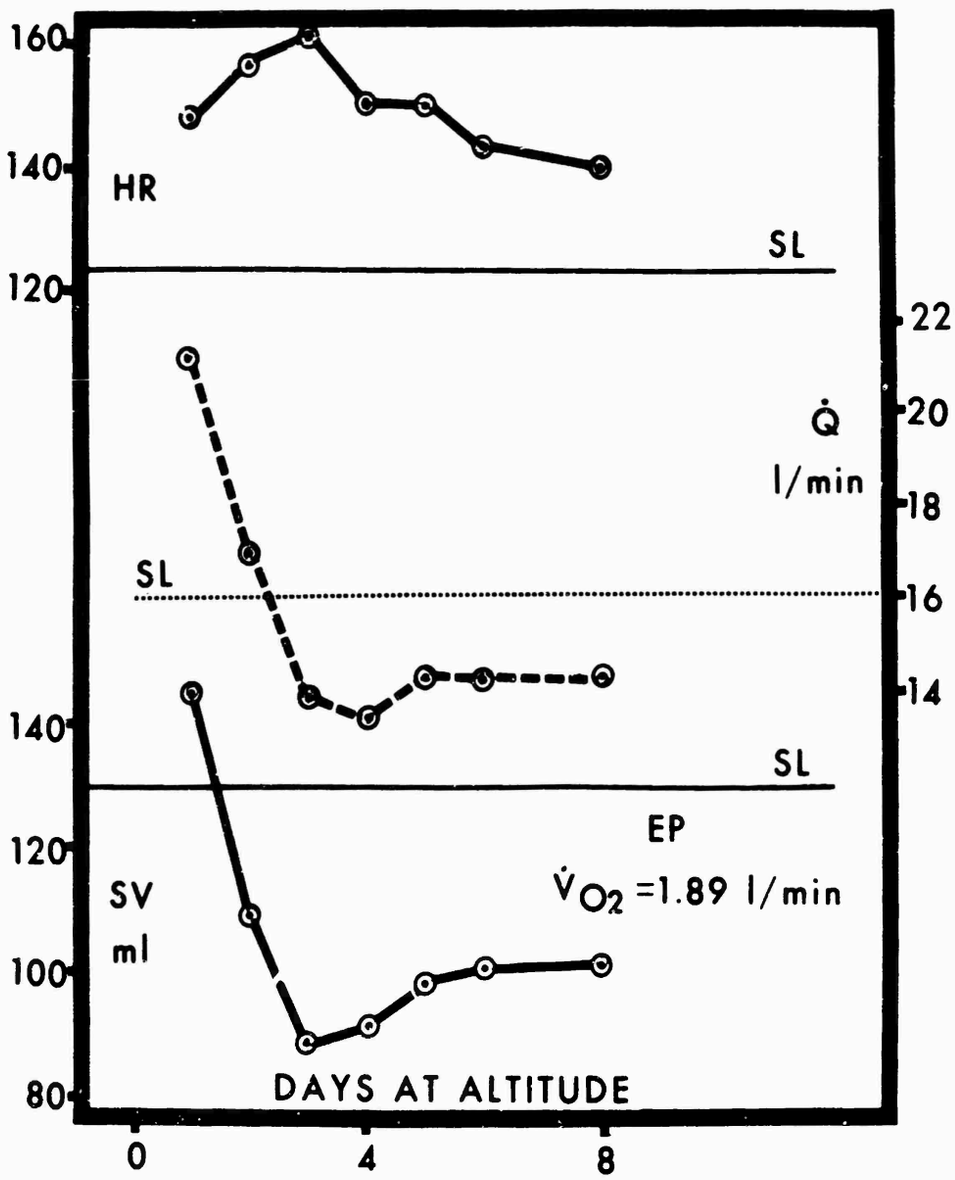

Figure 3. Cardiac output ($\dot{Q}$) and its components SV and HR in one subject, EP, exercising at a single submaximal work load requiring a $\dot{V}O_2$ of 1.89 l/min. Values at sea level (SL) are indicated by the three horizontal lines. Serial data over the first 8 days at 3800 m are plotted (Θ). Reference 6.

Vogel, Hansen, and Harris (12) also determined $\dot{Q}$ during the first 4 days at 4300 m, but daily measurements in the same individual were not obtained. The 8 subjects were normal, healthy, nonobese soldier volunteers, 18 to 24 years of age, whose state of physical conditioning was not specified. Exercise was performed with the subject sitting on a bicycle ergometer. Each subject exercised at a "mild" (50 Watt) work load for 15 minutes, followed without rest by a "moderate" load (65% of maximum) for an

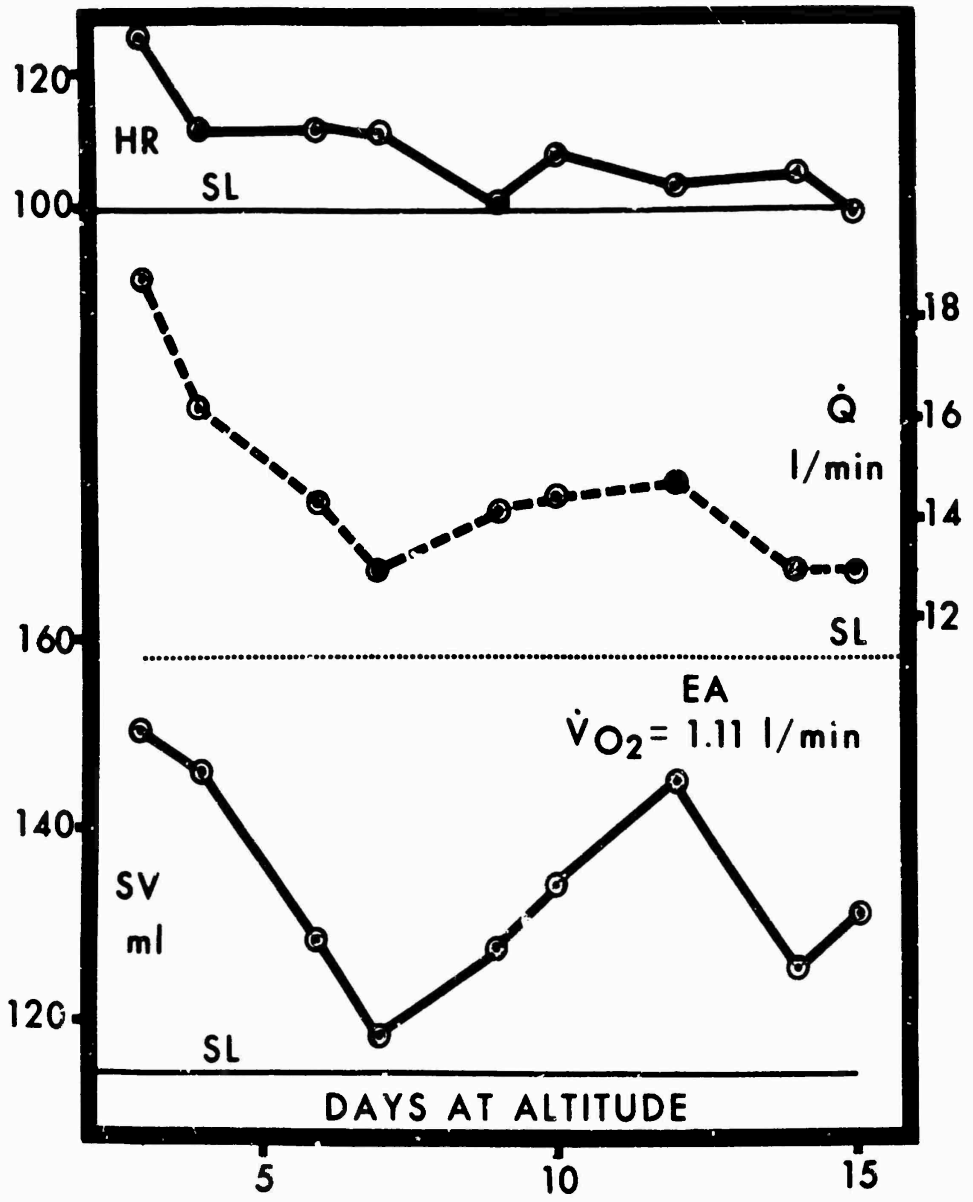

Figure 4. Cardiac output ($\dot{Q}$) and its components SV and HR in one subject, EA, exercising at a single submaximal work load requiring a $\dot{V}O_2$ of 1.11 l/min. Values for sea level (SL) are indicated by the three horizontal lines. Serial data from the 3rd to the 15th day at 4300 m are plotted (Θ). Reference 2.

additional 10 minutes, and culminating in a maximal effort producing exhaustion in 4-6 minutes, i.e., the subject exercised for 30 minutes without stopping. Cardiac output was determined by the dye dilution method.

Results are presented for only those 8 subjects who were taken "abruptly" from sea level to 4300 m. (A second group was taken "gradually" with one week sojourns at 1600 m and 3500 m before

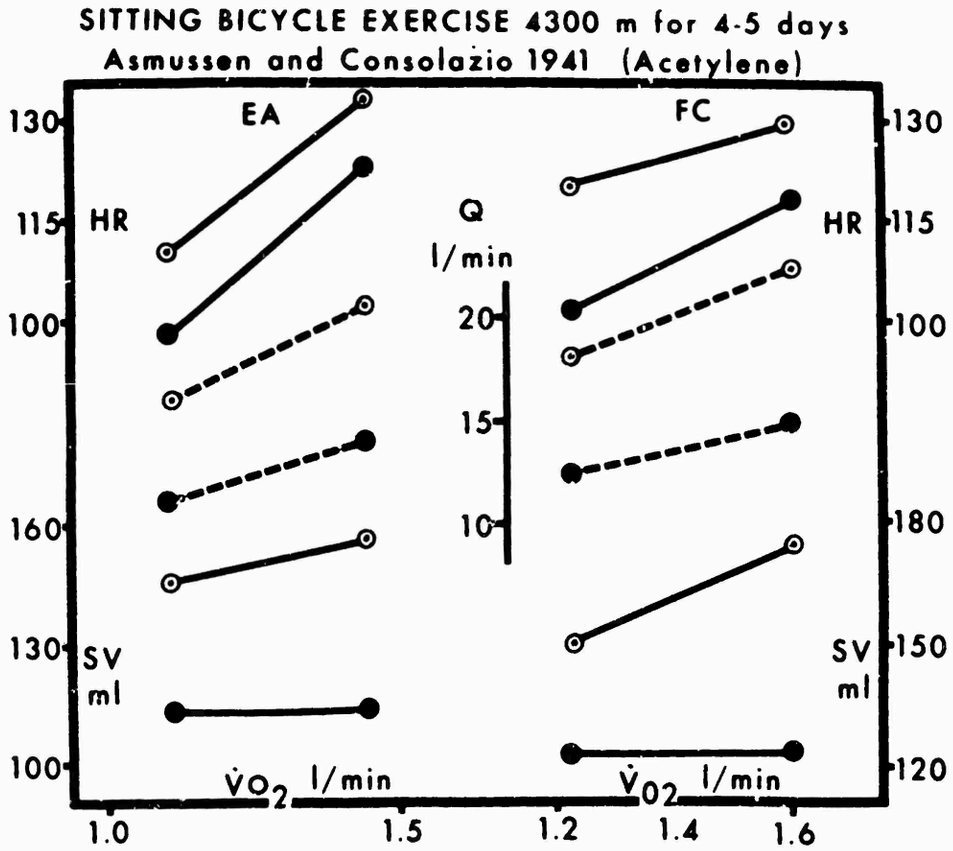

Figure 5. Individual values of $\dot{Q}$, SV, and HR for each of two subjects, EA and FC, during submaximal exercise at sea level (●) and after 4-5 days at 4300 m (Θ). Reference 2.

arriving at 4300 m). The original data were published as ml/kg for $\dot{V}O_2$ (5) and for $\dot{Q}$ (12). Actual body weights were not presented. However, from the published values for HR and SV, absolute $\dot{Q}$ could be calculated. Thus, it was possible to calculate that for these 8 subjects, average body weight was 71 kg at sea level, 71 kg after 1-4 days at 4300 m and 69 kg after 15-18 days at 4300 m. Absolute values for $\dot{V}O_2$ were then calculated for sea level and 1-4 days at high altitude.

Ascent to 4300 m produced a decrease in maximum $\dot{V}O_2$ of only 14% while maximum HR declined from 186 to 177. At both levels of submaximal $\dot{V}O_2$, HR, SV, and $\dot{Q}$ were greater than at sea level (Fig. 6). During maximal exercise, despite the reduction in maximal HR, $\dot{Q}$ was actually greater than at sea level (15.9 compared with 14.7 l/min) indicating a greater SV.

One to Four Weeks at Altitude

The 8 subjects in the preceding investigation were studied again after they had been at 4300 m for 15 to 18 days (12). During exer-

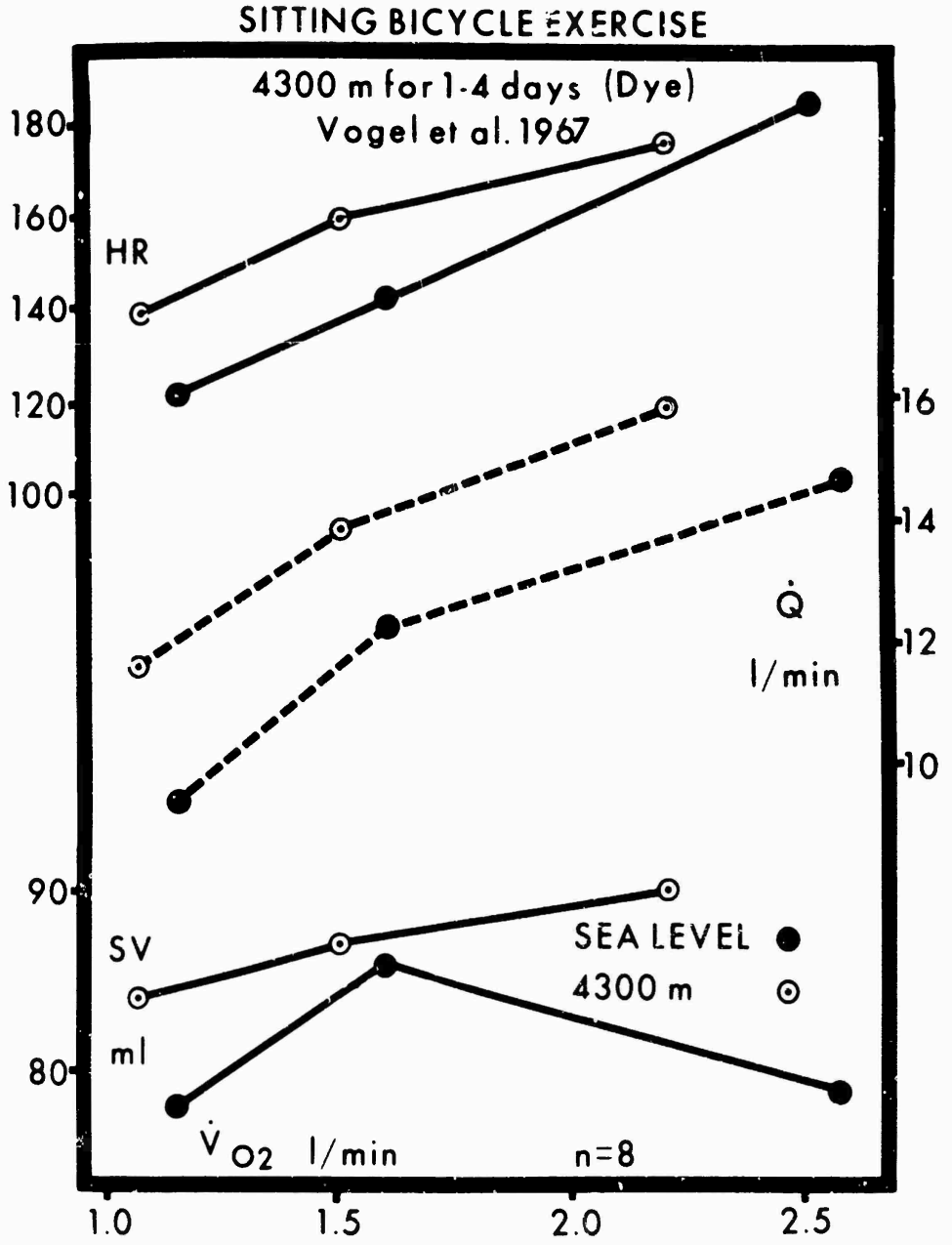

Figure 6. Average values for $\dot{Q}$, SV and HR from subjects (n=8) exercising at sea level (●) and after 1-4 days at 4300 m (Θ). Reference 12.

cise, the same work loads were employed as in the studies at 1-4 days, and since $\dot{V}O_2$ could not be obtained, it has been assumed for the purposes of this analysis that the values for $\dot{V}O_2$/kg were also the same. With an average body weight of 69 kg, this gave slightly lower absolute values for $\dot{V}O_2$. These approximations are considered to be sufficiently accurate for plotting the data in Fig. 7.

After more than 2 weeks of adaptation to 4300 m, $\dot{Q}$ for a given $\dot{V}O_2$ was almost the same as it had been at sea level. This resulted from a slight decrease in SV and a slight increase in HR

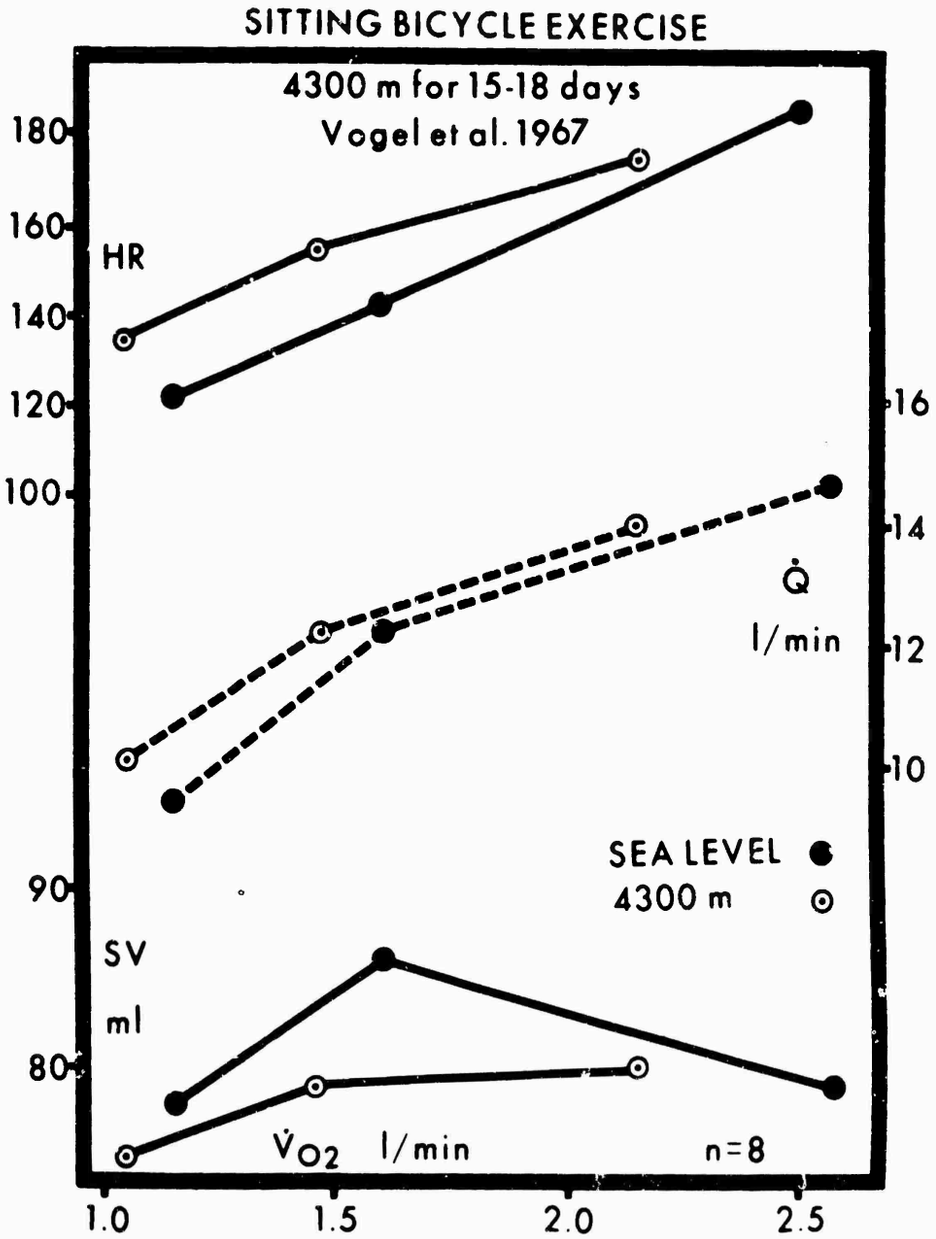

Figure 7. Average values for $\dot{Q}$, SV and HR from subjects (n=8) exercising at sea level (●) and after 15-18 days at 4300 m (⊙). Reference 12.

(Fig. 7). With maximal exercise, $\dot{Q}$ was slightly less than at sea level (14.0 compared with 14.7 l/min) and maximum HR was depressed from 186 to 175 while SV was not changed.

In the study by Klausen (6) described earlier, data were obtained from 3 men after 3 to 4 weeks at 3800 m. At each of 2 submaximal levels of $\dot{V}O_2$, $\dot{Q}$ was less than it had been at sea level as the result of a marked reduction in SV which was not offset by a higher HR (Fig. 8).

Asmussen and Consolazio (2) also repeated their observation

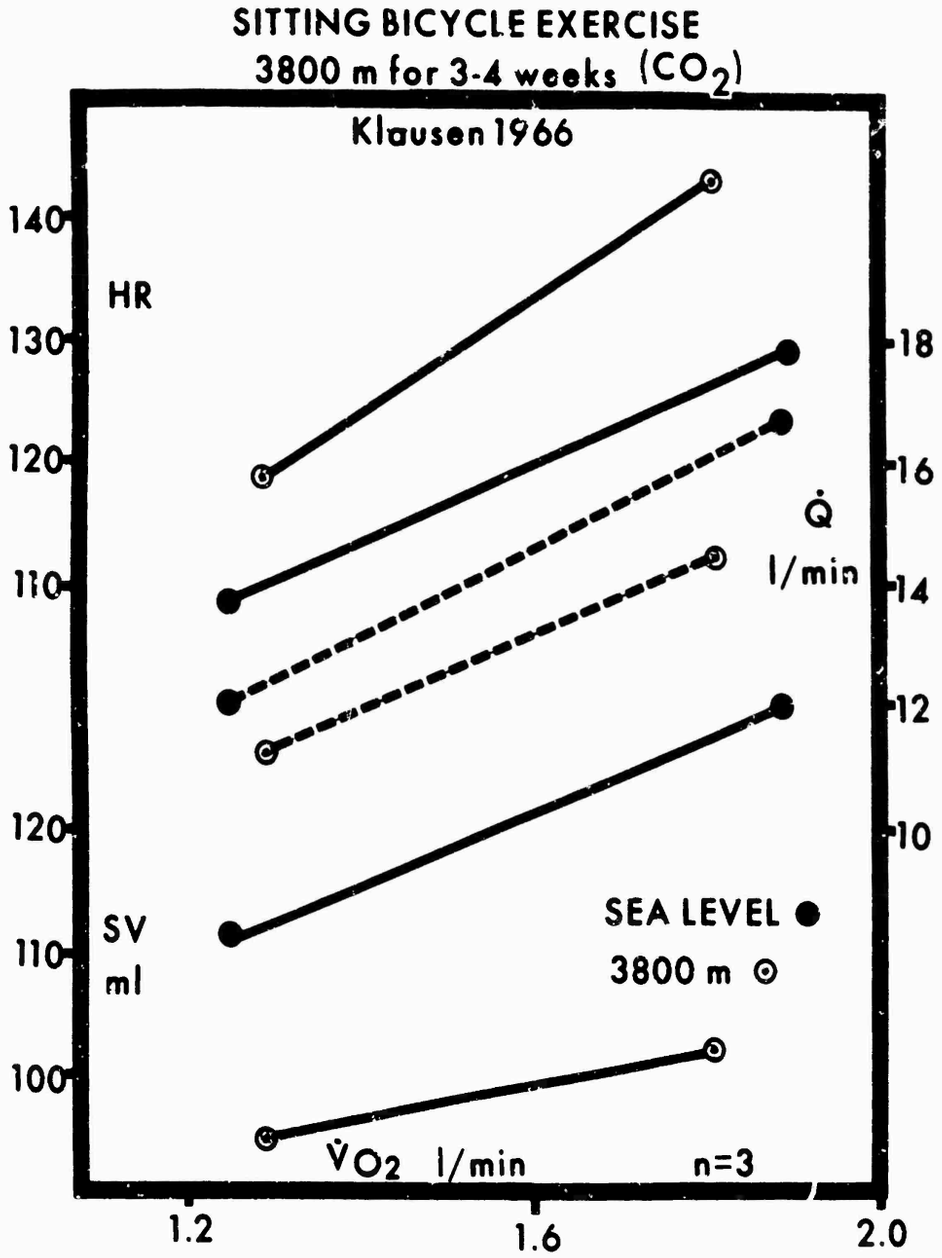

Figure 8. Average values for $\dot{Q}$, SV and HR from subjects (n=3) exercising at sea level (●) and after 3-4 weeks at 3800 m (⊙). Reference 6.

on 2 subjects after 15 days at 4300 m. During submaximal exercise, $\dot{Q}$ remained greater than it had been at sea level as a result of an increase in SV and little change in HR (Fig. 9).

Also working at 4300 m, Grover *et al.* (4) studied 3 young men performing maximal exercise while seated on a bicycle ergometer. They were 20 to 21 years of age and in excellent physical condition at the beginning of the study, although they were not athletes. A work load was selected which produced exhaustion in

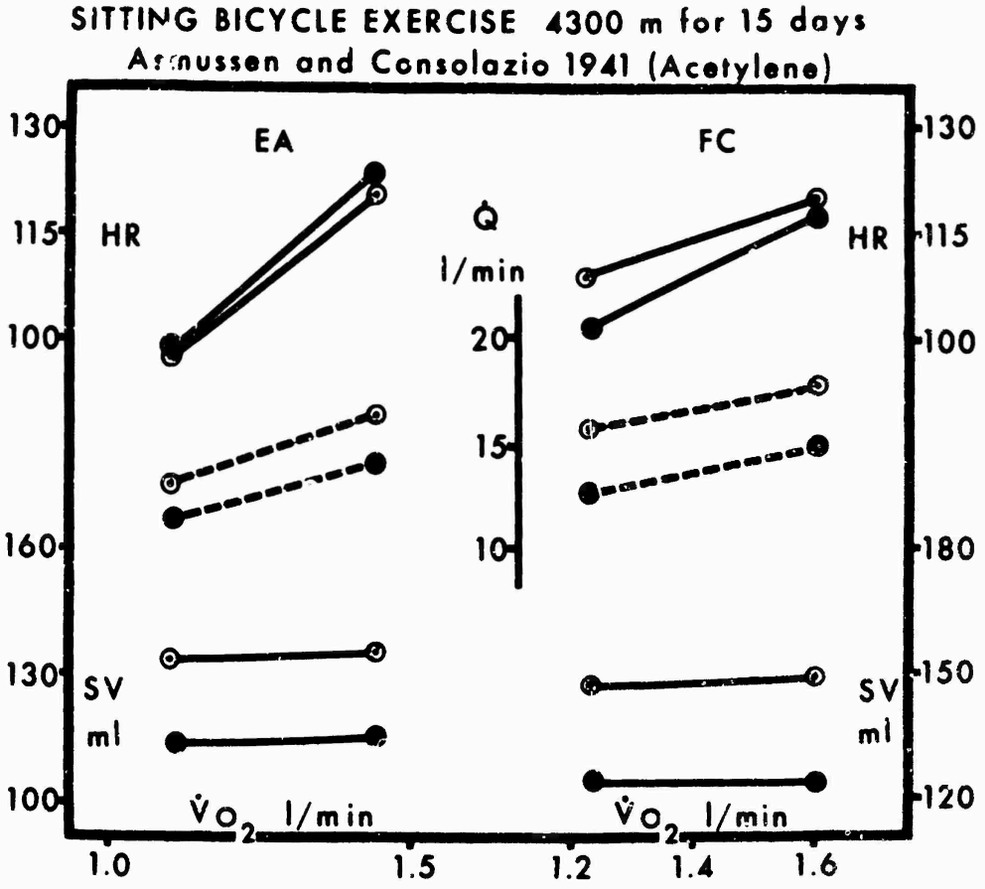

Figure 9. Individual values of $\dot{Q}$, SV and HR for each of two subjects, EA and FC, during submaximal exercise at sea level (●) and after 15 days at 4300 m (Θ). Reference 2.

6 minutes. Cardiac output was determined by the dye dilution technique. After 14-15 days at 4300 m, maximum $\dot{V}O_2$ was reduced 30%. Maximum HR remained unchanged in 2 subjects, and decreased in the third from 187 to 166. Maximum $\dot{Q}$ and the associated SV were significantly reduced in all 3 subjects (Fig. 10).

At the lesser altitude of 3100 m, Alexander, *et al.* (1) studied 8 young men who ranged in age from 22 to 33 years. All were sedentary and none participated in any regular physical conditioning program. Cardiac output was determined by the direct Fick method for oxygen which required cardiac catheterization. Hence, the subjects were studied in the supine position while performing leg exercise with a bicycle ergometer. The subjects exercised at 4 submaximal work loads, each lasting 9 minutes, and separated by 15 minute rest periods. Cardiac output was determined during the final 2 minutes of exercise when steady state conditions had been established. After 10 days at 3100 m, for each level of $\dot{V}O_2$, $\dot{Q}$ was significantly less than at sea level as the result of a marked reduction in SV, with little change in HR (Fig. 11).

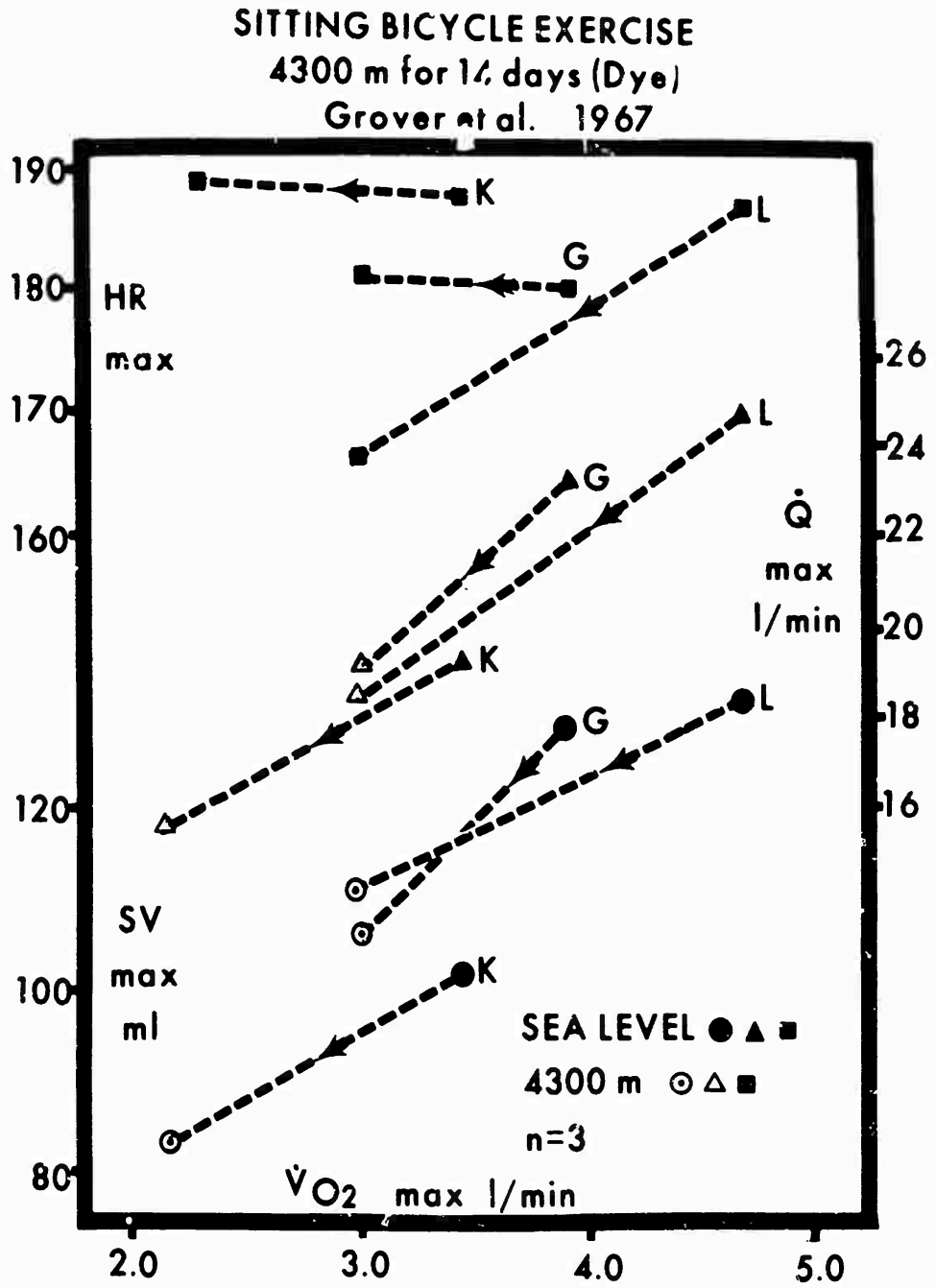

Figure 10. Individual values of $\dot{Q}$, SV and HR for each of three subjects, K, G, and L, performing maximal exercise at sea level (closed symbols) and after 14 days at 4300 m (open symbols). Dashed lines with arrows indicate the decrease in maximum $\dot{V}O_2$ at 4300 m and the associated changes in $\dot{Q}$, SV and HR. Reference 4.

Prolonged Exposure to Altitude

Pugh (8) made observations on 4 men 23 to 35 years old. They were members of the Himalayan Scientific and Mountaineering Expedition 1960-1961, and had been at 5800 m for 2 to 3 months

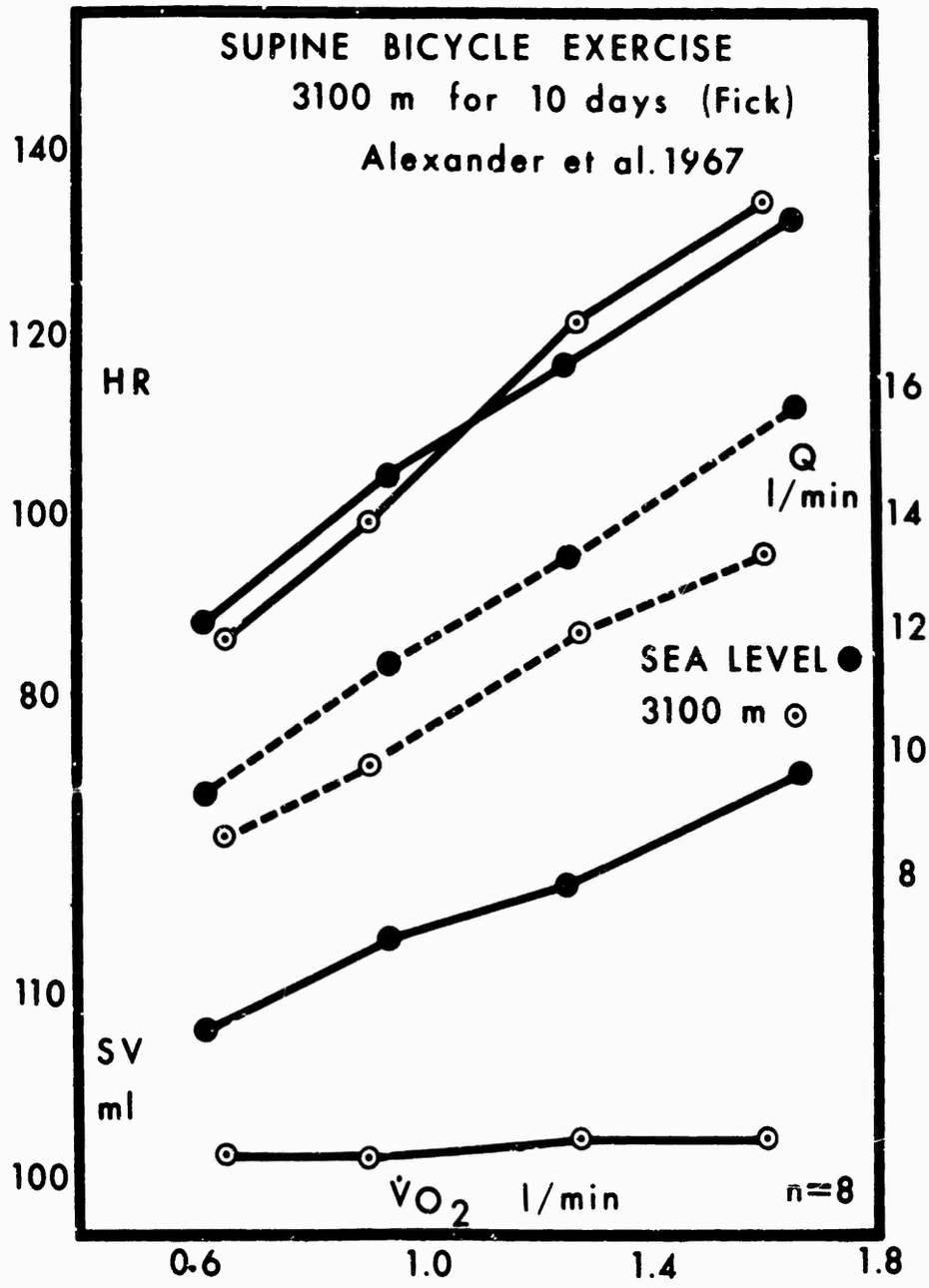

Figure 11. Average values for $\dot{Q}$, SV and HR from subjects (n=8) during four levels of submaximal exercise at sea level (●) and after 10 days at 3100 m (⊙). Reference 1.

although they had been above 4600 m for 4 to 7 months. While they were in reasonably good physical condition, there was some evidence of physical deterioration at this extreme altitude. Exercise was performed in the sitting position on a bicycle ergometer at both submaximal and maximal work loads, the former lasting 11 minutes and the latter producing exhaustion in 5-6 minutes. Only 2 periods of exercise were performed on any

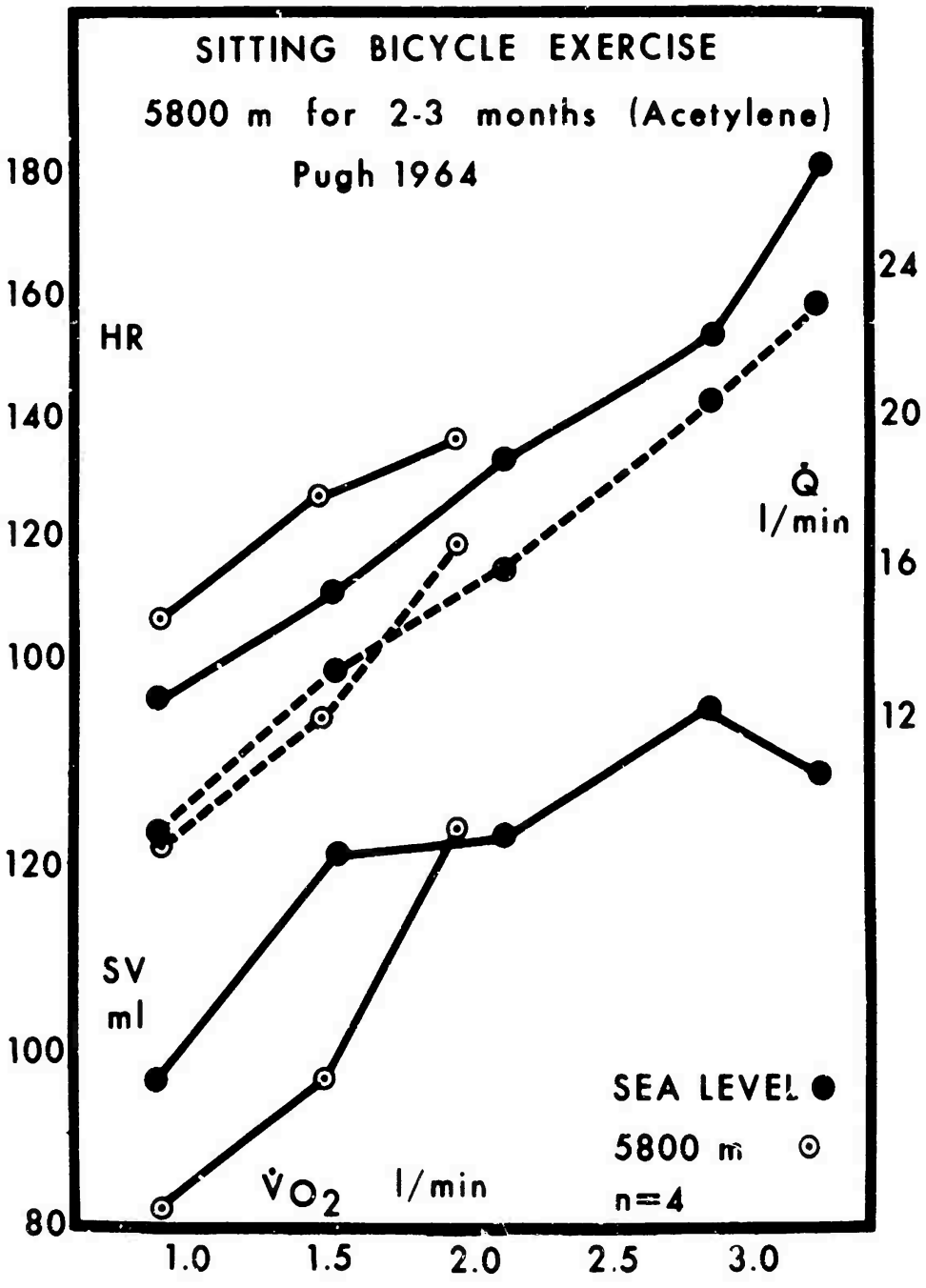

Figure 12. Average values for $\dot{Q}$, SV and HR from subjects (n=4) exercising at sea level (●) and after 2-3 months at 5800 m (⊙). Reference 8.

one day. Cardiac output was determined by the acetylene rebreathing method.

Maximum $\dot{V}O_2$ was reduced 40% and maximum HR was lowered from 182 to 136. At submaximal $\dot{V}O_2$, $\dot{Q}$ was the same as at sea level, while SV was reduced and HR increased (Fig. 12). However, maximum $\dot{Q}$ was reduced from 23.7 to 16.8 l/min, while the associated SV was little changed from the sea level value.

Discussion

Acute hypoxia in normal man at rest produces tachycardia and an increase in $\dot{Q}$. However, changes in SV are dependent upon posture. If the subject is supine, SV increases, (7) but if the subject is in the sitting position, SV decreases (9). During the first hour at altitude (Fig. 1), exercise in the sitting position is also associated with an increased $\dot{Q}$, tachycardia, and a SV which is decreased at submaximal work loads, but which reaches pre-hypoxic levels with maximal exertion. It is therefore rather surprising to find that after 1 or 2 days at altitude, SV has increased to values considerably greater than at sea level (Fig. 2, 3, 4). Values for SV of 150 ml (Fig. 4) and 163 ml (Fig. 2) are indeed remarkable for subjects whose SV was less than 120 ml during similar exercise at sea level, suggesting that the accuracy of the measurements of $\dot{Q}$ should be questioned.

With the passage of several days, there is a progressive decrease in $\dot{Q}$ primarily related to a decreasing SV (Fig. 2, 3, 4). The time course of these changes appears to vary from one individual to another. Therefore, after e.g. 4 days, SV may still be greater than normal in one subject (KK) but less than normal in another (EP). Undoubtedly these differences between individuals will influence average values for any group as in Figs. 5 and 6.

The behavior of $\dot{Q}$ with maximal exercise during the first days at altitude is important. Figure 6 indicates that the maximum value of $\dot{Q}$ at 4300 m was greater than the maximum value measured at sea level. This latter value of $\dot{Q}$, 15.9 l/min, was obtained at a $\dot{V}O_2$ of 2.6 l/min. Examination of Figures 1 and 12 reveals that for a $\dot{V}O_2$ 2.6 l/min at sea level, $\dot{Q}$ was found to be 20.5 l/min by Stenberg (11) and 19.0 l/min by Pugh (8). Therefore, the $\dot{Q}$ of 15.9 l/min obtained by Vogel *et al.* (12) at sea level is surprisingly low, and it is with reference to this low control value that $\dot{Q}$ was found to increase at high altitude. A partial explanation for the unusual sea level data may be indicated by the declining SV (Fig. 6). A decrease in SV after 30 minutes of continuous exercise has been observed by other investigators (3, 10). Obviously in studying the cardiovascular response to exercise, the nature of the exercise test is important. It may well be that a test of 30 minutes duration will give results which are more applicable to man's capacity for sustained exertion than will the 5 minute test.

After the first week at high altitude, there is general agreement on the cardiac response to submaximal exercise (Table 1). For a given $\dot{V}O_2$, SV is apparently decreased (Fig. 7, 8, 11, 12); the

Table 1. Changes in cardiac output during submaximal exercise following ascent to high altitude.

Δ HR	Δ SV	Δ $\dot{Q}$	ALTITUDE	FIGURE
1-5 days				
+	+	+	3800 m	2, 3
+	+	+	4300 m	5
+	+	+	4300 m	6
More than 1 week				
±	-	-	3100 m	11
+	-	-	3800 m	8
+	-	0	4300 m	7
+	-	0	5800 m	12
0	+	+	4300 m	9

increased values of SV found by Asmussen and Consolazio (Fig. 9) have been questioned on the basis of methodology (6). The HR may or may not be increased enough to offset the smaller SV, and hence $\dot{Q}$ may be unaltered (Fig. 7, 12) or decreased (Fig. 8, 11). However, as a consequence of the decrease in SV and/or a reduction in maximum HR, the maximum value of $\dot{Q}$ appears to be reduced after one or more weeks at high altitude (Fig. 7, 10, 12, Table 2). The mechanisms by which SV and maximum HR are reduced at high altitude remain to be described.

Table 2. Changes in maximum cardiac output following ascent to high altitude for more than one week

ΔHR_{MAX}	ΔSV_{MAX}	$\Delta \dot{Q}_{MAX}$	ALTITUDE	FIGURE
-	0	0	4300 m	7
-,0	-	-	4300 m	10
-	0	-	5800 m	12

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GENERAL DISCUSSION

DR. STAUB: This has been a stimulating morning. It is an area that I do not work in, so I am always eager to learn more about cardiac function and metabolic problems. It seems to me, however, that what you are looking for is the most sensitive portion, that is, the first part to break down in what Alf Holmgren calls the oxygen conduction path. If that is true then studying the maximum exercise level or maximum oxygen intake, or whatever you choose to call it, is not the place to look. I should think you would want to look for the anaerobic threshold which Wasserman, *et al* (1), found by the single-breath respiratory quotient method to be between one and one and one half liters VO_2/min in normal healthy men at sea level. At any exercise level above the anaerobic threshold you are doing non-steady state exercise which means you cannot keep it up indefinitely. The relatively low level of exercise at which anaerobic metabolism begins to increase signifies that the most sensitive portion of the oxygen conduction path lies in tissues, either in the metabolism to blood flow distribution (M/Q), which tends to improve during exercise in normals, or in the diffusion of oxygen from the capillary into the mitochondria as Dr. Tenney was discussing. Therefore, although cardiac output may be limiting under certain exhausting conditions and pulmonary diffusion may be limiting under very freakish circumstances, the usual limitation to exercise at sea level or altitude lies in the tissues. Of course, the heart itself is a tissue so there is nothing contradictory about having a depressed myocardium. I would like Drs. Buskirk, Tenney or Grover to comment on their view of the most sensitive part of the oxygen or metabolic conduction pathways.

DR. GROVER: I think you have put your finger on the most sensitive part. Perhaps Dr. Tenney might like to comment.

DR. TENNEY: Well, you have already been exposed to my prejudice. I think the sensitive portion of the conduction pathway does lie in the tissue and so I am bound to agree. I think it is interesting to make different approaches sometimes to the problem of the call for oxygen. We have stressed exclusively in the last two days the problem of oxygen deprivation in the environment.

There is another kind of special oxygen need based on body size. It is well known that the call for oxygen increases (per unit of body weight) in smaller animals, and so one might ask the question from the point of view of comparative physiology. What is the solution to the problem in that situation, and does it illuminate the question of sensitive point in the conduction path? The two diffusion barriers are in the lungs and in the periphery. With increased oxygen need, on the body size basis, the major adjustment is in the lungs (2) and the secondary adjustment is in the periphery (3). When the stress is oxygen deprivation (high altitude), it is our experience the lung has turned out to be a trivial site for morphological adjustment (4) and although the pulmonary diffusion capacity appears to be slightly increased, the fact is the major adjustment takes place in the periphery.

DR. ROY: Could I take three minutes to show a slide and ask three questions? It was a very fascinating talk that you gave. Now, Figure 1 shows what happens to a group of soldiers who were studied – this is resting, no exercise – at sea level, at 14,500 feet, at 16,000 feet, compared to the natives and then compared to soldiers who developed high altitude pulmonary hypertension, which we think is our variation of mountain sickness.

The cardiac index from sea level to 14,500 feet changed only slightly, (from 4.0 to 4.5 $l/m^2/min$) but at 16,000 feet it increased to 6.0 $l/m^2/min$. In the native it went much higher. But, as soon as chronic mountain sickness developed, unlike the observations on the Peruvian Indians, the cardiac output decreased. The pulmonary blood volume increased until they got chronic mountain sickness.

We were talking about the performance in mountains this morning, i.e., of running. In an army center we are dealing with conditions which face a soldier. We studied soldiers carrying loads of 16, 22, 28, 30 and 40 kilograms, at sea level, 5,000, 8,000, 8,500, 11,000, 13,000, and 15,000 feet, expressed as the rate of walking in meters per minute. If you compare the 40 kilogram load, you find that at 15,000 feet a soldier cannot walk more than

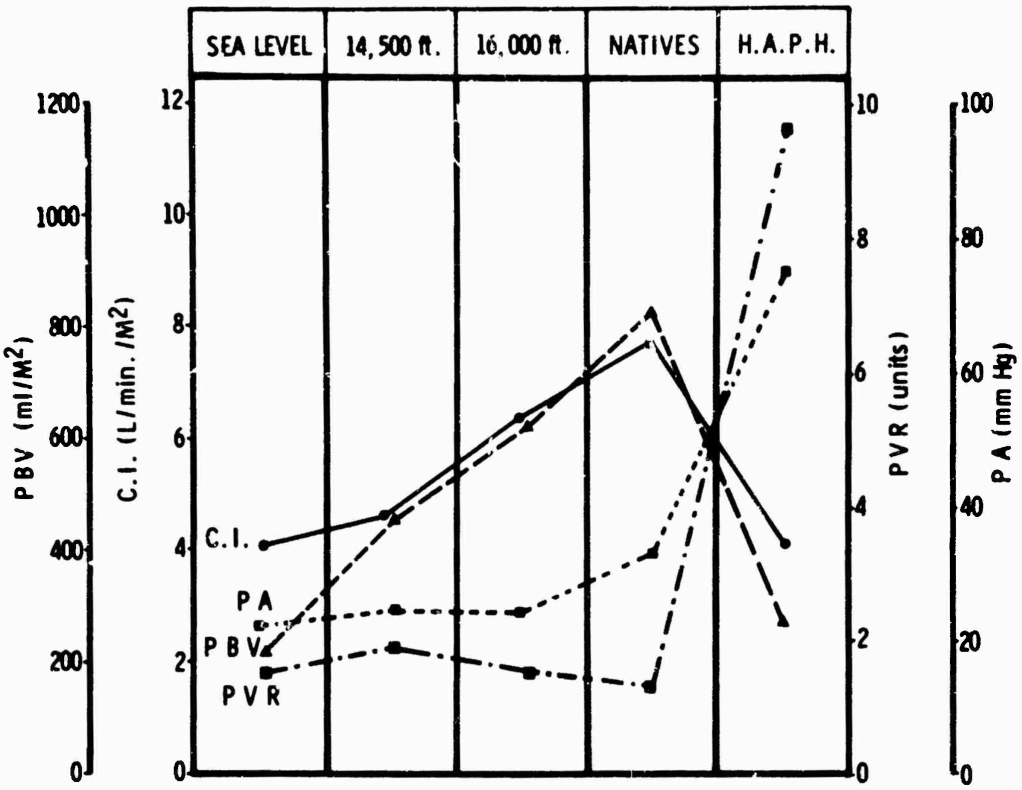

Figure 1.

45 meters per minute whereas at sea level with the same load he walked 90 meters per minute. We now recommend a 22 kg load.

At sea level they may walk at 98 meters per minute, but at 15,000 feet they will be able to walk only 60 m/min. This is of great practical importance, and is, as Dr. Staub mentioned earlier, related to oxygen consumption before one gets to the anaerobic level, which we found to be one liter.

I should like to pose a question for endocrinologists. What happens to a group of people who are acclimatized, brought down to sea level, and airlifted again to 12,000 feet? In one study, test subjects who were acclimatized consistently excreted greater amounts of 17-ketosteroids than the non-acclimatized. Dr. Surks, would you like to comment on that?

DR. SURKS: I really have no particular comment to make about that finding. It certainly has not been observed before and I really can think of no endocrinologic or metabolic reason for it.

All the data that we have regarding the steroids are, as I have indicated. ACTH seems to be increased but we know, of course, that this is not the end of the chain; that in control of the pituitary there is a brain and the hypothalamus. We are finding, these days, numerous other factors. The one regarding this system is corticotrophin-releasing factor and this may be the first step in

the chain. We do not know anything about the regulation of cortotrophin-releasing factor, what induces its secretion into the pituitary system even at sea level, so there is really no point in trying to speculate on what will happen at altitude.

DR. GROVER: I think the relationship between load and speed is related to working capacity. Do you want to comment on that, Dr. Buskirk?

DR. BUSKIRK: As I interpreted the information presented, there is a reduction in the voluntarily selected walking speed with load carriage at altitude. I am sure that one would see this same reduction in walking speed in troops engaged in exercise at altitude. One question, however, whether voluntary reduction in walking speed is related to a decrease in actual work-capacity at altitude. These men are working at 50% or less of their working capacity. I would assume they could do much more work than this if they had to.

DR. GROVER: Yes, but don't you think if a man knows he has to do a given job for several hours he will select a work load that is approximately 40% of his maximum, and if his maximum working capacity at high altitude is reduced, then 40% of that maximum is going to be less also?

DR. ROY: I agree with Dr. Grover. My data support this assumption. For the same amount of oxygen consumption the soldier is capable of carrying only 40% of the load he is able to carry at sea level. This is of practical importance, as in mountain warfare soldiers have physically to carry equipment.

DR. GROVER: How soon after ascent to altitude were these measurements made?

DR. ROY: After two years.

DR. GROVER: And these were resting outputs?

DR. ROY: Yes.

DR. GROVER: These results are different from others that I have seen (5) but at the same time I have not seen measurements at the altitudes you are referring to. In general, resting cardiac output is similar at high altitude as sea level. You are showing an increase.

DR. ROY: This is acclimatized; the native also is higher than at sea level.

DR. RICHARDSON: Dr. Roy, it is not clear whether the natives were at higher altitude when measured.

DR. ROY: No, between the two heights that I said, 14,500 and 16,000 feet.

DR. GROVER: I can only say that in people acclimatized to high altitude in the Andes, at altitudes of 12,000 (6) to 14,000 (7)

feet, the resting cardiac output is the same as at sea level. So, your results surprise me a little. I cannot explain it.

DR. ROBINSON: Dr. Buskirk, would you comment on depression of maximum heart rate at altitude. As I recall from your paper, your athletes did not get much of a decrease in maximum heart rate at altitude. I would also like to ask Dr. Grover and Dr. Visscher to comment on possible mechanisms of the depression of maximum heart rate at altitude.

DR. BUSKIRK: If you look at the individual points that were plotted in our slides in some individuals, the maximal heart rate was depressed but not in all. There is a progressive depression in maximal heart rate with time and the lowest values were found after about 45 days at an altitude of 4,000 meters.

DR. ROBINSON: We observed a substantial decrease in maximal heart rate at altitude in our five-week study in 1964.

DR. GROVER: I do not have much experience in this but it does seem to me that there is a great deal of individual variability in this phenomenon, and it is also related to the altitude. In other words, you do not see a reduction of any consequence at altitudes of 3,100 meters (8). You have to go over 4,000 and then, as in our four subjects, two had a reduction and two did not (9). In terms of athletes being less prone to this than non-athletes, I do not know.

DR. VISSCHER: The reason that I thought this might deserve some more discussion is that quite obviously it is a critical factor in determining work capacity, maximal work capacity at high altitude, as you point out; and I wondered whether there might not be some change in the setting of reflex regulatory mechanisms that might account for it. That is, our restriction in heart rate depends on parasympathetic influences and these might overcome sympathomimetic influences under certain circumstances. I wonder whether it might not be central nervous system rather than peripheral tissue effect that might be determining it.

DR. GROVER: Are you suggesting that if you gave atropine, the maximal heart rate might increase?

DR. VISSCHER: Well, I think it would be an interesting test.

DR. GROVER: I do, too.

DR. ROBINSON: We have actually atropinized men and found that partially blocking the vagi had no effect on maximal heart rate in exhausting work. Apparently the heart is completely released from vagal inhibition during exhausting work.

DR. HULTGREN: I should like to ask Dr. Grover to comment a bit further on the concept that cardiac performance limits maximal work capacity at high altitude. As I see it cardiac performance could be limited in two ways: It could be limited by

the heart not being able to respond adequately to a strong signal for more cardiac output. This is the case in a heart that is diseased. The second possibility is that the signal for more cardiac output is not strong enough and the heart itself is intrinsically able to perform adequately. It seems likely to me that the second possibility is more reasonable since as I understand from your data and the data of others there is no evidence that filling pressures are abnormally elevated, either on the right side or the left side during bouts of heavy exercise at high altitudes. There is no evidence that pulmonary hypertension is occurring to degrees that might limit cardiac output either directly by obstruction of flow or by some reflex mechanism. Certainly there is no evidence that under strenuous exertion at high altitude acute cardiac dilatation or failure has been observed clinically, and there is no evidence that prolonged heavy work at high altitude has any unfavorable effect upon the heart. So, it would seem, therefore, that the heart is capable of delivering the blood that is necessary but perhaps the signal from the periphery for more cardiac output is deficient. It may be analagous to the situation in myxedema where the heart is able to work adequately but the need for a higher cardiac output is not present.

I know you have suggested that the heart at high altitude may be analagous to the heart with diffuse coronary disease. Instead of having a restriction to flow imposed by a diseased vascular bed you have a diminished oxygen supply imposed by decrease in oxygen tension of the blood. But this may not be a good analogy since restriction to flow by narrowing the vessels has a more severe effect on cardiac function than the reduction of oxygen tension in the blood going through the coronary system.

DR. GROVER: The subject of coronary flow at altitude is, obviously, an important one and it is a subject we do not know a great deal about. There have been some recent studies of coronary flow measurements in patients with chronic obstructive airway disease and chronic hypoxia who are free of arteriosclerotic heart disease; and in contrast to the observations in acute hypoxia, these humans with chronic hypoxia have either a normal or a subnormal coronary blood flow (10, 11). We have some very limited observations at rest only which also suggest a decrease in coronary blood flow in normal man going to altitude (12). If this is substantiated, that coronary flow is not increased but even decreased, then this certainly would be an important factor in terms of oxygen delivery to the myocardium. With respect to other factors depressing it, I agree with you – those you enumerated do not explain the impairment.

DR. VISSCHER: I have another thought to suggest in connection with this limitation in heart rate. If the elevation in heart rate depends on the catecholamine levels, and if one reaches a point where anaerobic metabolism begins to take over and shifts in hydrogen ion concentrations might occur locally at sympathetic endings, one would expect that with increasing acidity, a given level of circulating or released catecholamine would have less effect in elevating heart rate. That is, the actions of epinephrine, norepinephrine, etc., are very much dependent upon hydrogen ion or hydroxyl ion concentration conditions. Now, would it be true that you might be reaching a point where the heart itself or, more important, module portions of the heart might be becoming acidotic?

DR. GROVER: Under certain maximal exercise situations significant acidosis does develop, and this may play a role.

We are going to have to stop shortly but before we close, I would like to call on Dr. Eguia of LaPaz, Bolivia.

DR. EGUIA Y EGUIA: Dr. Hegnauer, Dr. Grover, Professor Hurtado – I am a person who lives and performs at a high altitude. I actually live and work at 3,600 meters all the time and, too, I was born at this altitude. We have the unique opportunity to have a population around LaPaz of over 500,000 people. All these make the situation very good for the observation of many cases of pathology of High altitude.

The subjects which we have been studying here in this meeting like, for example, high altitude pulmonary edema and mountain sickness are the things which immediately come to mind. These are the things we see very often. But I think there is a distinct pathology around every case that is not necessarily related to these pathological conditions. These are merely the ones that are best known.

With relation to high altitude pulmonary edema (someone asked yesterday) I think that the relation to age is very important. Young people under 20 years of age have a greater tendency to get pulmonary edema, and it is more frequent in male than female. As Dr. Roy was saying yesterday, it is not a disease that is only localized in the lung, but is also related to lesions in the brain and in other tissues.

We have had the opportunity to see some patients who were in coma for periods of almost a week following pulmonary edema and brain edema, and even after that time they recovered, and they are still carrying on a normal life.

In this problem of pulmonary edema also, the difficult conditions of the area have a great deal of influence. I do not

believe that it is only the lack of oxygen, but one must consider conditions such as cold, humidity, radiation, and exercise, as well. Another important factor in pulmonary edema is prior pulmonary disease.

Also, I should like to make some comments about something that is very important. Not only does altitude increase red cells, and increase hemoglobin and hematocrit, but one also sees some cases of anemia, and it is for me a great opportunity to talk with this panel about what explanations they would have for persons who had been living in LaPaz but for one or another reason went down to a tropical area, almost at sea level, where they contracted diseases such as hookworm, and then came back to LaPaz for the treatment of anemia after the hookworm disease. I have here just two such cases. One of my patients was a female 30 years old who came walking in to the hospital with a hemoglobin of 7 grams, hematocrit of 25 and a red cell count of 2,580,000. These are cases that we can see in Bolivia and need an explanation regarding the process of adaptation for this situation.

About the comment that Dr. Monge made this morning: I think that the red cell count increases with age. I have done a study of over 200 control cases and I can say that the hematocrit, red cell, and hemoglobin increase as age increases. It is close to 60% hematocrit in persons over 50 years old.

A final comment which I should like to make is that at altitude not everything is bad. Maybe many of you who have never been at high altitude think we cannot live, or that living is very difficult. I can tell you about it. It is very wonderful to take a deep breath in the mountain. The air is clear, the sky is blue, it is beautiful. You are welcome to come over and visit us, and have some experience right there in the Andes.

Thank you very much.

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PANEL

BEHAVIOR AND PERFORMANCE

Chairman: Ross A. McFarland

REVIEW OF EXPERIMENTAL FINDINGS IN SENSORY AND MENTAL FUNCTIONS*

Ross A. McFarland

Guggenheim Professor of
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Harvard School of Public Health

It is appropriate that this Conference be concluded with a discussion of the influence of high terrestrial altitudes on behavior and performance. First of all, it is important to determine the physiological changes which occur in men and animals during acclimatization to high altitudes. It is equally important, from the point of view of military operations, to analyze what effects these changes will have on human capacities for carrying out essential duties, as well as on the general well-being of men exposed to such environmental conditions.

Since the early development of aviation, both in flight at moderate and at extremely high altitudes, a great deal of research has been carried out on the ability of airmen to adjust to various conditions of oxygen want. Although the introduction of pressurized cabins has solved many problems, others have been created, such as the low humidity resulting from recirculating the cabin air, or a failure of the aircraft cabin giving rise to a sudden loss of pressure. Some of the experimental results from studies relating to hypoxia during flight can be applied to the problems of acclimatization of man to high terrestrial altitudes. In interpreting the findings of the effects of high altitude, however, it is always necessary to indicate the conditions under which the studies have been carried out.

Techniques of Measurement

Before summarizing some of the experimental findings relating to the effects of hypoxia on man, it is in order to consider the

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techniques of measurement used in such studies, both in regard to completed and to projected ones. Only brief reference will be made to this subject here, since a more thorough analysis of this area will be presented later in this panel.

The subtle influence of hypoxia may often be masked by changes in the learning process or by "trying harder". Thus it becomes difficult to detect significant alterations in performance such as overall speed, number of errors, or total output. What appears to be required, therefore, are tests of performance which reflect deleterious effects of hypoxia in spite of attempts to overcome them, or tests which detect increased effort at the task. Recently, techniques have been developed in sensory and perceptual research which may be of value in developing measures of this kind.

Some of the primary features of such tests include: (a) a high degree of sensitivity, so that small changes can be readily measured; (b) precision of the physical measurements involved in the test; (c) independence of the results from the degree of conscious or unconscious effort which may be exerted; (d) stability of the function during control experiments when the physiological stresses are not applied, and (e) for more complex performance, including insight and decision making, tests which involved the timing of perceptual responses and information processing (18).

Measures of speed and accuracy combined. One way of adjusting one's performance to offset the deleterious effects of altitude might be to sacrifice speed for accuracy or vice versa. Such tradeoffs, however, need not indicate degradation in capacity. Until recently, there was no way of combining these two measures. With the development of information theory, a nonarbitrary way of combining measures of speed and accuracy into a single "rate-of-information-transmission" measure is available (5). In this way it is possible to determine the magnitude of a task-induced stress required to produce an environmentally interacting effect.

Tests that detect and scale increased effort. Two avenues of research offer tests of increased effort. One of these is concerned with capacity and/or peripheral attention. The measurement of performance on a primary task, with increased load on a secondary task is a good example of this area of testing. The effects of environmental stress can be measured in terms of the steepening gradient of these spare capacity measures (22, 25). The other area of research relates to physiological measure of arousal, and of tension, and so forth. A number of techniques for measuring not only muscular tenseness, but also, central nervous system activity and even specific components of neural reaction to signals have

been developed (29). Some of these measures appear to be promising for studying the deleterious effects of varying degrees of oxygen want.

In studies of the effects of noise or vibration on human performance there is evidence of strong interactions between such an environmental stress and task difficulty. The latter is very important in determining the amount of decrement that will appear under a given amount of stress (28). Task difficulty is a major variable. Failure to consider this fact has given rise to many of the discrepancies found in studies relating the influence of environmental stresses to performance. These studies have resulted in the hypothesis that the most demanding aspects of a complex activity are those which will be most sensitive to the effects of environmental stress. Furthermore the number of task elements affected by a given level of stress, and the extent of such impairment, depends on the total information processing load imposed by the task (14, 25). Future studies of the effects of high altitude will undoubtedly include some of these techniques of measurement.

Review of Experimental Findings in Short- and Long-Term Exposures

In recent years several extensive bibliographies relating to high altitude have been prepared by NASA, the USAF, the U. S. Army Research Institute of Environmental Medicine, and the Guggenheim Center for Aerospace Health and Safety at Harvard University (27). In the preparation of this paper, selected references have been reviewed and the experimental findings relating to sensory and mental functions plotted on graphs. Unfortunately only a few studies are available from prolonged residence at high terrestrial altitudes. Great caution must be observed, therefore, in interpreting some of the findings reported here to the problems of military operations at high terrestrial altitudes.

Sensory functions. In this review certain tests relating to vision will be emphasized, although several other psychophysical functions will be reported. Visual acuity and light sensitivity possess many of the desired qualities for precise measurement. The changes manifested by the visual mechanisms when its oxidative processes are disturbed are of considerable magnitude. Also, the measurements can be made very accurately. Experimental subjects are not aware of the changes in their own visual sensitivity and for this reason they cannot mask the impairment by exerting greater effort.

1. Effect of altitude on light sensitivity. The curve in Figure 1 shows the extent of the decrease in ability to see under low levels

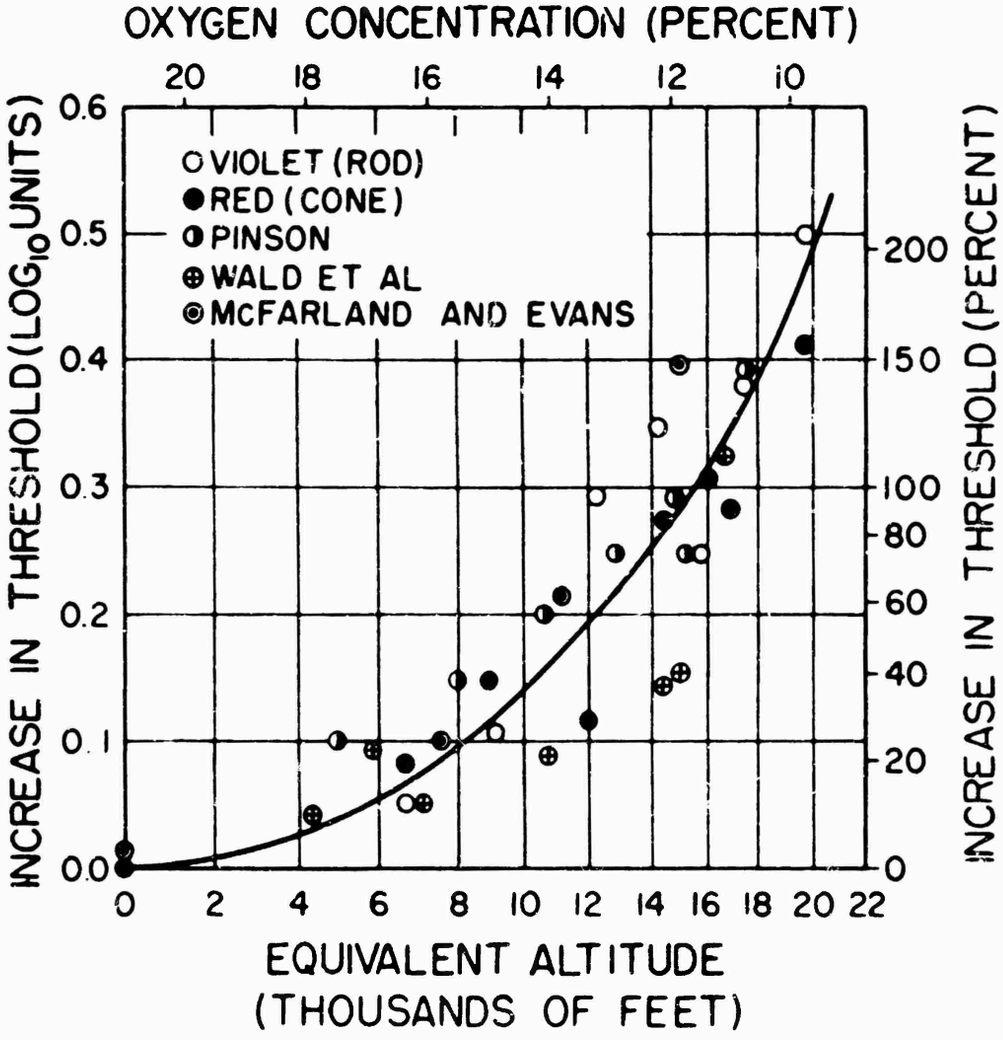

Figure 1. The effect of altitude on light sensitivity (17, 19).

of illumination in relation to altitude and oxygen concentration (17, 19). Light sensitivity is impaired at altitudes as low as 4,000 to 5,000 feet. At 16,000 feet ability to see may be reduced to 50 per cent of sea level performance. Hence, twice as much light would be required for perception of a given stimulus under these conditions.

2. Effect of altitude on critical flicker frequency. In recent years a great deal of attention has been given to the role of flicker fusion frequency (CFF) as a measure of basic neural activity. This test has been proposed as one of the most reliable ones as a measure of certain physiological stresses. The evidence suggests that conditions which decrease the blood sugar or oxygen supply increases CFF. Figure 2 shows that there is a decrease in the critical flicker frequency values as a function of altitude.

3. Effect of altitude on visual acuity. The effects of altitude on performance tests of visual acuity are shown in Figure 3 (21). The

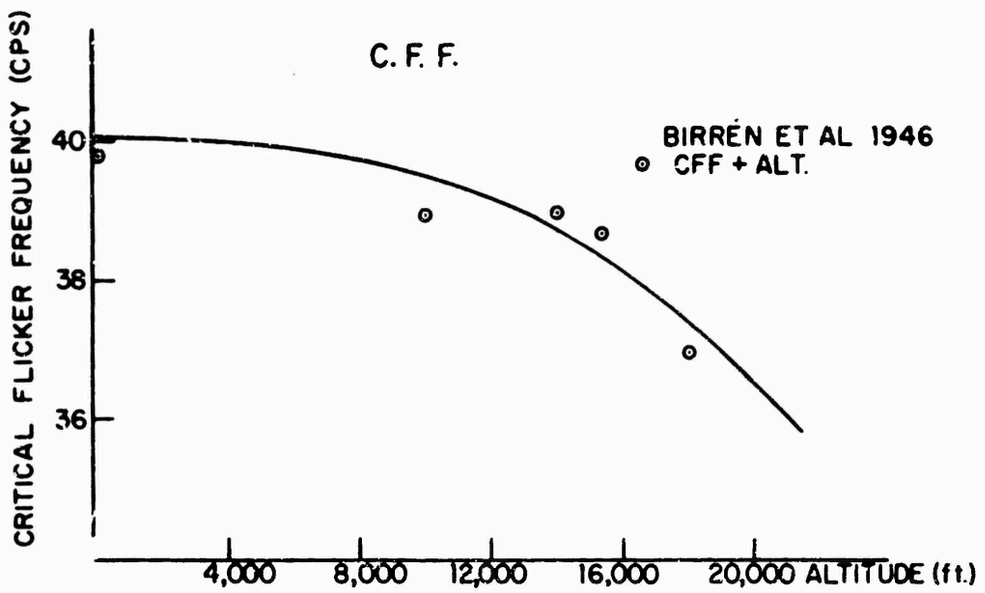

Figure 2. The effect of altitude on critical flicker fusion thresholds (4).

different curves represent testing at different intensities of illumination. At the higher illuminations there is little or no impairment until altitudes beyond 18,000 feet are reached. Under low illumi-

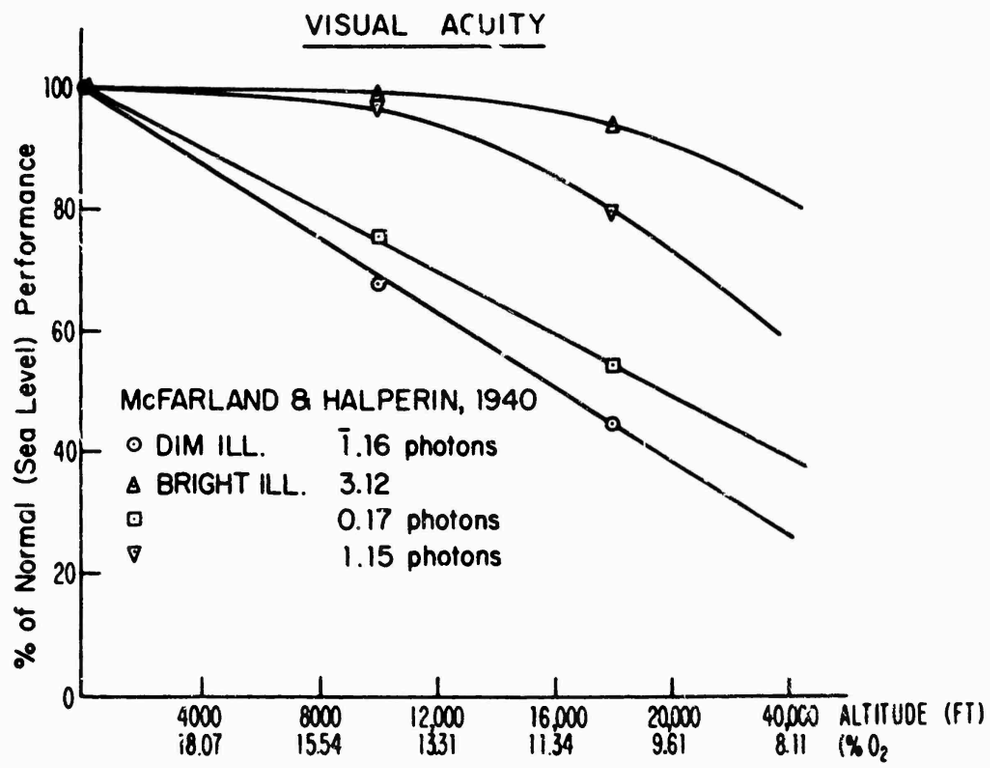

Figure 3. The relationship between log visual acuity and log retinal illumination with normal air and at high altitude (21).

nation however, a decrease in the ability to resolve a given target is apparent at about 8,000 feet. At 17,000 feet visual acuity is reduced to 50 per cent of the sea level value. Thus a target subtending almost twice the normal visual angle would be necessary for resolution under this condition.

4. Effect of altitude on the central visual field. The curve shown in Figure 4 summarizes the findings from several studies on changes in sensitivity of the central visual field in terms of changes in the extent of the angioscotoma in relation to altitude (2, 4, 8, 24). It may be seen that with short exposures there is virtually no change below 12,000 feet. Beyond 12,000-14,000 feet, however, the angioscotoma or area of defect increases rapidly in size. The influence of duration of exposure to altitude is also shown on the graph by the pairs of points at 10,000 and 17,000 feet. In each case the upper point represents the initial value, while the lower point is that obtained after 7½ hours of exposure to the given altitudes. Thus, both altitude and the duration of exposure to altitude influence the extent of impairment.

5. Effect of altitude on auditory sensitivity. The relationship between auditory sensitivity and altitude has received less atten-

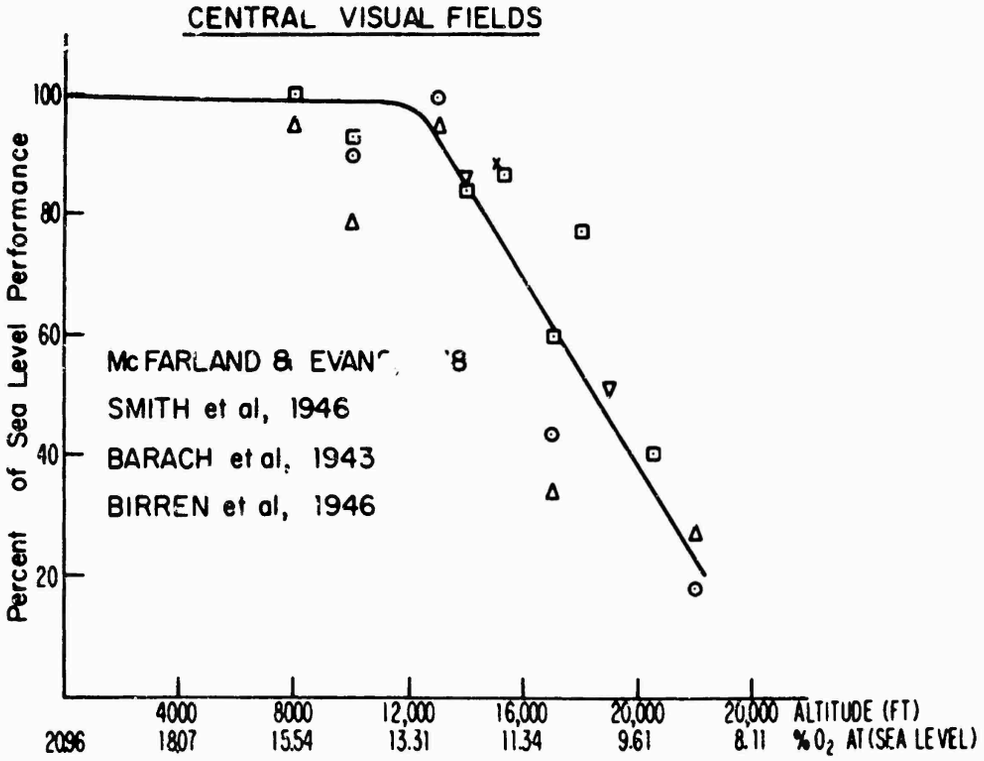

Figure 4. The changes in sensitivity of the central visual field in terms of changes in the extent of the angioscotoma in relation to altitude (2, 4, 8, 24).

tion than the visual functions. Although the findings of the studies reported are not entirely in agreement, it appears that auditory sensitivity is highly resistant to hypoxia (7, 10, 12).

The curves in Figure 5 show the average threshold in decibels at 8 frequency levels for members of a high altitude expedition at sea level and at 17,500 feet. The threshold for normal hearing is also shown. Although the expedition group show a decrement from the normal hearing threshold at the upper frequencies, a further impairment is observed at an altitude of 17,500 feet.

6. Effect of altitude on pursuit tasks. Figure 6 brings together the findings from four studies on the influence of altitude on visual pursuit tracking in relation to altitude (1, 2, 23). Although the points plotted represent four different tasks, all involve an alignment response to a changing input. It appears that tracking is not affected by altitude until 17,000 feet, beyond which performance drops off rapidly.

7. Effect of altitude on a code task and a conceptual reasoning test. The upper curve of Figure 7 shows the decrement in performance on a coding task (15, 16). There is a slow decrease in performance with increasing altitude beginning at 10,000 feet, and a more rapid impairment after 16,000 feet. The lower curve shows the decrement in performance on a conceptual reasoning task. A

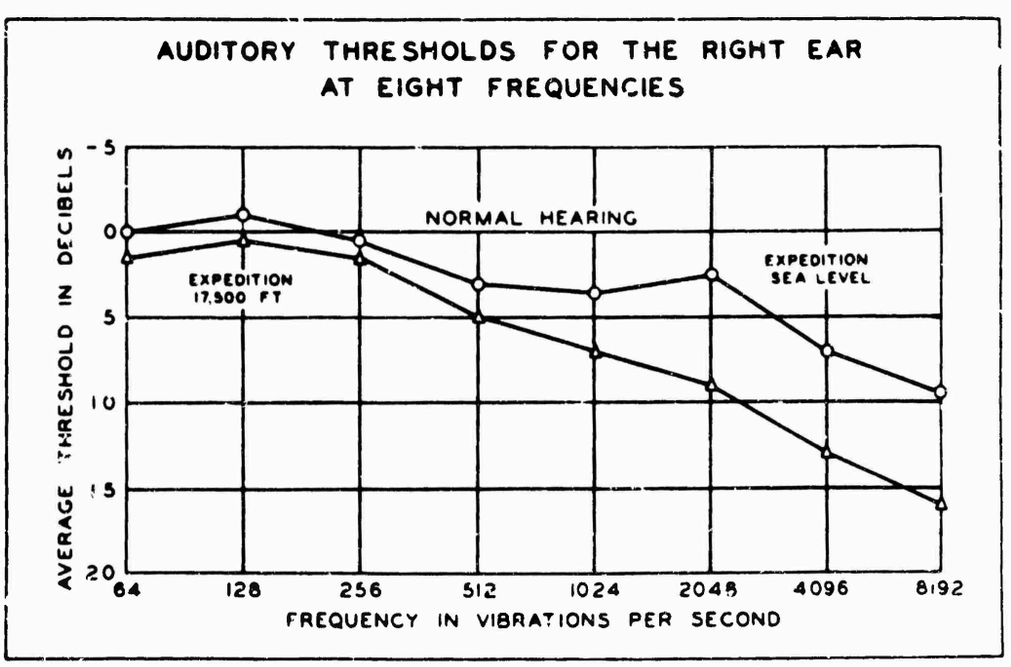

Figure 5. The influence of high altitude on auditory thresholds at eight frequency levels (16).

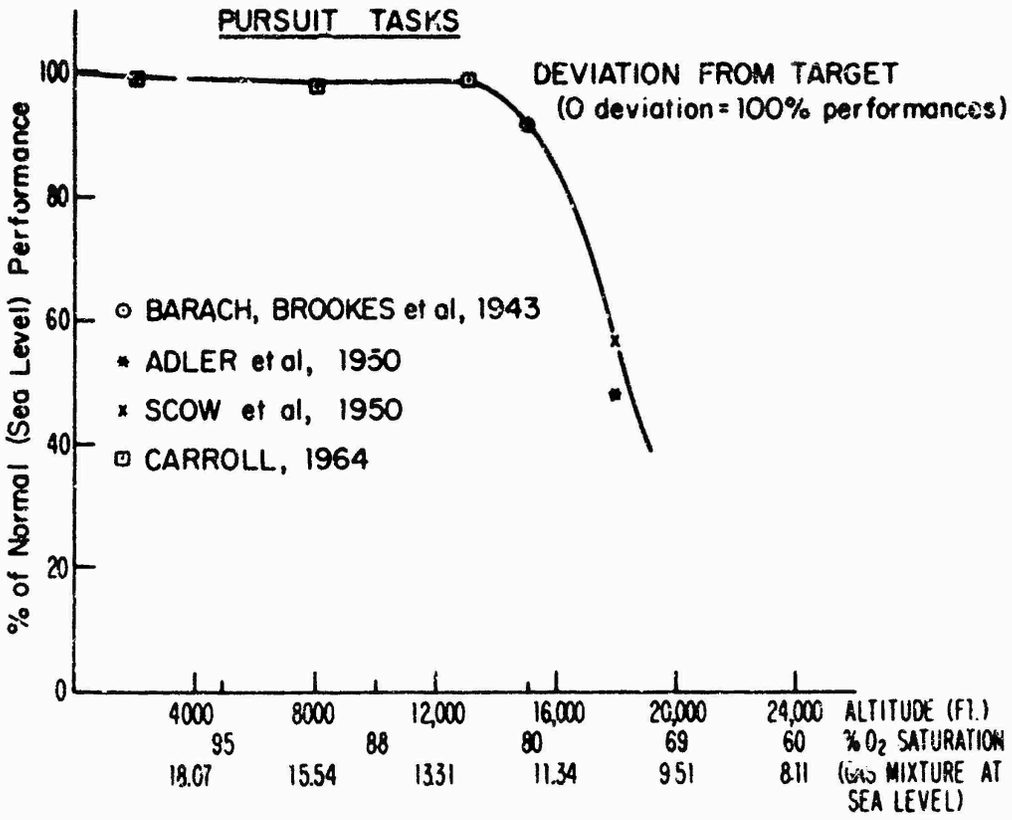

Figure 6. The impairment of performance on selected pursuit tasks with increase in altitude (1, 2, 6, 23).

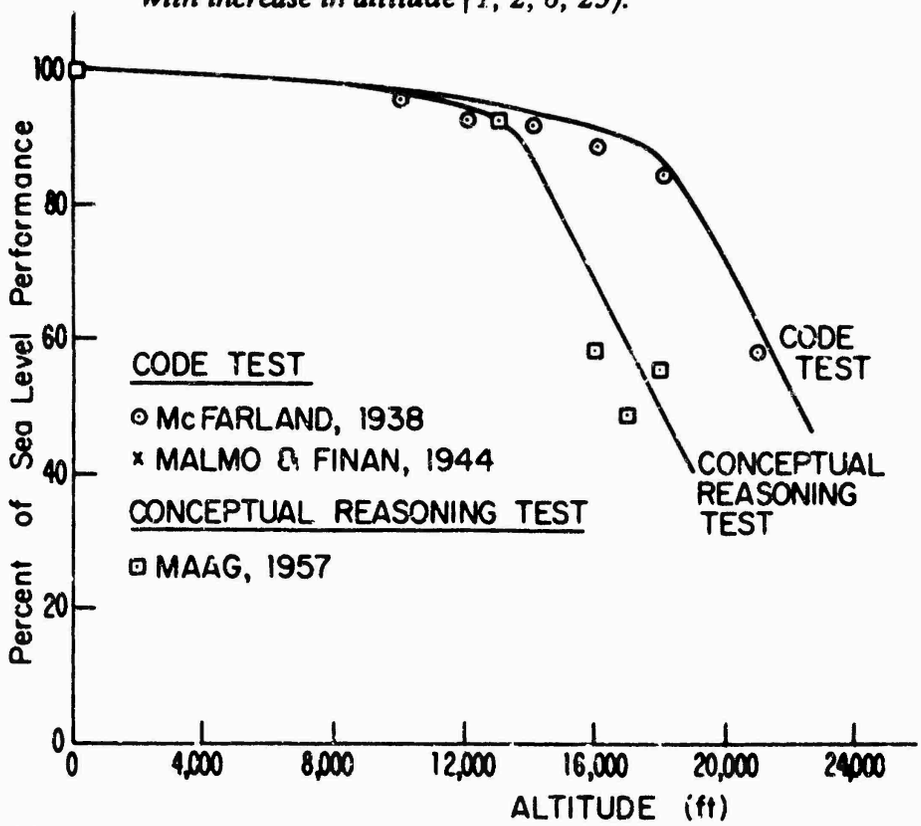

Figure 7. The curves show the increase in time necessary to complete a code test and a conceptual reasoning task in relation to altitude (13, 15, 16).

decline in performance at 12,000 feet is apparent, but performance falls off rapidly at 14,000-16,000 feet. Thus, there appears to be a definite decrement in mental functioning with altitude, but the altitude level at which serious impairment occurs may be a function of the difficulty and complexity of the task, with impairment on the more complex task occurring at lower altitudes.

8. Effect of altitude on memory. Data on the influence of altitude on memory functions have been summarized in Figure 8 (15, 16). The curve clearly shows increasing impairment in memory with increasing altitude. The points plotted represent (a) a paired word association task, (b) memory for pattern and position as measured by immediate recall, and (c) by delayed recall. A decrement in memory is apparent at 8,000-10,000 feet and shows a more rapid decline after 12,000 feet.

Relationship Between Performance and Altitude

An attempt will now be made to interpret the above review of sensory and mental functions in relation to the altitudes at which losses in function occur: (1) the altitude at which the effects begin; (2) the altitude at which the relative change is a reduction

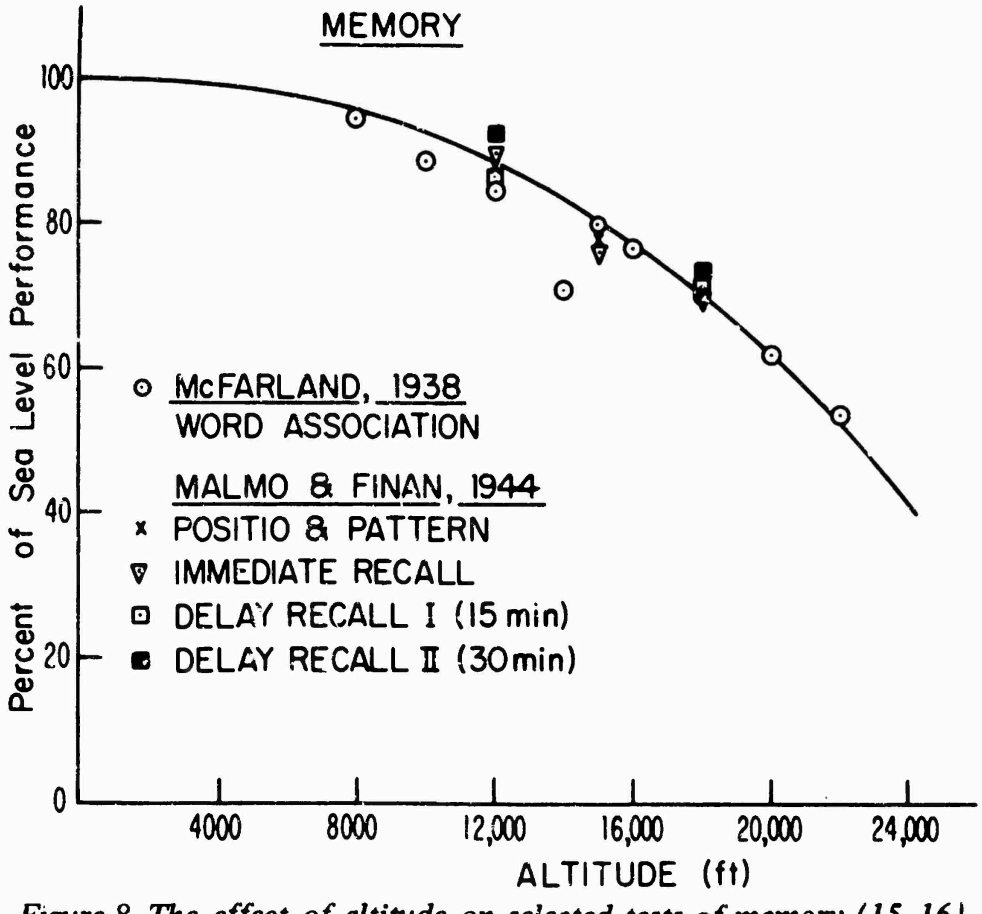

Figure 8. The effect of altitude on selected tests of memory (15, 16).

in sensitivity of approximately 25 per cent, and (3) the altitude at which performance is unacceptable (40 per cent). It should be kept in mind that the graphs which will be presented are based on limited data, and sometimes, inconsistent results.

The results of a series of visual functions are plotted in Figure 9. The curve for visual sensitivity clearly indicates the data for dark adaptation, or light sensitivity, provides the most sensitive test. The visual processes are initially impaired at 4,500-5,000 feet and reach unacceptable levels of impairment at 10,000-12,000 feet. This is an altitude well below that producing oxygen saturation levels which might be considered unacceptable along physiological lines.

The results of a series of mental tests, including pattern perception and decision making, are plotted in Figure 10. It would

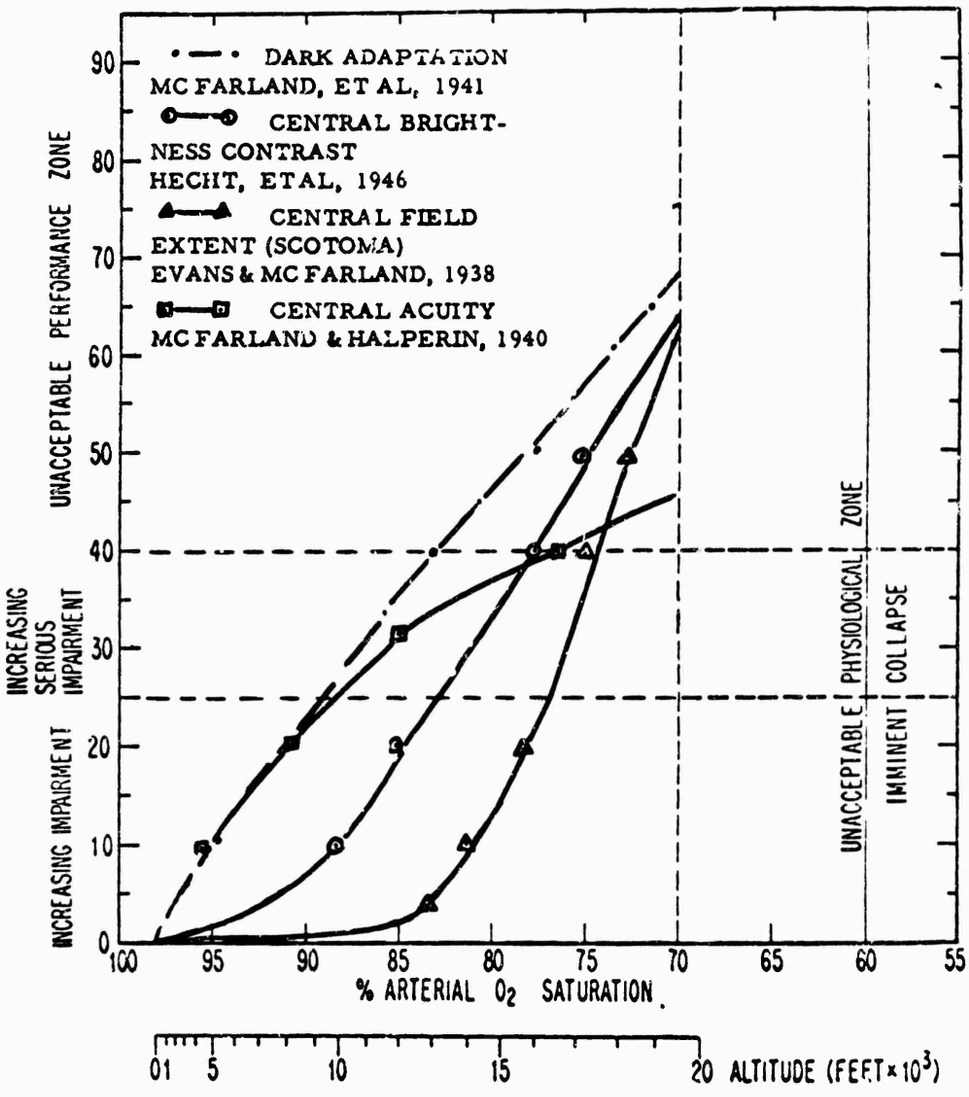

Figure 9. The degree of impairment in performance of four visual functions in relation to oxygen level and altitude.

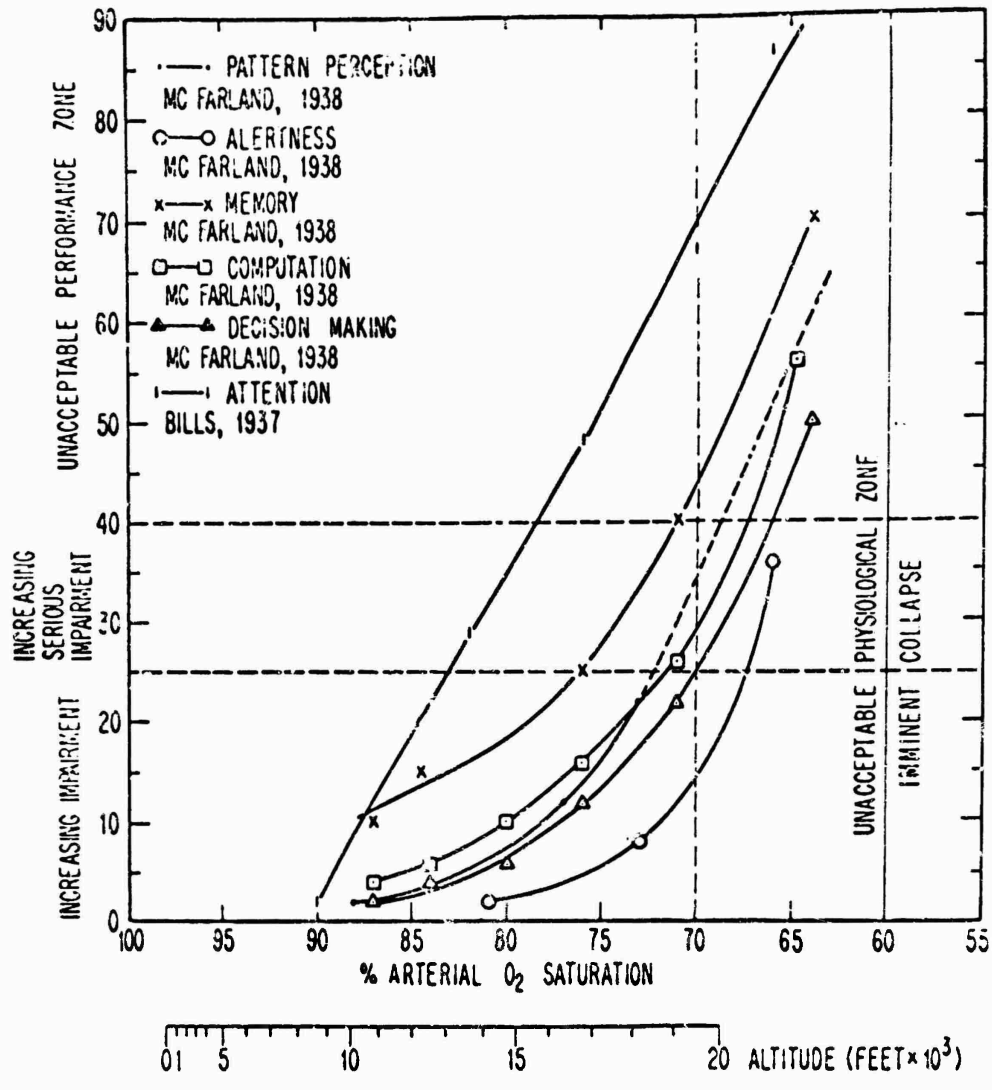

Figure 10. The degree of impairment in performance of six mental tests in relation to oxygen level and altitude.

appear that performance tests in these areas can be carried out at higher altitudes than for selected sensory tests. For example, such tasks can be performed successfully at altitudes in the neighborhood of 18,000-19,000 feet, where the blood oxygen saturation has dropped to 70-75 per cent.

In Figure 11 the relationship between arterial oxygen saturation and altitude is plotted for a series of performance tests in unacclimatized subjects. From this chart one can observe the zones of minimal impairment for both sensory and mental functions. It is quite obvious from this figure that blood oxygen saturations between 70-75 per cent, or altitudes of approximately 18,000 feet represent the threshold for unacceptable performance, and higher altitudes might be expected to give rise to serious impairment.

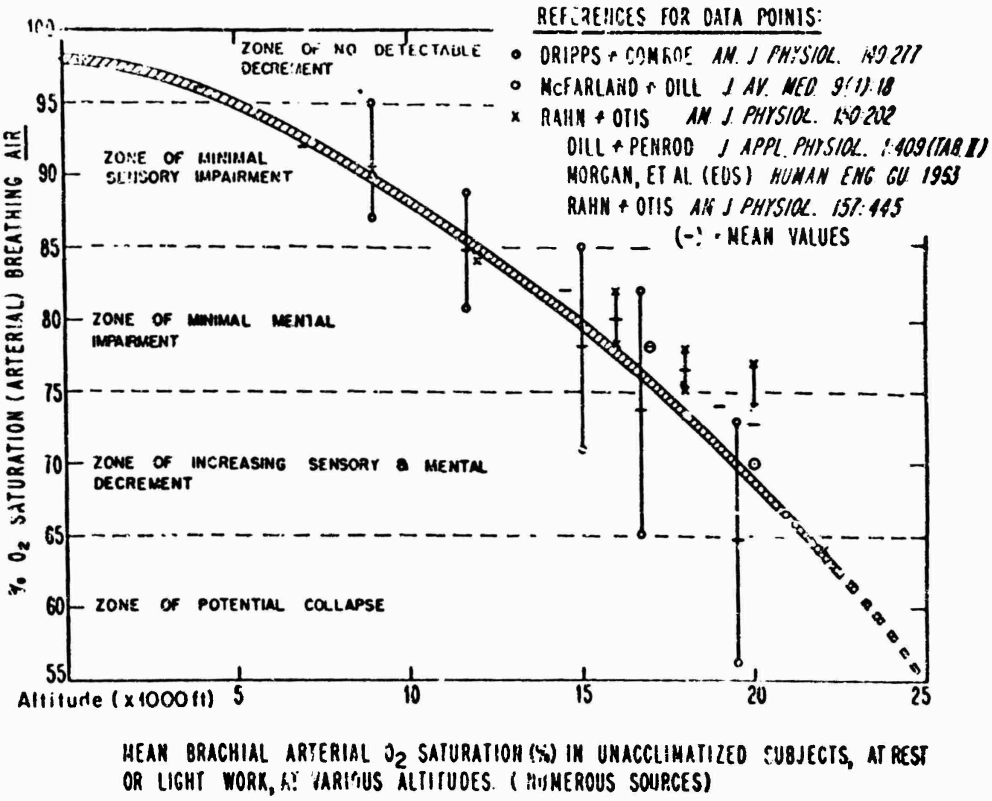

Figure 11. The relationship between arterial oxygen saturation and altitude for several performance tests in unacclimatized subjects (30, 31, 32, 33, 34)

Limitations of the Experimental Findings

In the brief listing below, reference is made to some of the limitations and deficiencies in this field.

1. One of the most important problems deserving of consideration relates to the extent to which laboratory studies under decreased partial pressure, or total pressure, can be comparable to experiments carried out in mountainous areas during short or long time periods of acclimatization. It is obvious that additional studies are needed which might be considered comparable to military operations, if such are the major points of interest. The observation can be made with certainty that large numbers of people have become successfully acclimatized to very high altitudes. However, the rates of exposure and the specific altitudes which unacclimatized men in our military services can reach, for example, remain to be clearly defined.

2. The second major gap in our knowledge about the effects of high altitude concerns the limited variety of tests and functions which have been measured. Information relating to judgment of distance, proprioception, vestibular function, and cutaneous

responses is lacking. Little or no investigation has been made into these areas (26). The evidence for impairment in the extent of the peripheral field, a function that is of great importance to a soldier in the field is meager and contradictory (9). No data were found on peripheral motion acuity, the ability to detect an object moving in the peripheral field.

3. One of the most difficult problems encountered in measuring performance concerns the control of both the learning process and motivation. It has been clearly established that it is necessary to have subjects well practiced if the effect of an environmental influence such as high altitude is to be successfully appraised. Also, motivation is an extremely difficult variable to control.

4. The variation in response from person to person has proved to be an important aspect of study of the effects of high altitude both in the laboratory at sea level and in mountainous areas. Individual variability is of great importance, therefore, and places great emphasis on initial selection of personnel in regard to age, physical fitness and ability to perform, among many other factors.

5. The combined effects of altitude with other variables such as (1) drugs or sedatives for sleeping, (2) alcohol, (3) carbon monoxide from cigarette smoking, and (4) diet, are factors which must be considered.

6. Other difficult factors to control are the influence of clothing, temperature extremes, and other variables that are apparent in the military situations. Most psychological tests and procedures which are easily carried out under laboratory conditions are difficult to adapt to field and military operations. Much remains to be done, therefore, in developing tests which would be relevant to military personnel operating at high terrestrial altitudes.

7. In reviewing the published literature in this field, it is quite obvious that the more recently developed methods of measurement for the study of environmental stresses, such as altitude, have not been widely used. Some of these more promising methods should be explored with respect to hypoxia as an important variable.

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THE EFFECTS OF OXYGEN AND CARBON DIOXIDE ON LEARNED MOTOR BEHAVIOR

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The ascent to altitude presents the physiologist with a most complex and interesting problem. We have picked one aspect of this environmental change and have engaged ourselves in the task of unravelling the series of events resulting from a decrease in inspired oxygen. Our approach has involved the simultaneous utilization of behavioral and physiological measures. Our experimental preparation for the studies enabled us to continuously monitor neural reactivity, motor behavior (1), respiratory activity, heart rate (2), blood gases and acid-base balance (3).

A typical animal is illustrated in Figure One. The animal can have three monopolar brain electrodes and a ground connection, a diaphragmatic electrode and two catheters – one in the abdominal aorta and one in the vena cava. Utilizing this preparation, or animals with partial preparations, we have carried out a series of studies which may eventually lead to a better understanding of the factors which determine performance in low oxygen environments. Graded levels of hypoxia produce proportionate decreases in central nervous system reactivity, as measured by self-stimulation rates, i.e., by how many times per minute a rat will press a lever to receive a brief electrical pulse into the hypothalamus (1). The degree of impairment in behavior is, however, not absolute, being dependent upon some central factor, most likely the number of neurons (involved in the particular motivational system) which are electrically stimulated. This experimental finding of greater decrements in performance with lesser reward levels may provide a fruitful model for the effects of "motivation" on performance at altitude. This hypothesis has been extensively discussed in a recent paper by Annau and Weinstein (1). The phenomena can be clearly seen in Figure 2. The top curve shows

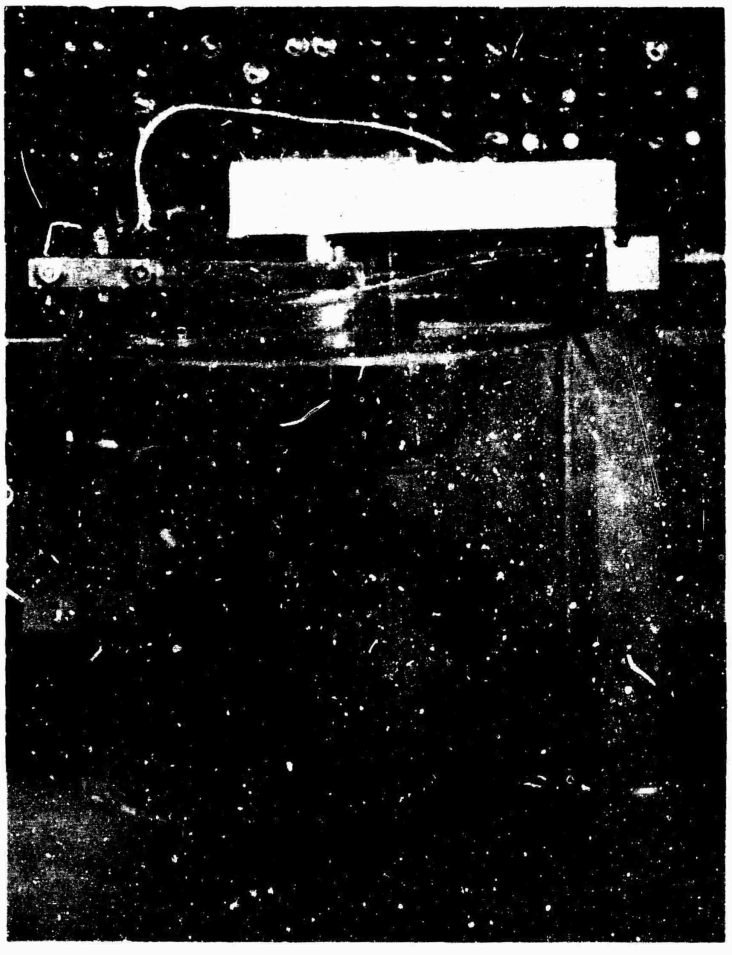


Figure 1. A typical experimental animal with skull-mounted electrodes.

the effects of 14, 12, 10 and 8 percent oxygen on self-stimulation rates at high current levels. The bottom curve shows the effect of the same oxygen levels on self-stimulation rates at low current levels.

We can now ask what other factors besides motivation will determine performance levels in low oxygen environments. The first factor examined was the effect of added carbon dioxide. We know that hypoxia produces alkalosis and hypocapnia, both of which probably contribute to the decrement in neural function either directly or through secondary mechanisms which affect tissue oxygen. The addition of carbon dioxide produces graded levels of increase in performance. This is illustrated in Figures 3, 4, 5, 6, where we have added 1, 2 and 3 percent carbon dioxide to 14, 12, 10 and 8 percent oxygen, using a group of high-motivation animals. Each one percent of carbon dioxide produces a behavioral effect equivalent to the addition of 2 percent oxygen to the inspired air.

In terms of blood gases, one percent carbon dioxide increases arterial oxygen pressure from 25 to 28 millimeters of mercury and

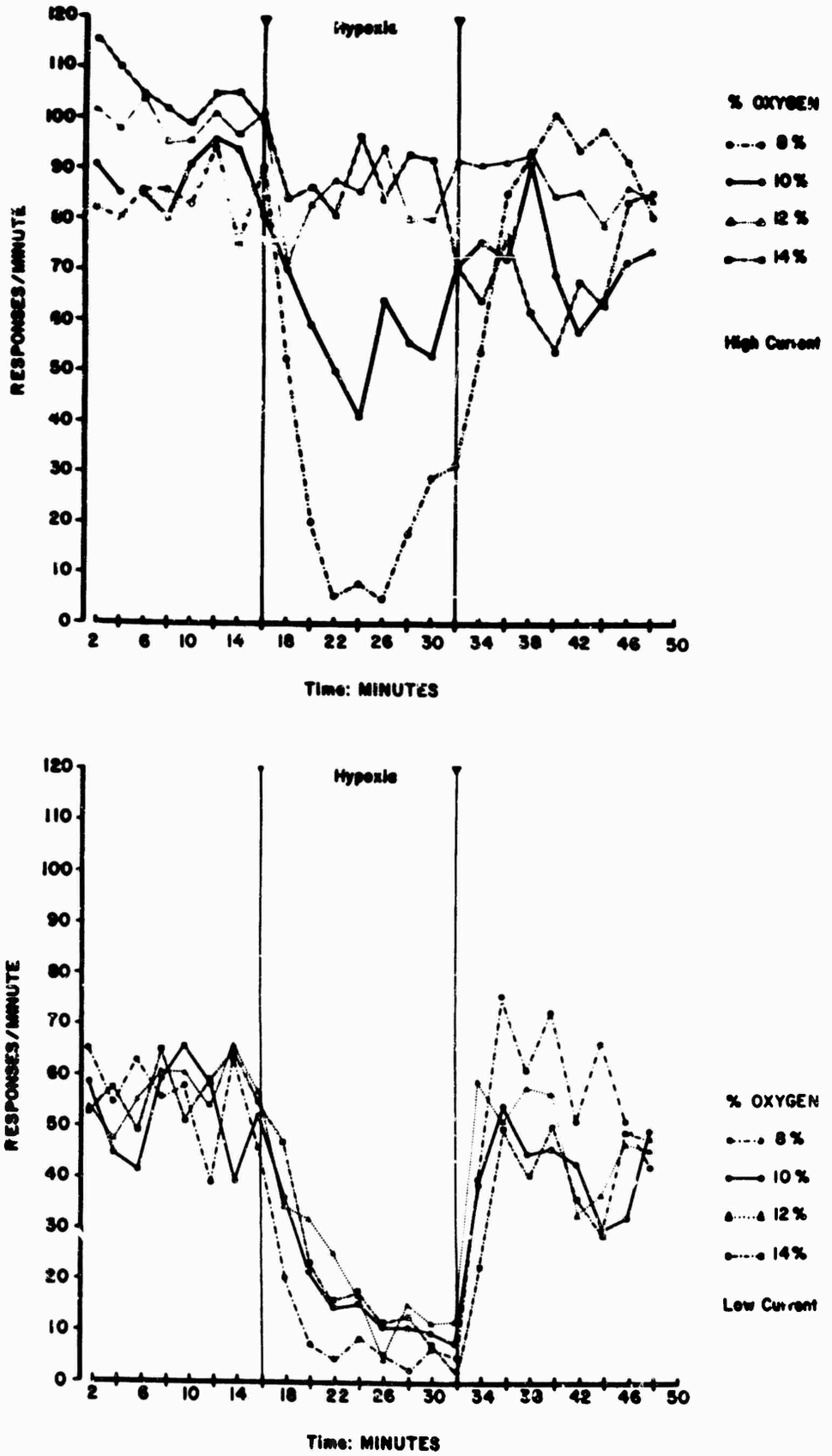


Figure 2. The effects of hypoxia upon self-stimulation at high and low current levels.

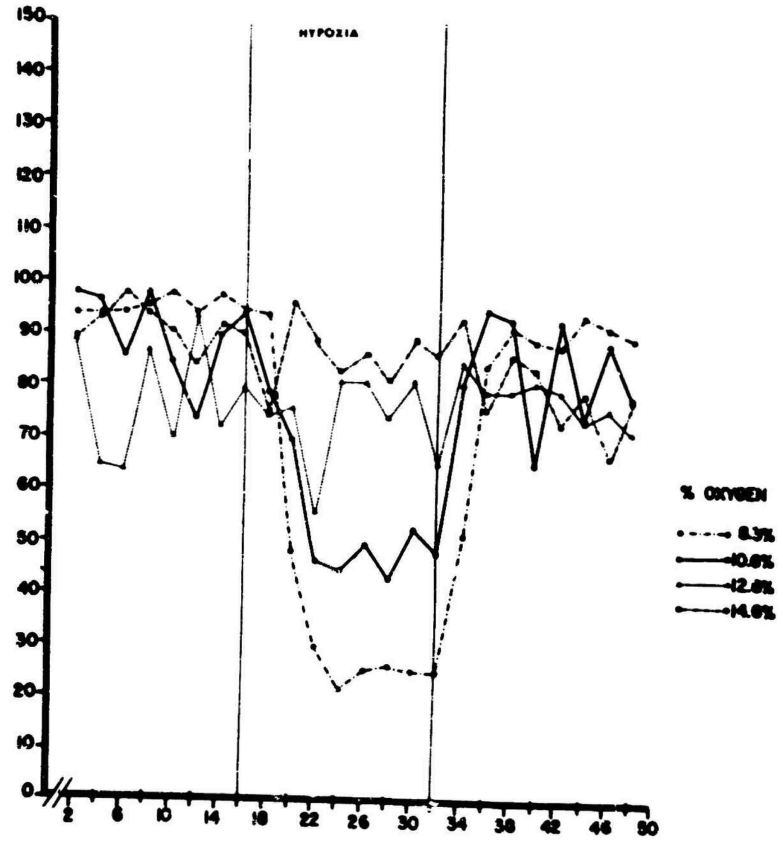


Figure 3. Effects of 1, 2 and 3 percent carbon dioxide on self-stimulation in 14, 12, 10 and 8 percent oxygen.

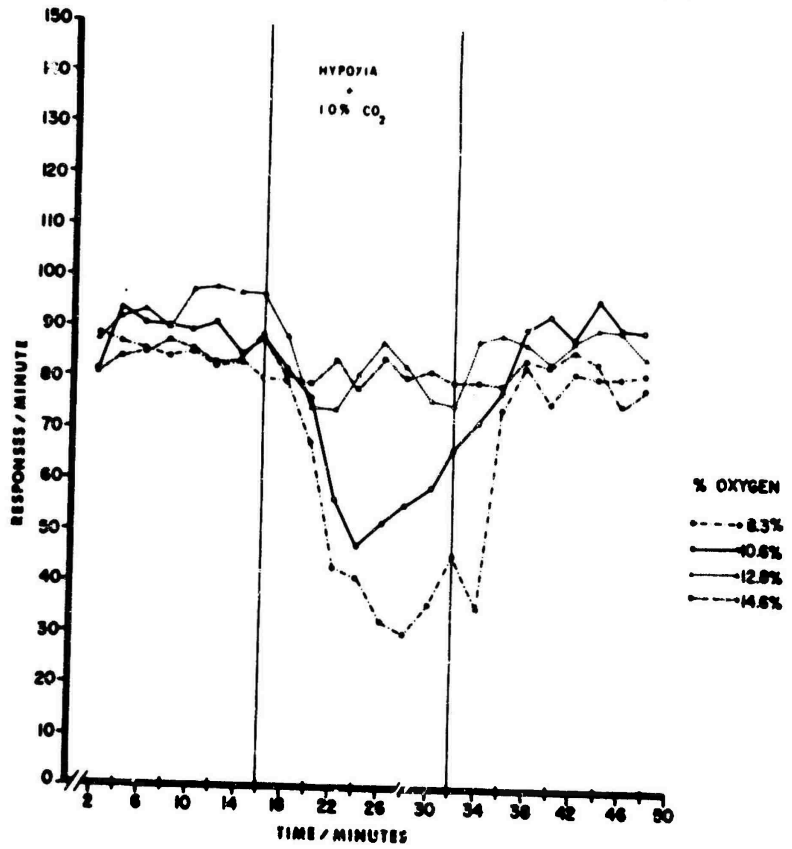
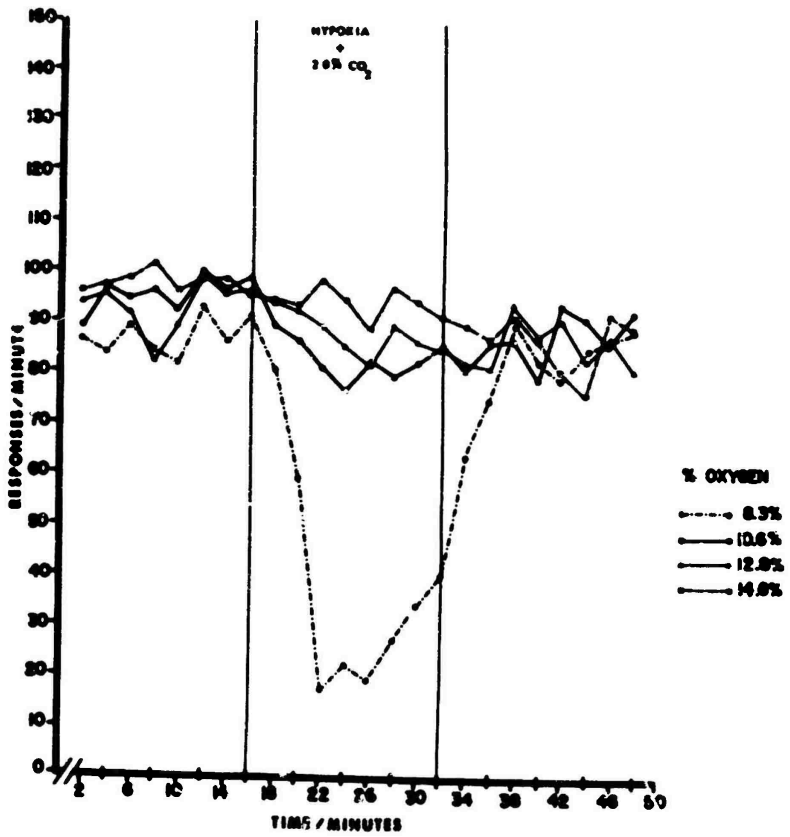


Figure 4. See legend for Figure 3.



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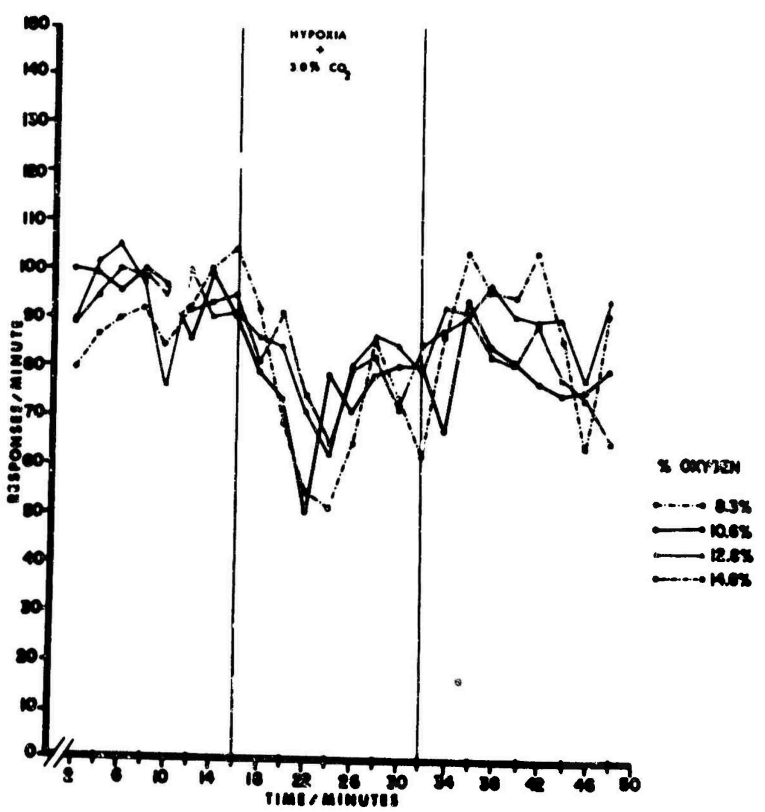

Figure 6. See legend for Figure 3.

the pressure of carbon dioxide from 23 to 27 millimeters of mercury in 8 percent inspired oxygen; whereas a 2 percent increase in inspired oxygen increases the arterial oxygen pressure from 25 to 30 millimeters of mercury, and the pressure of carbon dioxide is increased from 23 to 25 millimeters of mercury (Figures 7, 8). The behavior in the two situations is identical, and we would conclude that arterial oxygen pressure and the pressure of carbon dioxide might both be determining performance.

If we now look at arterial pH, we can see that one percent carbon dioxide drops pH in eight percent oxygen from 7.59 to 7.49. There is, however, no significant drop in pH when the inspired oxygen is increased to 10. This can be seen in Figure 9. We must now establish whether pH determines performance in low oxygen environments. In order to do this, we have administered a carbonic anhydrase inhibitor Cl 11,366* in a dose of 20 milligrams per kilogram, one hour before a two-hour low oxygen exposure (3, 4, 5). Carbonic anhydrase inhibition increased self-stimulation rates in 8 percent oxygen from 22 responses per minute to 40 responses per minute which was significant at the .025 level. In terms of blood gas and acid-base balance, the drug

2-Benzine 1,3,4-Thiadiozol 5-Sulfonamide

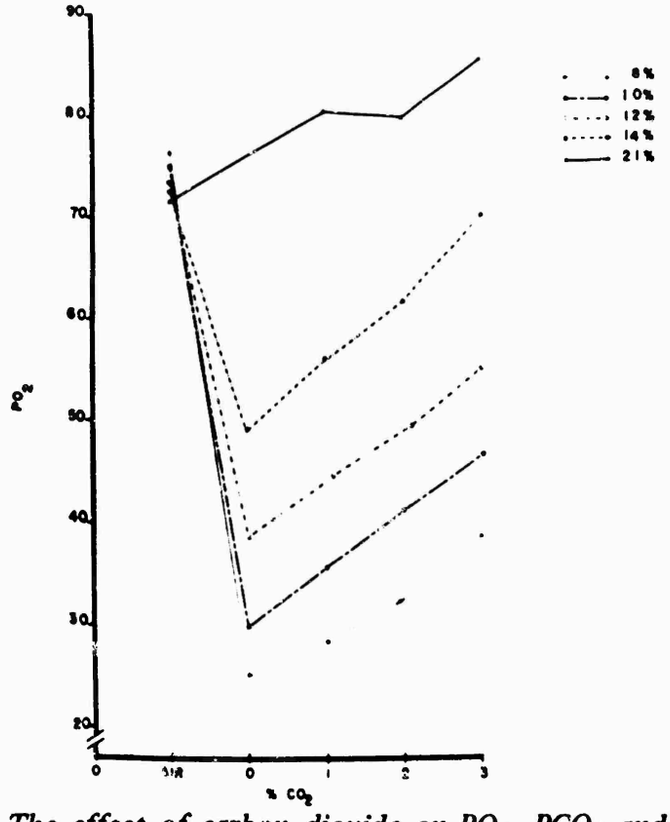

Figure 7. The effect of carbon dioxide on PO_2, PCO_2 and pH of arterial blood.

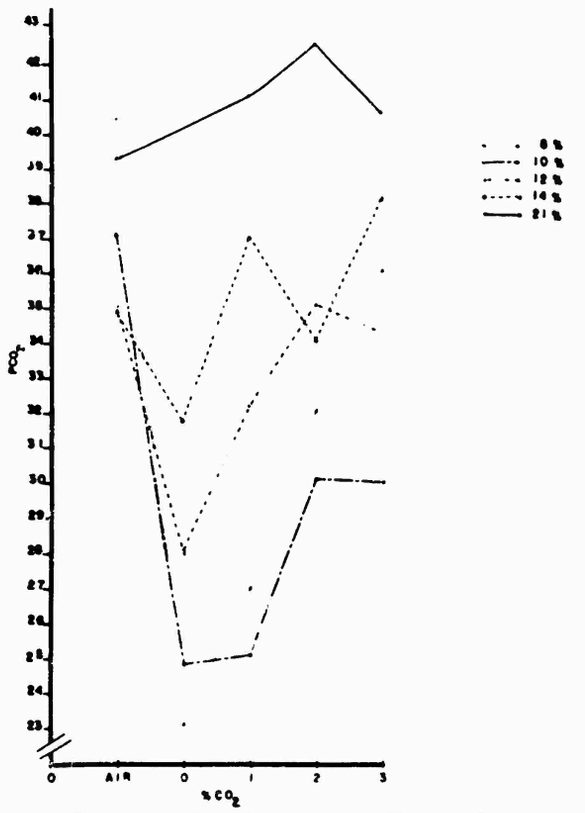

Figure 8. See legend for Figure 7.

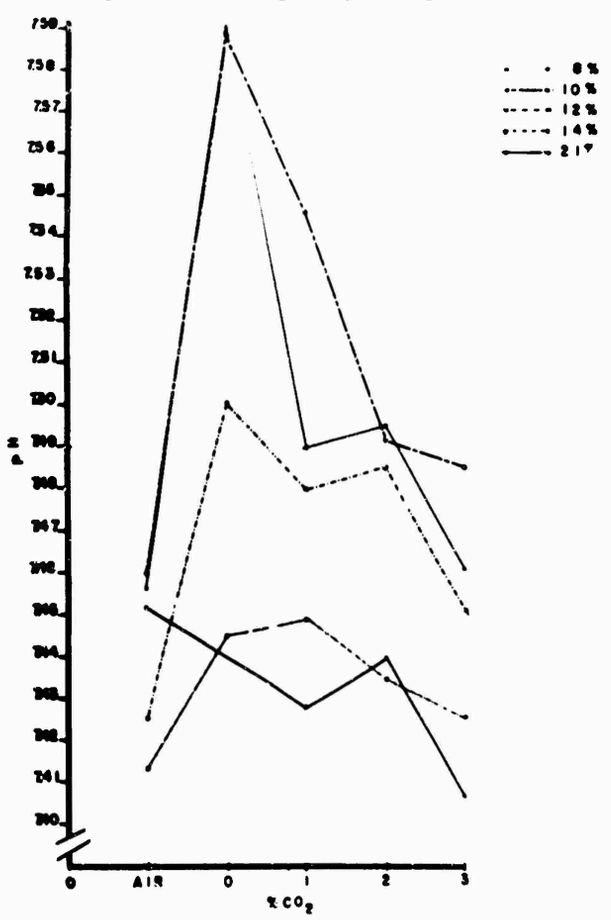

Figure 9. See legend for Figure 7.

administered in this way increased the oxygen pressure only 1.7 millimeters of mercury (which was not significant) and carbon dioxide increased only 1 millimeter of mercury (not significant); the pH decreased from 7.63 to 7.52. This pH decrease with minimal oxygen and carbon dioxide increase produces a behavioral improvement equivalent to the addition of 1.0 percent carbon dioxide or 2 percent oxygen. It thus seems likely that all three factors – pH, PCO_2 and PO_2 – are capable of altering neural function and performance in low oxygen environments.

These data illustrate that physiological and behavioral measures, when in a quantitative form, can be highly predictive and of significant theoretical use.

I would like to describe another set of experiments which we are now undertaking. We have already demonstrated that exposure to low oxygen environments produces a quantifiable, reproducible decrement in self-stimulation rates. The question which we now pose is: can this decrement in performance be obtained by the independent presentation of stimuli that were associated with the hypoxic exposure, i.e., whether the decrement in performance is classically conditionable. In this experiment, an animal is trained to self-stimulate. He is then placed in a test chamber every day for a two-hour test period. During this time a hissing sound is produced for a two-minute period, every 16 minutes. It is demonstrated that this does not in itself cause a decrease in self-stimulation rate. After one day, the classical conditioning procedure begins and the animal is placed in either 6 percent or 8 percent oxygen for two mintes, the hissing sound being present only during the period of low oxygen breathing. After 10 of these conditioning trials, we carry out a test trial in which the hissing sound alone is presented. Now, there is a suppression of self-stimulation identical to that produced previously only by the low oxygen. This can be demonstrated consistently. A further demonstration that this suppression has been conditioned can be obtained by presenting the hiss alone for several trials. It becomes apparent that its ability to suppress self-stimulation is temporary and after 4-6 presentations it looses its effect. By once again pairing it with low oxygen, the hiss regains its ability to stop the self-stimulation.

Let us now look at the sequence of events which occur. this time including the animal response in the scheme. The hiss comes on, the inspired oxygen drops, the animal hyperventilates, the pH rises, the animal becomes hypocapnic and hypoxic and stops self-stimulating. Notice that in this scheme, hyperventilation, a somatic motor act, precedes the cessation of lever pressing. The

question we now ask is whether the hyperventilation might become a conditional signal for hypoxia and like the hissing eventually lead to a cessation of lever pressing. Before answering this, I should mention that in earlier studies we established that CO_2 breathing for short periods does not markedly affect self-stimulation rates in air increases the rate during hypoxia. Given these facts, we proceeded to see what would happen if we added CO_2 to the hypoxic mixture presented during a conditioning trial of a well trained animal. To our surprise, there was no improvement in performance and in fact the suppression seemed more profound. Thus it was obvious that CO_2 acted differently in conditioned animals than in unconditioned ones. The next logical step was to present CO_2 alone and when this was done, self-stimulation rate dropped just as if the animal was breathing low oxygen. From these experiments, it is clear that a respiratory change can it itself act as a conditional signal for hypoxia and that this effect may lead to decrements in performance in otherwise adequate environments.

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PROBLEMS INVOLVED IN OBTAINING OBJECTIVE MEASUREMENTS OF THE EFFECTS OF BIOLOGICAL RHYTHMS AND MODERATE DEGREES OF HYPOXIA IN HUMAN SUBJECTS

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Rapid air transportation and mountainous areas of operation provide a question which, experimentally defined, concerns the joint effects of hypoxia and time displacement upon human performance. Considering the practical implications involved, one might expect the question to have elicited considerable research. Such is not the case. The single effects of hypoxia have been investigated extensively and, to a much lesser extent, so have the single effects of time displacement. However, the joint effects of these two factors, each of which have been shown to deleteriously affect human performance, have received little or no experimental attention.

The one possible exception may be the study reported in 1947 by White (5). The objective of this study was to determine the cumulative effects of prolonged exposure to oxygen deficiency. The method consisted of periodically assessing physiological and psychological functions of passengers on a flight around the world in an unpressurized aircraft. Unfortunately, the joint effects of hypoxia and time displacement upon performance were obscured by "practice effect," i.e., with repeated testing (code substitution and arithmetic addition) performance tended to improve. This, of course, reveals one of the problems inherent in the study of time displacement and hypoxia. There are other methodological problems, equally critical, which can be best illustrated by a short summary of a series of studies (1, 2, 3) designed to appraise the effects of time displacement by intercontinental flight upon (1) the phase shift of the circadian period manifested by different physiological functions and (2) human performance during the period of phase shifting. Three such flights were conducted – an East-West and a West-East flight which permitted a comparative

analysis of bidirectional time displacement and a North-South flight which permitted an appraisal of those effects solely attributable to prolonged flight.

Method

Schedule of Assessment. For each of these flights, biomedical assessments were made on: (1) alternate days during the week immediately prior to flight; (2) during a 2-3 week period at the overseas destination beginning with the day of arrival; and (3) during the week following return to the environment of origin beginning with the day following arrival.

These biomedical measurements were repeated at 0700, 1100, 1500, 1900, and 2300 hours (local time) on each day of assessment. During each of these five periods of assessment, several different psychological functions were sequentially measured by standardized procedures. Simultaneously, measurement was also made of several different physiological functions. Time required for a period of assessment was approximately 25 minutes.

Assessments. Rectal Temperature – Internal body temperature was measured by a portable, indicating bridge circuit, calibrated to a thermistor rectal probe, which was inserted to a depth of 10 cm, worn continuously throughout each assessment day, and removed only for bathing or evacuation. During the waking portion of the day, the subject read and recorded his own temperature to the nearest 0.1° C at one hour intervals; for the remainder of the day, a technician recorded the sleeping subject's temperature at the same interval.

Evaporative Water Loss – For each assessment period a small plastic capsule was sealed to the skin at the center of the left palm. Measurements of evaporative water loss from this area were made continuously throughout each assessment period, evaluating both steady-state, "basal" levels during rest, before and after each assessment period; and increased evaporative rates during identified assessment increments.

Heart Rate and Respiratory Rate – A light-weight, plastic and elastic chest strap was improvised to house three silver electrodes for heart rate measurement and a mercury-in-rubber strain gauge to monitor respiratory rate as a function of changes in chest circumference.

Reaction Time – The speed of manual response to three successive presentations of a single auditory stimulus, three successive presentations of a single visual stimulus, six successive and randomly determined presentations of one of three possible visual stimuli, and finally to one presentation of a single auditory stimu-

lus was measured at each of the indicated times of assessment during each assessment day.

Decision Time – This was obtained for each assessment period by subtracting the mean time of responding to the three presentations of a single visual stimulus from the mean time of responding with the correct response to the six presentations of one of the three different visual stimuli. This value was taken to represent the average time required to "decide" which of the three possible responses was the correct response to be made.

Subjective Fatigue – The level of subjective fatigue was measured by means of checklists, developed by the scale discrimination method, and shown to reflect significantly the effects of perceptual motor work and also the effects of pharmacological treatment (4).

Subjects. Four healthy, adult male volunteers were drawn from professional and technical research staffs for each of the three flights. During all periods of assessment, preflight, overseas, and post-return flight, the subjects were quartered in wards permitting supervision of activity. They also were instructed to maintain their daily living habits in accordance with the local time of the overseas destination immediately following arrival and were supervised to insure compliance with these instructions.

Results

East-West Flight. This consisted of a flight to Manila and return to Oklahoma City. Time of departure was 1800 hours CST, total time in transit 23½ hours, time of arrival in Manila was 0730 hours local time, and time displacement was 10 hours.

As was revealed by plotting of mean values, time displacement of the extent concerned effected a primary shift of phase of the circadian periodicity manifested by rectal temperature, heart rate, and palmar evaporative water loss. Also revealed was marked dissociation of the phase relationships. For rectal temperature and heart rate, completion of the primary phase shift required no less than four days. For palmar evaporative water loss, no less than eight days were required. A complete comparison of these findings with those obtained following return to Oklahoma City cannot be made owing to the unavoidable differences in flight scheduling. The most critical difference consisted of an overnight layover in Los Angeles. Despite this difference, however, it may be appropriate to report the observed differences in dissociation. Following return to Oklahoma City, the shift of phase for rectal temperature and heart rate occurred not at the same but differential rates whereas the shift of phase for palmar evaporative water loss occurred at a rate approximately that for rectal temperature.

In the case of psychological functions, impairment was observed during the primary period of transition. More specifically, mean reaction time, decision time, and subjective fatigue evidenced statistically significant increments but, in contrast to the time lags of the physiological phase shifts, the duration of these increments was extremely short. By the second day, the day following arrival in Manila, no significant impairment was observed. Return to Oklahoma City also effected psychological impairment of similar duration but to a lesser extent.

West-East Flight. This was a flight to Rome and return to Oklahoma City. Time of departure was 1400 hours CST, total time in transit 15½ hours, arrival time in Rome was 1230 hours local time, and time displacement was 7 hours.

The mean values obtained suggest several differences attributable to bidirectional time displacement. In contrast to Manila, the time lags of these primary phase shifts appear to be greater. Completion of the shift required approximately six days for rectal temperature, eight days for heart rate, and in the case of palmar evaporative water loss the shift of phase was not complete on the eighth assessment day – the last day of full assessment. The foregoing also indicates possible bidirectional difference in dissociation of phase relationships. In Manila, phase shifts for rectal temperature and heart rate were closely associated. In Rome, these phase shifts were dissociated.

Bidirectional differences were revealed also by the psychological functions measured. Whereas statistically significant impairment of reaction time and decision time was obtained in Manila, significant impairment of these functions was not evidenced in Rome. Only subjective fatigue was found to be significantly affected.

Return to Oklahoma City occasioned an equally notable difference in that circadian periodicity appeared to be manifested only by rectal temperature and heart rate. Further, for these two functions, shift of phase had not been completed up to and including the last day of assessment – the fifth day following the day of arrival in Oklahoma City.

North-South Flight. Originally, the purpose of this flight was to appraise the single effects of prolonged flight primarily upon psychological functions so these could be compared with the joint effects of prolonged flight and time displacement. The expectation was that, irrespective of direction of flight, such joint effects would produce the greatest psychological impairment. To a substantial extent, this expectation was derived from anecdotal evidence which indicated a close relationship between the lag

times of physiological phase shifts and the duration of subjective feelings of general maladjustment such as disturbances in the regimen of eating and sleeping. As has been indicated, however, the impairment of psychological functions which did occur was not only of very short duration but, more importantly, was not produced to any extent of functional significance by the joint effects inherent in the West-East flight. Moreover, it was this particular flight which evidenced the greatest time lags of physiological phase shifts. This suggests considerable independence between phase shifting of physiological functions and integrity of psychological functions and, in addition, the possibility that the psychological impairment produced by the East-West flight was attributable to the single factor of prolonged flight. To test this specific possibility, the North-South flight was conducted. It originated in Washington, D. C. and its destination was Santiago, Chile. Time of departure was 1900 hours EST, total time in transit 18 hours, arrival time was 1300 hours EST.

As expected, the phase of the periodicity manifested by the physiological functions was unaffected. Less expected were the psychological findings. Of the changes effected in these functions by 18 hours of flight, only the increment in subjective fatigue was found to be statistically significant. The conclusion would seem to be that time displacement and prolonged flight do produce impairment of subjective well-being but do not engender any commensurate change in the efficiency of the psychological functions assessed.

To illustrate the phase shift of the circadian period, the mean hourly rectal temperature obtained during each of the three flights have been plotted in Figure 1.

Examination of the preflight curves reveals the circadian periodicity and amplitude of stored heat typically manifested under normal circumstances, i.e., rectal temperature is shown to steadily increase beginning with awakening, plateau between 1400 and 2000 hours, then decline and continues so to the beginning of the subsequent biological day. What happens to this circadian periodicity following arrival in Manila and Rome is also revealed. Very briefly, one can see the extent to which the temperature curve is out of phase initially with the local time of Manila and Rome, the shifting of the curves into phase with local time with successive days, and, finally, the total time required for the completed phase shift.

The lowermost curves obtained from the North-South flight present equally clear but contrasting findings in that phase displacement and, in turn, shifting of phase are not evidenced. This,

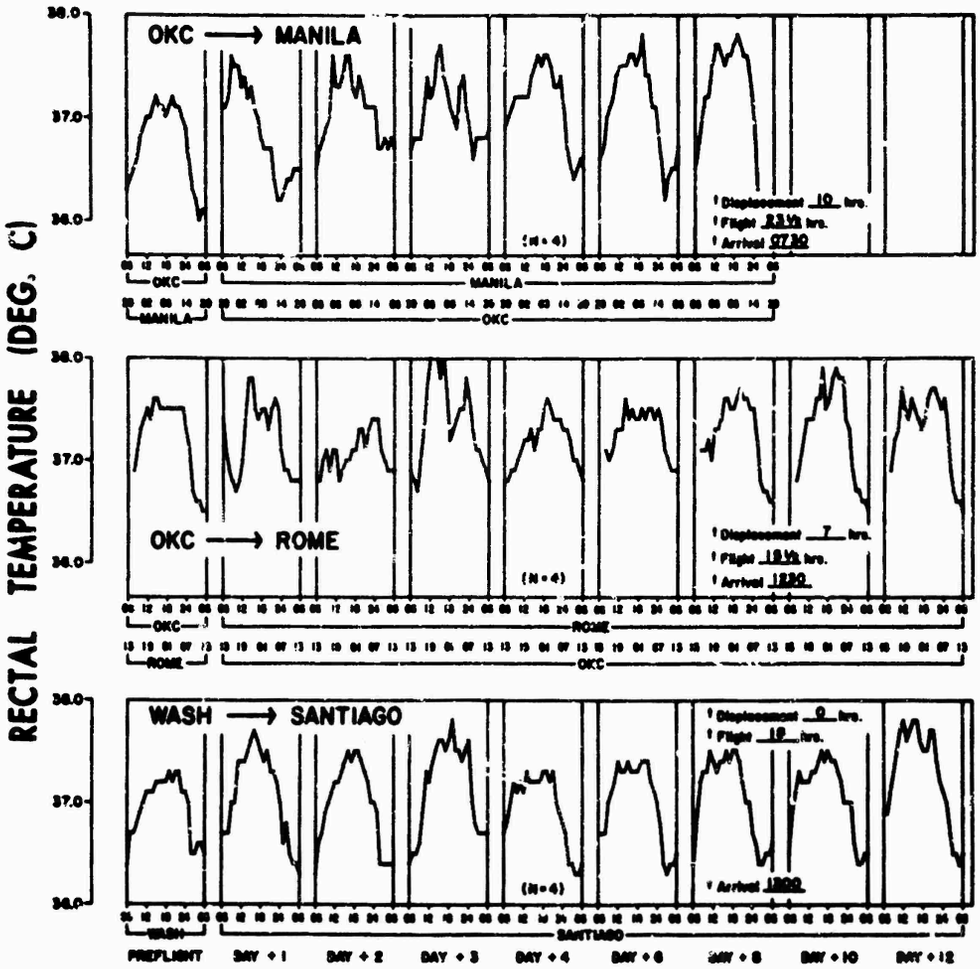


Figure 1. Mean hourly rectal temperature obtained prior to flight and following flight to overseas destination.

of course, is fully in accord with what one would predict. To illustrate the extent and duration of psychological change the mean daily values for subjective fatigue, reaction time, and decision time have been plotted in figures 2, 3, and 4 respectively. It should be repeated that the changes in reaction time and decision time seen in the West-East and North-South flights were not found to be statistically significant.

What has been presented should reveal several points of consideration which provoke problems of methodology. The extent to which these are resolved will determine the degree of success of any investigation of the joint effects of time displacement and hypoxia.

Performance Functions. The functions assessed in the studies reported were very simple functions. They were selected on the basis of the following requirements:

1) Time required for assessment – with the necessity of repeated assessments throuhout the day, the period of assessment

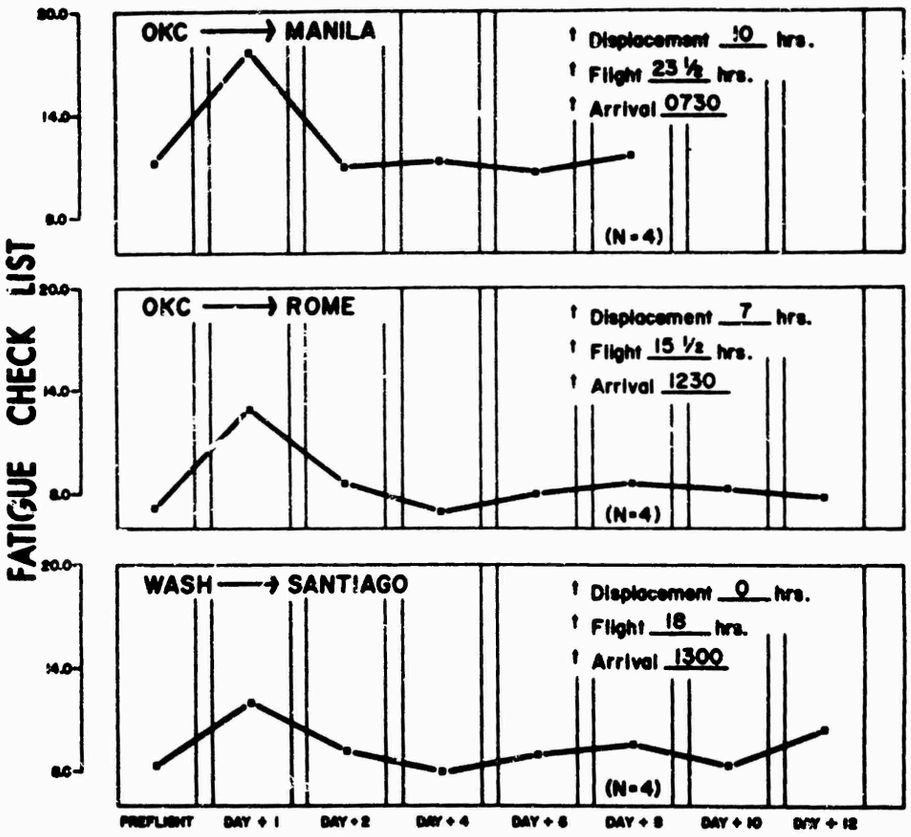


Figure 2. Mean daily ratings of subjective fatigue.

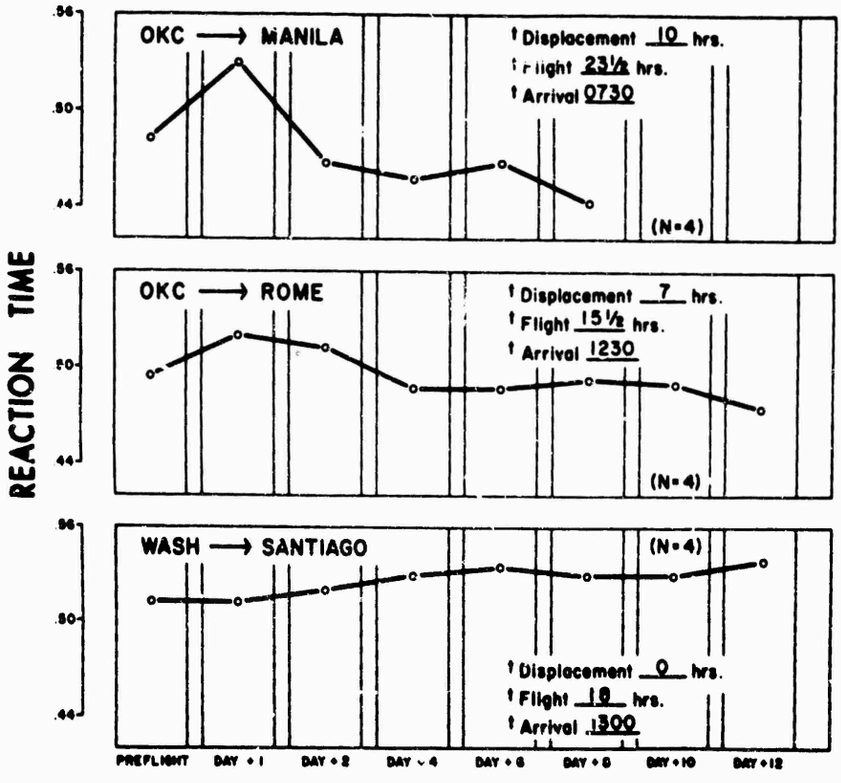


Figure 3. Mean daily reaction time.

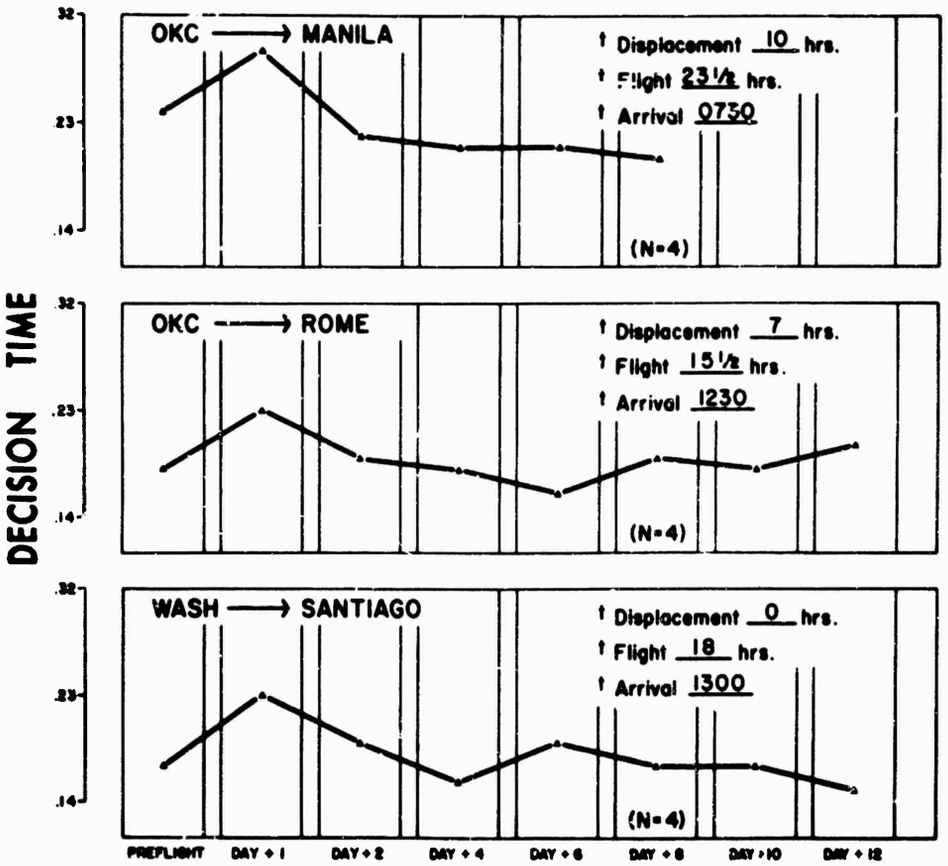


Figure 4. Mean daily decision time.

cannot be of such a duration as to attenuate the motivation of the subject or to invite fatigue.

2) Reliability of the apparatus – while overseas, the time required for replacement of malfunctioning parts or parts damaged by shipment is prohibitive. Further, this problem cannot be completely alleviated by back-up measures.

3) Sustentation of subject motivation – assessment on alternate days for a period of 4 or 5 weeks is extremely demanding and even with a system of substantial rewards, it is imperative that the tasks performed by the subject elicit his interest or, better, challenge him.

4) Minimal practice effect.

In future investigations, more complex functions should be assessed because of their greater relevancy to skills and job requirements and because of the possibility that such functions, in contrast to the more simple functions, are more susceptible to the joint effects of time displacement and hypoxia. The problem will be to satisfy the requirements given above.

Individual Differences. Figures 5, 6, 7 and 8 are presented for the purpose of demonstrating the nature and extent of inter-

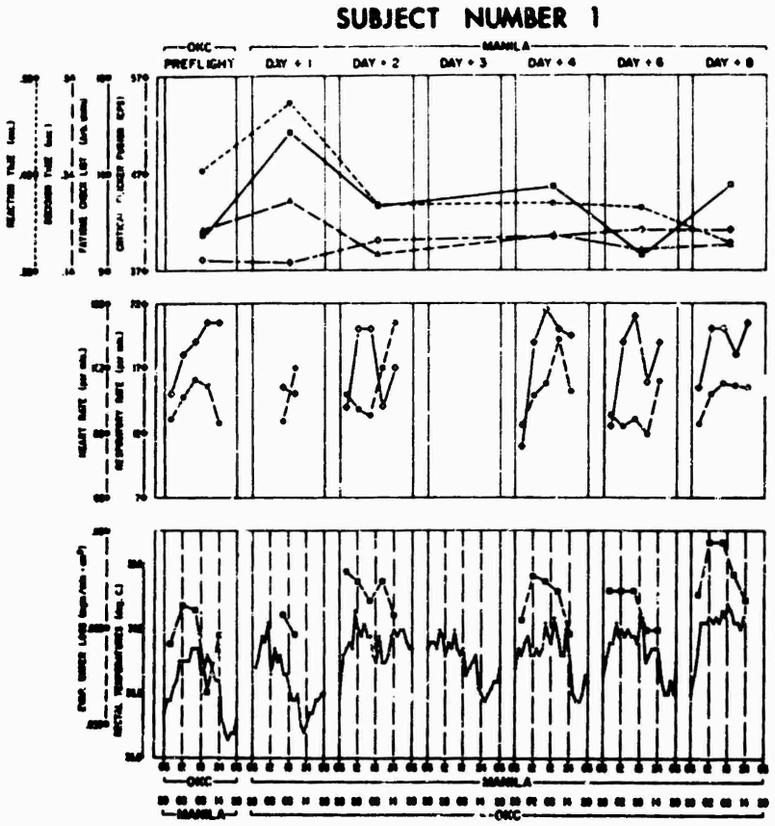
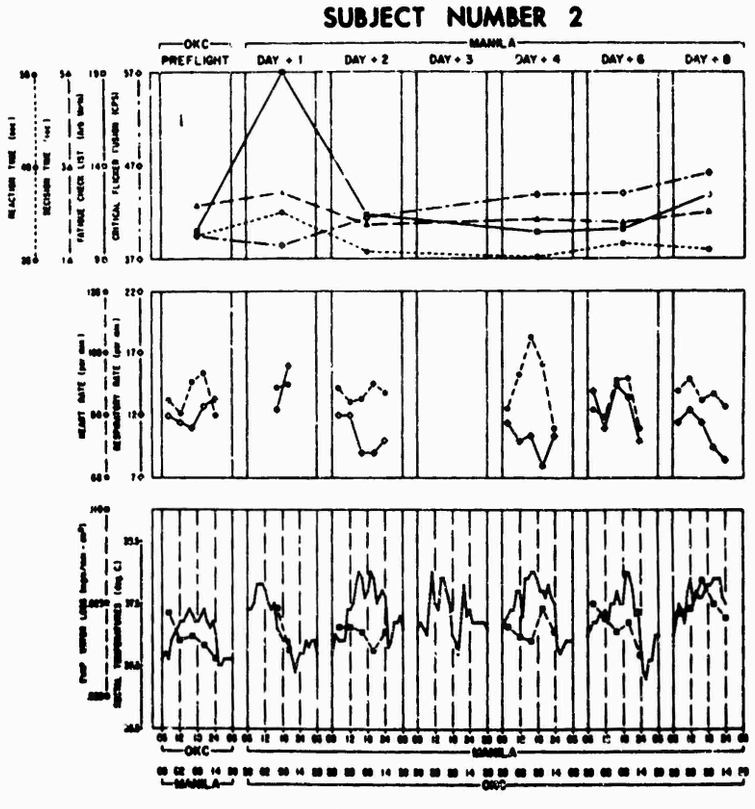


Figure 5.



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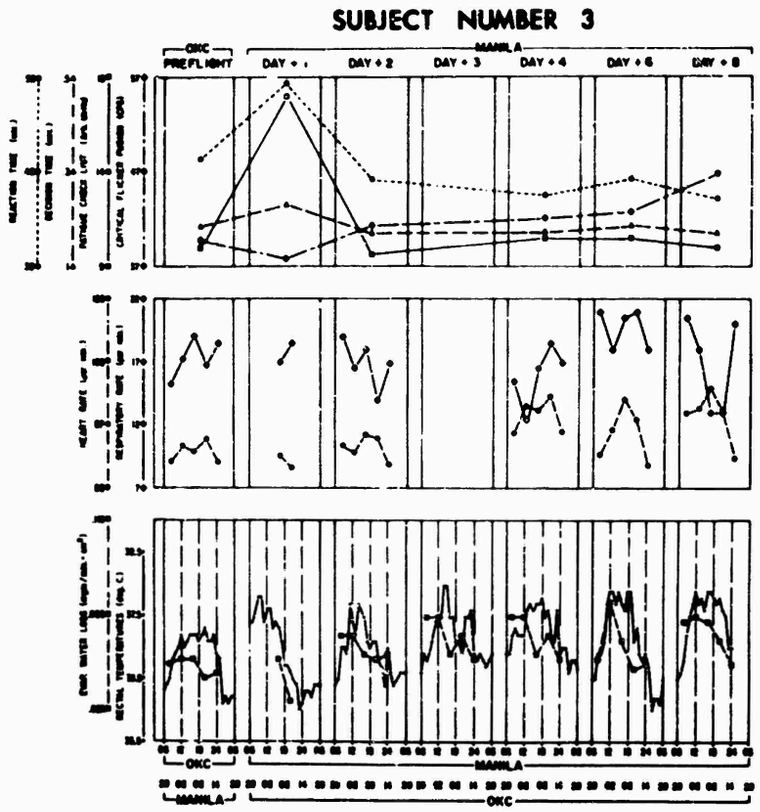

Figure 7.

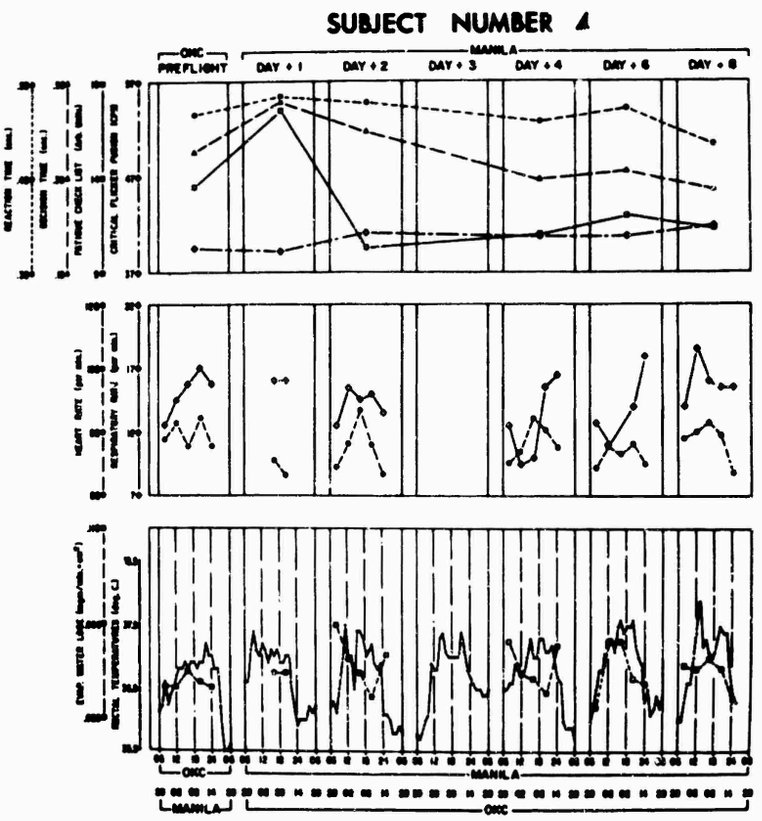

Figure 8.

individual variation. The values plotted represent the measurements obtained for each hour in the case of rectal temperature and for each of the five assessment periods in the case of palmar evaporative water loss, heart rate, and respiratory rate. For the psychological functions, the values represent the means of the measurements made during the five periods of assessments.

Time Lag. One would expect considerable individual variation in time lag and the extent of this variation is indicated by the four graphs. For rectal temperature, the time required for shift of phase ranges from two to six days. What the mean time lag would have been had 30 or more subjects been used is indeterminable. The more interesting point is that the range of individual variation would have been greater than has been indicated by the data presented here.

Dissociation. As revealed by mean values and as has been indicated earlier, the shifting of phase for rectal temperature and heart rate remained associated relative to time whereas palmar evaporative water loss did not. As can be seen, this general statement applies only to one of the four subjects. In this regard, Subject 1 (Fig. 5) provides quite interesting data. Here, the time lag for rectal temperature is approximately six days; for palmar evaporative water loss, four days; for heart rate, the time lag cannot be determined because the periodicity manifested so clearly by this function during preflight is not evident in Manila. Further, following the shifting of phase revealed by the rectal temperature curve on Day + 2, the phase then appears to revert back to the reference of Oklahoma time on Day + 3.

The problems generated by such variation include the necessity of assessing a meaningful spectrum of physiological functions, subject populations sufficient for valid generalizations which, in turn, raises the problem of costs, and finally strict control for a systematic manipulation of variables pertinent to circadian periodicity. One such variable, for example, is the physical activity engaged in by the subjects. For certain of our subjects, the effects of this variable were to mask almost completely the ongoing shifting of phase of the physiological functions assessed. This suggests, as one interesting approach to the study of phase shifts, the experimental comparison of restricted, normal, and extended expenditures of physical activity. At present, extrapolation from one condition to another may not be appropriate.

Cost and Logistics. The costs involved in the air transportation of subjects, technicians, apparatus, and equipment constitute a problem so obvious as require no further discussion. Less apparent are certain logistical considerations.

1) Scheduled shipment of apparatus and equipment – On none of the three flights did all of the apparatus and equipment arrive at the scheduled date regardless of whether shipment was by MATS or commercial air freight. To overcome this problem, an advance man was sent to the overseas destination 3-4 weeks prior to the scheduled arrival of the subjects for the purpose of tracing, locating, setting-up, and calibrating the apparatus.

2) Overseas research and housing accomodations – In the flights reported, these accomodations were provided by hospitals which, at the outset, appeared to be the most appropriate source of testing, sleeping, and eating facilities. However, accommodating a party of healthy men and providing for their unusual requirements is a definite inconvenience for any busy hospital. Further, a metropolitan hospital cannot provide healthy men with the recreational facilities desired for the subject's off-time duty.

3) Diet – In the studies reported, the attempt to minimize diet change was unsuccessful. The result, despite medication, was the inevitable temporary intestinal disorder.

There is, of course, an alternative to achieving time displacement by flight across many time zones. Subjects can be committed to an isolation chamber, e.g., an altitude chamber and, with a strict control of the time cues of the real sociophysical day, other time cues can be utilized and manipulated so as to displace accustomed biological time. In this approach, however, there is inherent a critical problem in that such an environment necessarily is one of sensory impoverishment. The problem consequently is that of extrapolation to the normal environment of accustomed sociophysical stimulation.

These then are some of the methodological problems to be encountered in the investigation of the effects of time displacement and hypoxia upon human performance. For the most part their precise nature was not fully known until after the design and execution of the studies reported. Consequently, the intent underlying their discussion is to enhance the definitiveness of future investigation.

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GENERAL DISCUSSION

DR. BILLINGS: Dr. McFarland, have you had the opportunity, since your original work, to follow these functions during the course of acclimatization to find out how close to one's original control values one gets after a period of time at altitude?

DR. McFARLAND: No, I do not know of any studies that have been made of these.

DR. WEINSTEIN: About six months ago we presented, at Natick, preliminary results of studies which are somewhat applicable, and rather surprising. If you have an animal showing a decrement in performance in 8% oxygen, and simply put him into 8% oxygen every day for 16 minutes, then for the first three days you see virtually no change in performance. On day 4 the animal improves slightly, and the next day he shows additional improvement. After 9 days, in 8% oxygen, 16 minutes exposure per day, the animal is performing as if he were breathing approximately 14% oxygen. We are now doing a series of studies to measure PO_2, oxygen saturation, hematocrit, pH and PCO_2 over this 9-day period. It has been demonstrated that hematocrit will change with just 15 minutes daily exposure to hypoxia. I think the question of performance changes with acclimatization is a very real one and it is quantifiable (in terms of neural reactivity). It does not require continuous exposure.

DR. BILLINGS: But, by the same token, apparently the decrement you observed does not require hypoxia either.

DR. WEINSTEIN: That is correct and this is why we are studying blood gas and blood acid-base changes. I am not yet willing to call this true acclimatization. When you deal with performance in hypoxia, there are, just as you mentioned, many other factors

which might be relevant besides true acclimatization. There is an acclimatization-like effect on performance that occurs with very brief hypoxic exposure. How much of this is due to the things we call acclimatization in terms of blood acid-base balance, blood gases, and tissue changes, is another question.

DR. GERBEN: I should like Dr. Weinstein to comment on some studies that we have done which are related to his. We replicated his interaction between current level and hypoxia with a slightly different procedure. We allowed the subject to regulate the duration of the stimulation by holding down the bar and keeping the stimulation on for as long as he held down the bar. Weinstein had a constant stimulus duration of .25 seconds. Using our procedure, it was found that as current increased, the response-duration decreased; but hypoxia had no effect on the response duration. Also, as the current increased, the inter-response interval during which the current was off also decreased. However, hypoxia lengthened the inter-response interval with a much more pronounced effect at the lower current level. This suggests to us that hypoxia was not acting on the neural reactions during stimulation, but was affecting the after-effects of stimulation, or some recovery process. Now, we would like to know how this fits into your hypothesis of the number of cells firing being the mediating mechanism.

DR. WEINSTEIN: I think there is a very distinct possibility that there is an effect of hypoxia on the recovery of neurons from continuous electrical stimulation. It is very hard to make any definitive comment about Dr. Gerben's results relative to ours simply because of the way in which the brain was stimulated. The way in which the neurons were activated by electric current was quite different in the two situations. We used a 60-cycle per second alternating current delivered for a very brief period (one quarter second). Dr. Gerben used a square wave pulse that went on at a frequency of 100 cycles per second. The effect of stimulus parameters must be further investigated.

DR. GERBEN: We did replicate the interaction between hypoxia and current level which you found on response rate, even with our different stimulus characteristics. Our procedure, however, allowed the measurement of additional temporal aspects of behavior.

DR. ROBINSON: Dr. Hauty, could you give us more details concerning the sleep factor in this cycle which is reversed when one flies from here to Rome, or from here to Tokyo? What advice do you give aircrews who make these flights perhaps once or twice a week, back and forth?

DR. HAUTY: The subjects were instructed to lock on to the local time of the place of destination as soon as they arrived. This pertained to sleeping eating, etc. And, of course, they had a house mother or house father to see that they did. This was quite important because otherwise you have to roust them out of the sack in the middle of the afternoon.

The thing that I did not mention is that we received unsolicited complaints from the subjects for the first four or five days depending on individual variability. These complaints all centered about their generally upset state. One subject referred to it as "discombobulation". They had trouble sleeping, they woke up at the wrong time, could not go to sleep at the right time, some GI trouble. Many of the subjects would say: "Just as soon as I get in shape then I will be able to know these performance tests just like I used to back in Oklahoma." All the time they were saying this and feeling this, they were still performing just as well as they had back in Oklahoma following one night of sleep.

DR. ROBINSON: How about the time factor for repeat trips?

DR. HAUTY: I did not get into that. What has been reported represents the first phase of this particular study. The second phase was to use as subjects inter-continental air-carrier crews, to look at the factor of habituation or repeated exposure to this particular condition. We did not get into the second phase. A very real question does exist regarding the extent to which people do habituate to this. And it is at present unknown. We have quite a bit of information but this is, again, all subjective

THE EFFECT OF HIGH TERRESTRIAL ENVIRONMENT ON TWO DIFFERENT TYPES OF INTELLECTUAL FUNCTIONING

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It is a common observation of people who have experienced a long-term exposure to high altitude environments that the act of thinking is made more difficult by this situation. However, very few investigators have subjected this phenomenon to study by experimental means. McFarland (3) demonstrated that a rapid ascent to altitudes above 14,000 feet produced diminutions in performance on a number of types of intellectual tests known to be sensitive to organicity. He also found that a standard intelligence test was insensitive to this change in environment. One particular test that changed rather dramatically in this situation was one involving coding; this is the digit symbol substitution test of Weschler (DSST).

A more recent study, conducted in a simulated high altitude environment, has also demonstrated the sensitivity of the DSST to a rapid transition from a low to a high altitude environment (2). It would appear that the particular intellectual skills involved in coding type tasks are sensitive to changes induced by a rapid movement to a high altitude. However, at this time, we do not know what the underlying factors associated with this decrement in performance might be.

Mirsky and Kornetsky (4) have demonstrated that the DSST and the continuous performance test (CPT) of Rosvolt are both sensitive to a large number of psychotropic drugs. They have also shown a differential sensitivity of these two tests to the actions of these agents. They have hypothesized that drugs which produce an initial period of burst rhythm on electroencephalographic recordings tend to produce the greatest relative decrement in the DSST; whereas, those drugs which produce only a slowing of the predominant frequencies of the EEG have their greatest relative effect

upon the CPT. These authors have contended that this discrepancy in sensitivity is a function of a difference in the factors that the tests are measuring. It is their contention that the DSST is a measure of a simple mental operation and, thereby, is more sensitive to drugs with some intoxicating properties; whereas, the CPT is a test of simple attention, and therefore, is most sensitive to those agents producing sedation. Since these results had been verified with a number of chemical agents the purpose of the present experiment was to determine the relative effects on these tests of a high mountain environment.

Methods

The subjects were 16 young male soldiers selected from a population at Fort Sam Houston, Texas. Subjects were screened to ensure that none of them had a recent high altitude exposure, were medically fit and had at least a normal intelligence All subjects were volunteers and were studied under the provisions of the regulations of the Surgeon General of the Army.

The DSST was executed in the standard manner (2). Alternate forms of the test were prepared by randomly associating different numbers with different symbols so that the test could be given on a number of occasions with the same subjects. The CPT was executed with the use of a memory drum. Lists of a sequence of 30 groups of letters were prepared for the memory drum. Each group of letters had five letters within it. Approximately 20% of these groups had an "X" at some position within the group of five letters. The memory drum presented one group of letters each second to the subject. A tachistoscopic lens was used to allow an exposure time of 1/25th of a second for each letter group.

The subjects were measured on the DSST every day for five days preceding their exposure to high altitude and for five days at the high altitude. CPT was measured twice at low altitude and twice at high altitude on the first and third day after arrival. The high altitude environment was that of Pikes Peak, Colorado, an altitude of 14,110 feet. Subjects were taken to this altitude within a day from the sea level site at Fort Sam Houston, Texas.

Results

The results were analyzed by means of an analysis of variance. Figure 1 graphically portrays the curves for the two tests and the interruption of the curves by high altitude. From these data it can be seen that a significant decrement was produced in the DSST by an exposure to high altitude; whereas, no such decrement could be shown in the CPT. This was confirmed by the statistical analysis ($P<.01$ for DSST and $P<.42$ for CPT from expected values).

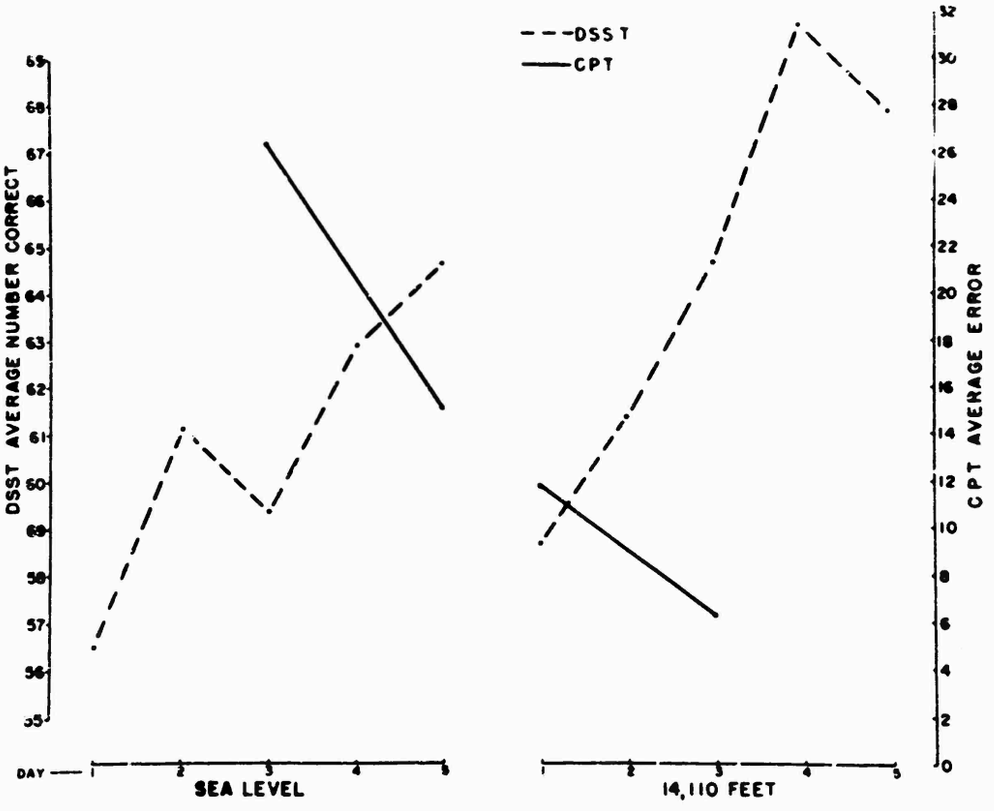

Figure 1. A comparison of the DSST and CPT performance scores on the various replications of the tasks at sea level and on the first three days of exposure to a high altitude. The effects of high altitude should be noted as deviations from an expected monotonic practice curve.

Discussion

On the basis of these data it would appear that the effect of high altitude is analogous to that found by Mirsky and Kornetsky for intoxicating substances. The lack of effect on the CPT would seem to indicate simple, short-term attention is little affected by high altitude environment; whereas, the decrement in the DSST would indicate that even very simple mental operations are affected by this situation.

One can also observe from Figure 1 that the performance on the DSST type of mental functioning seems approximately to have returned to normal after four days at high altitude, i.e., that point which would have been predicted by assuming that the learning curve of the DSST is the usual rising monotonic function approaching a limit.

The present results lead to speculations as to what might be the effect of high altitude upon other types of intellectual function-

ing. If we may assume that high altitude acts in a fashion similar to sedative-intoxicant drugs, we might also predict a lowered capacity for creative endeavors (1) and hindrances in associative memory (3, 5). On the other hand, certin types of intellectual functioning should be rather resistant to the effects of high altitude. Specifically, those tests involving judgment and evaluation (1) and tests involving only simple attention (4). A great deal of further research will be necessary to evaluate the utility of the hypothesis of assuming that high altitude acts similarly to a sedative-intoxicant in terms of human intellectual functioning.

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EXPERIMENTAL TECHNIQUES FOR THE MEASUREMENT OF ENVIRONMENTAL STRESSES, WITH SPECIAL REFERENCE TO ALTITUDE*

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Studies of the effects of the environment on human performance have been strongly motivated by a search for performance changes which might be correlates of physiological findings. If one stands back for a moment and takes an overall view of the field certain convictions emerge:

1. Where correlations between performance and physiological changes are suggested, they often suggest a dependence of the performance on an organ or response modality which in turn is specifically dependent on the physiological change. For example, the performance of people at tasks which depend critically on vision is susceptible to altitude as the result of a visual oxygen lack.

2. More often than not the correlation of performance and physiological effect does not appear in experimental studies. Although a real correlation may exist, it can be masked in two ways. First, there may be a performance effect which occurs prior to or after the physiological change. When this happens, the effect may be larger or smaller than might be expected from the physiological change. A recent study by Shulte (10) with human subjects found that the error and speed of color naming during exposure to carbon monoxide was altered prior to detectable biochemical and physiological changes. A second example is found in a study by Murphy (8) who reported that animals exposed to constitutents of auto exhaust exhibited altered oxygen uptake and transport as well as decreased voluntary running behavior. The same exposure levels were not high enough for a detectable change in CO hemo-

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globin. Finally, by way of example, most if not all performance effects which appear at altitude appear well *after* physiological and biochemical effects can be demonstrated.

A second kind of study shows no performance effects until physiological changes are severe. For example, simple reaction times do not appear to be affected until perhaps 18,000 feet. This is a very interesting kind of finding because it suggests two alternative explanations, i.e. that either there is no performance effect until approaching physiological collapse, or that there is an effect, but it is being compensated for somehow up to that point.

Many investigators interpret the lack of correlation between performance and physiological states as a reflection of events going on in the central nervous system (CNS). Accepting this interpretation, it would seem there is a need for experiments concerned with specific, observable sensory and motor dependencies on physiological states and experiments concerned with unobservable, but inferrable performance dependencies on the CNS. Just accepting the need for considering both sources of effect raises questions about what we already think we know. For example, is the well-demonstrated loss in the ability to detect brightness differences due to a loss of retinal sensitivity or is it due to a CNS impairment such as, perhaps, a reduction in the subject's attention to the stimulus?

We not only lack an understanding of how performance depends on intervening neural processes, we also lack a basic knowledge about the processes themselves. As if this were not enough of a handicap, we must also cope with a failure to have even agreed on what kinds of task represent what kinds of performance. This failure to have an adequate task-performance taxonomy is reflected by a bewildering variety of ingenious experimental situations in the research literature and a confusing array of minutely detailed lists of activities called "task analyses" used to describe operational performance. Even if we agreed on any one task analysis system, it would be hard to relate it to the existing research literature.

We propose, therefore, to develop a task-descriptive system which may bridge the descriptive gap between the research and the operationally oriented literatures, to guess at the processes in the CNS, and to guess at the relationships between performance on the tasks and the central processes. We think we can do this meaningfully as long as we proceed in functional as opposed to anatomical terms, that is, if we ask not whether the brain has a specific process for carrying out some function, but whether it appears to be carrying out that function at all. If the brain appears to be carrying out a given function, then we may postulate that it does

so in terms of a specific underlying process, still without attempting to isolate the process or determine its nature except functionally. Finally, having established a means for describing task performances and a set of underlying processes, we may guess at the relationships between the two using what data may be available as a guide. We must emphasize that it is not our major interest to be correct in formulating a system; rather, we hope this system will be stated clearly enough to allow others to find out how we are wrong. The least that can be accomplished is a start toward organization of available performance data and toward the selection of future experiments on some kind of systematic basis.

The problem of task description may be treated in system terms at different levels of system analysis. At the most general level, the entire human organism is viewed as a component in a system as shown in Figure 1. Using this paradigm, we can think of information being transmitted between components and as being operated upon within components. Something that operates upon information within a component we shall think of as a *process;* the transfer of information between components will be called a *task.* The distinction between tasks and processes is important and must be retained because as we break the system down into more molecular views, what is a process in the larger view becomes a series of tasks among sub-system components. For example, the transfer of information between components in Figure 1a are tasks; those tasks involving man as a component are clearly man-machine tasks. Figure 1b shows that what appears to be a single human process in Figure 1a may be considered a series of tasks when analyzed on a more molecular level. Similarly, each of the components in Figure 1b represents a process which could be viewed as a series of tasks on a still more molecular level of analysis.

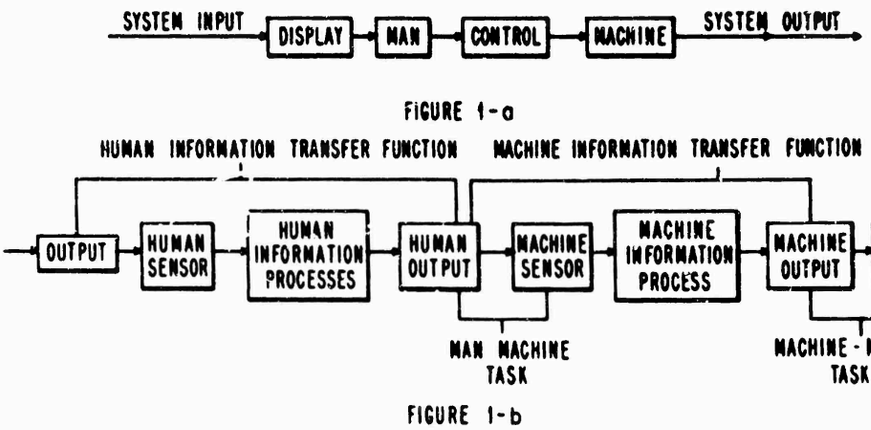

Figure 1. Schematic of man-machine systems at a general level of analysis (1-a), and at a more detailed level of analysis (1-b).

After much argument between ourselves and with other colleagues we have decided that we need consider only four basic classes of task. We have called these Tracking, Switching, Searching, and Identifying. Other tasks are combinations of these four. In order to develop a means for predicting performance on these tasks we are attempting to develop a model for the human information transfer function in terms of the underlying processes on which it depends.

Figure 2 presents a flow diagram of the processes which we are considering at this moment to be those on which the task performances depend. This figure has three parts. On the left may be seen the data-getting processes. These involve the sensory processes which receive information from the external world and from the internal world. The latter represents internal stimuli such as proprioceptive stimuli resulting from responding. Searching is a task which uses the kind of responses indicated and which provides for the reception of data by the sensory processes.

On the right hand side of the figure are shown data-sending processes which are considered to be coded responses of one sort or another. Tasks depend upon both data-getting and data-sending processes, but this dependence is assumed to be largely related to

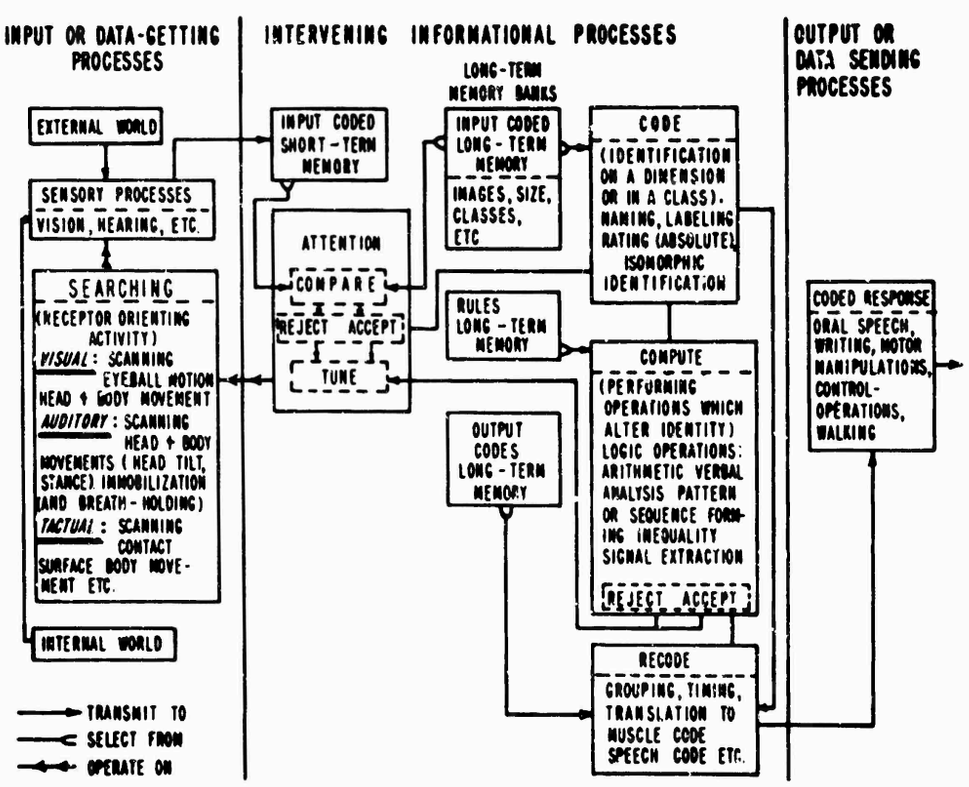

Figure 2. Schematic of proposed task relationships carried out among input, intervening and output processes.

the specific effect of the environment on the specific sensory or motor modality involved. In a given case, where a particular modality is affected by the environment, it would be possible to re-arrange the situation so as to use a different modality to accomplish the same task. In other words, a task is a functional event.

Whereas the input and output processes are observables, the intervening CNS processes are not yet. The figure shows these processes as we have guessed at them. Within this scheme, a task concerns the transfer of information between the boxes shown. The titles of the boxes are processes, i.e., they represent operations on data. Of considerable importance are the following assumptions about these processes:

1. All of these processes may be affected by the physiological states which result from environmental exposures. However, we are assuming that long-term memories are not affected short of important brain damage.

2. Attention not only acts upon data by Comparing, but it also has a task function, i.e., it tunes or directs Searching. In the sense that Searching may be made wider or narrower, the attentional process may act as a compensatory mechanism to offset decrements in other processes. Similarly, Comparing may be speeded up to offset short-term memory losses.

Table 1 presents a list of the four basic tasks with their definitions and a statement of the intervening processes considered to be most important to most instances of the tasks. It is understood that generally all processes are involved in all tasks, but that some processes are more important to some tasks than to others. This table also lists some more complex tasks and indicates the basic tasks upon which they are supposed to depend.

Returning to Figure 2 again, the intervening processes may be related to the tasks by the following postulates:

1. The further along the intervening process is in the sequence, the more resistant it is to physiological changes which result from environmental exposures. Thus, altitude would be expected to be more damaging to short-term memory and to attention than to computing and coding. Tasks which depend very importantly on short-term memory and on attention, within limits, would be expected to be most susceptible.

2. As the environmental exposure becomes more severe in a physiological sense, the attentional tuning becomes more narrow. This may actually act to increase performance by reducing the possibility of responding to distracting or interfering stimuli. However, when the tuning becomes so restricted that stimuli associated

Table 1. Table of Tasks and the Processes on Which They Depend Most Importantly

	Task	Short-Term Memory	Attention	Coding	Computing	Notes on Sensory and Motor Functions
Tracking:	Alignment of a response with a changing input. Examples: Pursuit, compensatory, walking, aiming.			*	*	Depends importantly on input rates and on fineness of manipulation required.
Switching:	Discrete, action which changes the state of the next component in a system.					
	a) Simple Reaction		Minimal			
	b) Choice Reaction		Importance increase w/no. choices	Incr. w/no. choices		
Searching:	Exposure of sensor to different places or at different times – signal seeking. Examples: monitoring, reconnaissance.					
	a) Simple Orienting		*			
	b) Successive Orienting (Scanning)	*	*			
Identifying:	Naming or coding a detected signal.					
	a) Simple Naming		*	*	Special cases	
	b) Multiple Naming	*	*	*		
	c) Communication with syntax (successive naming)	*	*	*	*	
Complex tasks consist of combinations of the above. For example:						
Problem Solving:	Successive searching plus identification, plus choice reaction	*	*	*	*	
Reading:	Successive searching, identifying, and tracking	*	*	*	*	
Handwriting:	Tracking plus communication with syntax	*	*	*	*	

with the tasks are missed, performance decrements begin to appear. As the tuning becomes still more narrow the decrements increase in magnitude. As a corollary, we are also supposing that at some very high level of exposure, this process reverses itself and attention becomes very broad in its tuning; this results in disorganized behavior.

3. The greater the number of intervening processes which are important to the task, the more susceptible the task.

From these postulates we may deduce that simple tasks will be more resistant to environmental stressors and that where performance is maintained without loss at relatively high exposure levels, compensatory changes in attention should be sought as an explanation.

We are analysing the literature for selected physiological effects: arterial oxygen saturation, pulse rate, oxygen consumption, and respiration rate in particular. These measures have been selected not only because of their importance to altitude studies, but because they are also important to the study of other environmental conditions in which we are interested. Once we have quantitative physiological functions, we can use one or more of these functions in a particular case as a means for establishing equivalances among hypoxic conditions. For instance, arterial oxygen saturation is a measure which makes available the results of both altitude and breathing mixture studies in a common term and it is on the basis of this common term that we shall make our predictions.

Secondly, we are analysing the literature on performance with regard to our descriptive system. In spite of the wide variety of specific tasks used, we are grouping those together which fall into one of our task categories. The general function relating the performance data to the physiological variable is considered to reflect the joint effect of all of the important processes on which the task depends. Experiments utilizing the same task may yield different results depending upon the specific sensory and motor conditions involved, however, a general function relating physiological and performance factors is expected to be found. We are also analysing the literature for specific sensory and motor effects, but shall not present those data at this time.

Although the general relationship between a task performance and a physiological measure reflects the joint effects of all of the important underlying processes, simple tasks may be found in each case which depend more importantly on one process than any others. The data representing these tasks then can be used to provide an estimate of the dependence of that particular underlying process on the physiological variable.

One other point should be made before presenting samples of what we have done so far. The altitude literature is very sketchy as regards performance data. Too many of the recent experiments available are nonparametric in nature; therefore, in most cases we have been forced to go back to the early literature in order to find acceptable parametric studies.

Figure 3 presents the first two of our task categories. The curves are plotted in terms of percent decrement from sea-level performance with altitude and arterial oxygen saturation on the abscissa. The upper graph presents data from four experiments using different pursuit tracking tasks. The general relationship is shown as the solid line and it may be seen that the different pursuit tasks are highly similar in their susceptibility. The dashed line presents data from two aiming tasks. Performance on the aiming task declines at the same rate as that on the more complex pursuit task until 15,000 ft., after which decrement on the simpler task is much slower.

The lower graph in the figure presents the same kind of information for the task we have called Switching. The lower curve represents a very simple 2-choice reaction time task. It may be seen that decrements did not begin until about 15,000 ft. Also shown on that curve is a single point, representing a simple reaction time task, i.e., one in which no choice was involved. The congruence suggest that the 2-choice situation used approaches the simple case in its demands. This figure also shows the percent change from sea level of a 3-choice reaction time task. The decrement is somewhat larger for the 3-choice case.

Both the 2-choice and the 3-choice curves in the figure are based upon color naming experiments, the measurements being time to name the colors. We shall use the error measures shortly as a means of describing the effects of altitude on an identification task. Of immediate importance is our decision that decrements in color naming as studied in these tasks are not sensory effects. This is suggested by Schmidt and Bingel's (12) finding of no effect on color saturation thresholds up to at least 18,000 ft. Since there are no psychophysical or other direct data suggesting a loss in visual color sensitivity, it seems reasonable to suppose that color naming tasks must depend upon other processes.

Figure 4 presents data in the same form as the previous figure. On the upper graph is presented the results of identification tasks. The dashed line is based upon the errors in naming three colors. The solid line is based upon a task requiring the transliteration of 50 letters of a code. In terms of our descriptions, these are both identification tasks which differ only in terms of the amount of

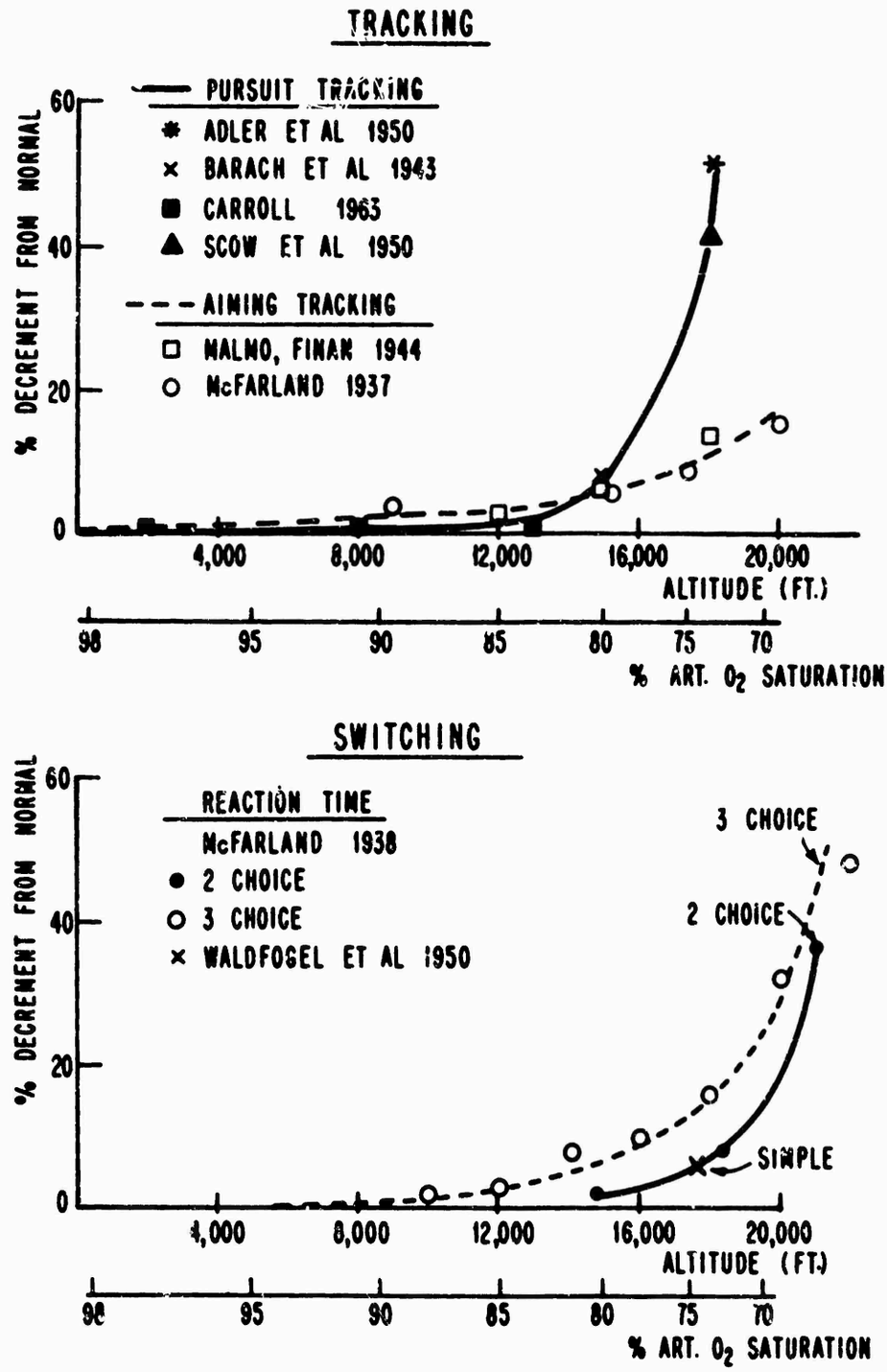

Figure 3. Tracking (3-A) and Switching (3-B) performance as a function of altitude and arterial O_2 saturation.

coding required. Since no search requirement was imposed we shall assume these tasks provide a relatively pure measure of the effects of altitude on the identification process, and we shall use the upper line as an estimate of the maximum altitude effect.

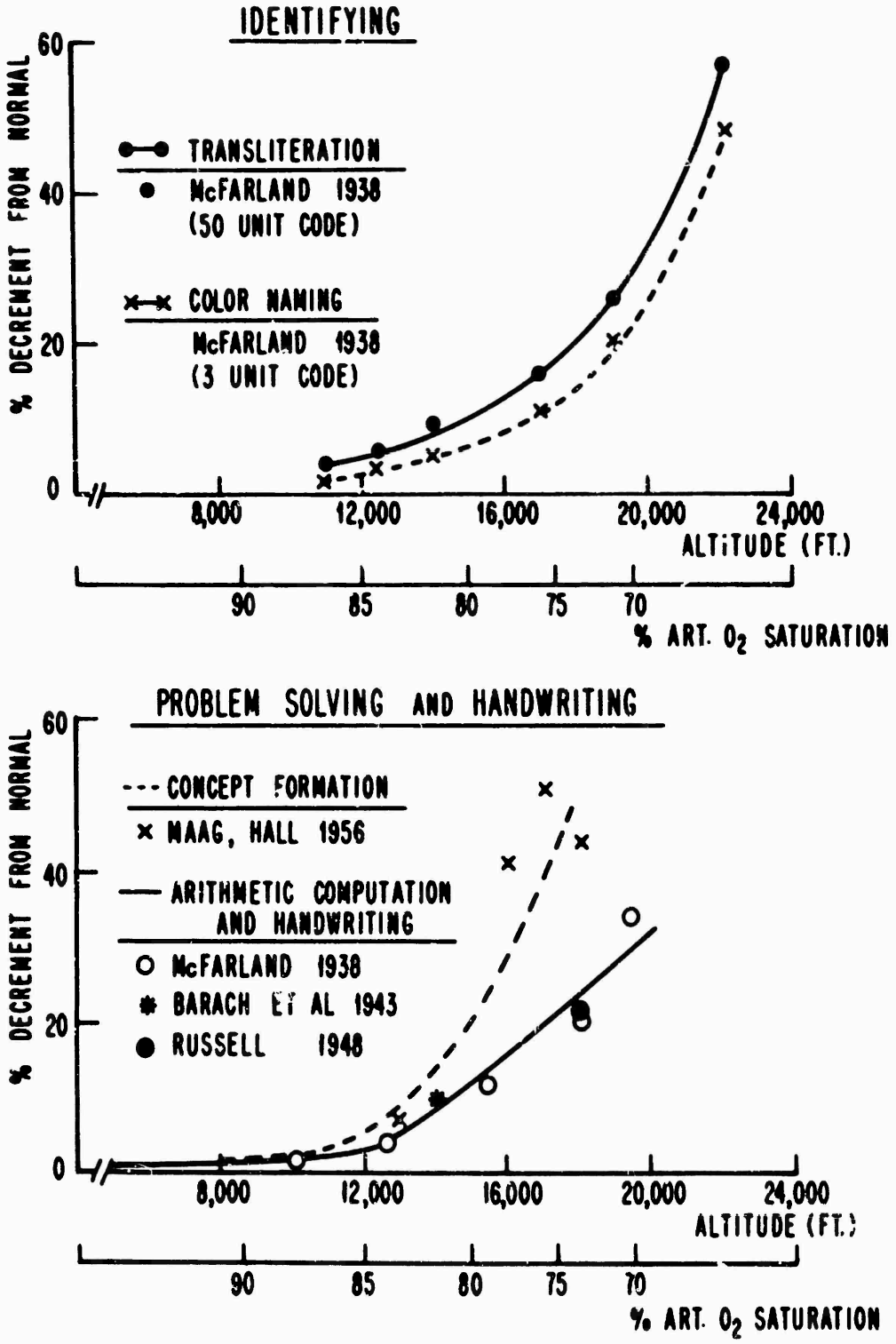

Figure 4. Identifying (4-A) and Complex Task (4-B) performance as a function of altitude and arterial O_2 saturation.

The lower graph presents examples of what we have called Problem Solving. The solid line is based upon points taken from two studies of simple arithmetic computation. The dashed line is based upon a concept formation task. The greater requirements

for short-term memory and for the computational process in the concept formation task is revealed by a much more rapid rise of the curve. This portion of the graph also presents data from McFarland (1938) showing effects of altitude on handwriting which we described earlier as a complex task involving sub-tasks of tracking plus communication with syntax. It is clear from the data that the relative effects of altitude on handwriting are the same as those for arithmetic computation.

In a high speed, discrete responding task, it is common to find instances of response blocking, i.e., pauses between successive responses. The frequency and length of block represents some kind of central impairment and is usually taken as a measure of impairment of the attentional process. Figure 5 presents the effects of oxygen deprivation on duration of response blocking in a high speed color-naming task (3). The lower graph reports data from three experiments using recall as the dependent measure. The similarity of results among these experiments may be seen.

Returning to Table 1, it can be seen that the only basic task for which we have not been able to find usable data is Searching. Looking at the processes on which the remaining basic tasks depend, we are now ready to take the next leap in our speculations. That is, if we can find data representing cases for each task so simple that we can discount the influence of more than one process as critical to the task, we can then use those results to reflect changes in the process. To do this we have taken the data from the graphs shown earlier as follows:

1. The aiming tracking curve was taken as being primarily dependent upon the computing process.
2. The transliteration curve was taken as representing a high level demand on the coding process.
3. The blocking curve was taken as representative of a high level of demand on the attentional process.
4. The recall curve was taken as representative of short-term memory.

Figure 6 presents these four processes as a function of oxygen saturation and altitude. In accordance with our first postulate, short-term memory and attention processes are affected at a lower altitude than processes further in the informational processing sequence. On the other hand, it is clear that there are reversals to the order of our predictions. For example, computation shows losses before coding and, although short-term memory shows losses before other processes do, the rate of decline is less.

What is the usefulness of the kind of analysis we have been trying to make? First of all, this kind of analysis aids in the identi-

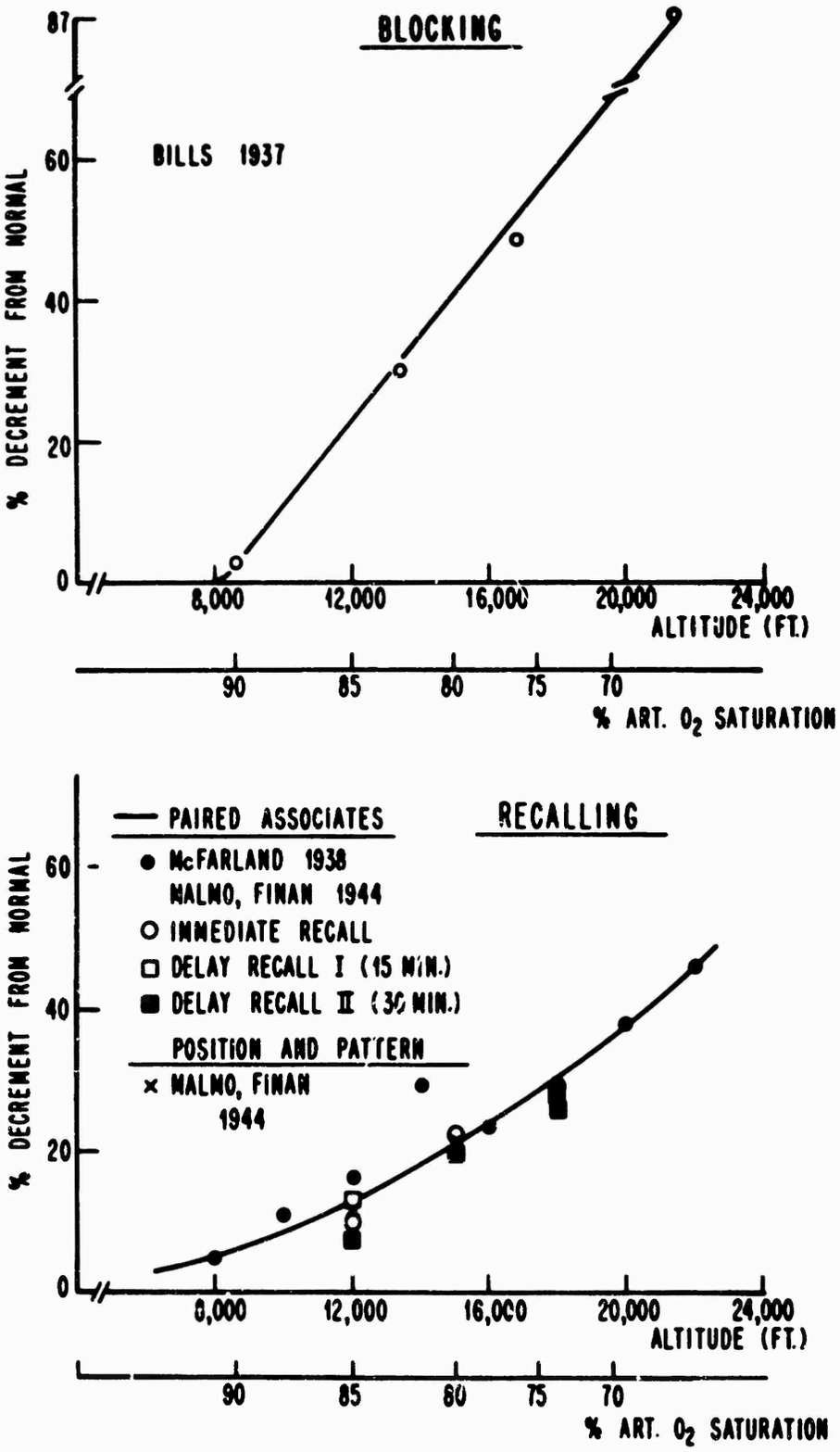

Figure 5. Blocking (5-A) and Recalling (5-B) performance as a function of altitude and arterial O_2 saturation.

fication of the important variables and processes. It provides a basis for determining the relative importance of both noncentral and central factors. Among the former are sensory and motor

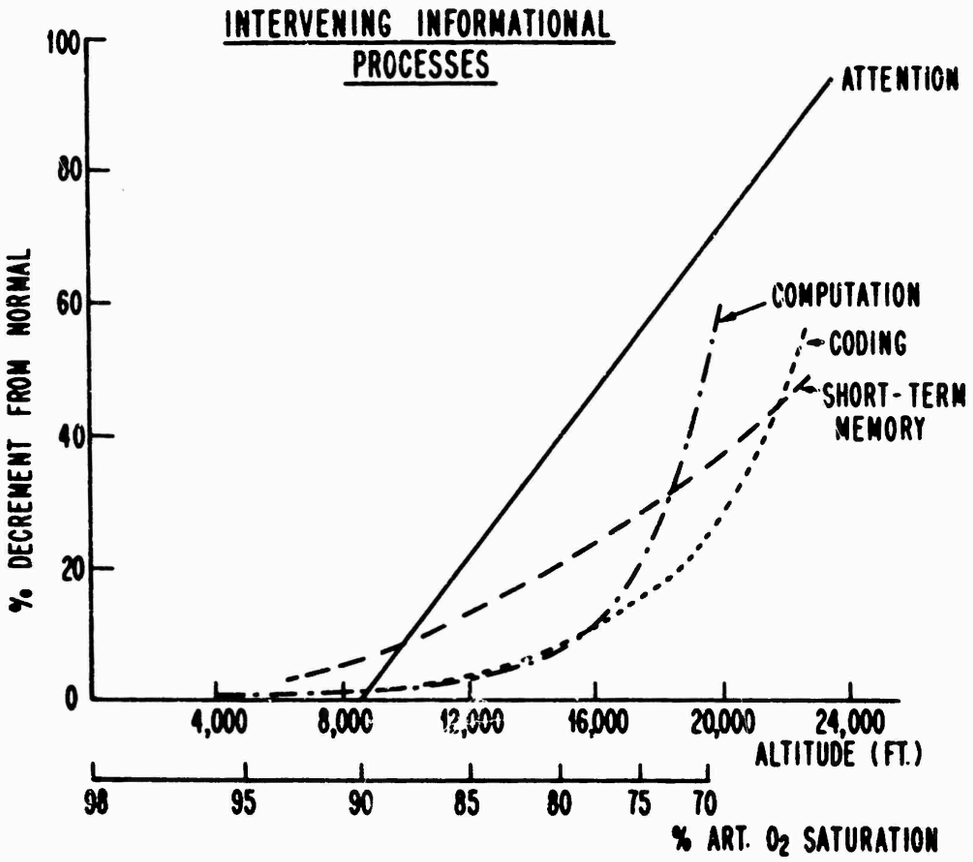

Figure 6. The effect of altitude and arterial O_2 saturation on the proposed intervening informational processes.

factors: among the latter are intervening influencing factors such as arousal, motivation and fatigue which will be discussed in a future paper. Secondly, we can use the analysis as a basis for predicting new results and for determining what new experiments are most needed. Finally, the analysis suggests the manner in which the human system staves off decrements, i.e., by compensatory activity of the attentional process. This suggests experiments in which the attentional process is studied in conjunction with each of the various tasks. Clearly, when the attentional process is no longer able to compensate a high level of stress reaction may be defined.

In summary then, we are speculating in the hope of organizing and we are organizing in the hope of having a systematic basis for the exploration of the effects of hypoxia on performance.

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SUMMARY OF THE EXPERIMENTAL STUDIES OF THE EFFECTS OF HYPOXIA ON BEHAVIOR

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Increased interest in the effects of high terrestrial elevations on the performance of soldiers has resulted in several research studies by psychologists at the U. S. Army Research Institute of Environmental Medicine. While there is an extensive literature on the effects of hypoxia and high elevations on the physiological responses of man, the literature on the effects of hypoxia on the psychological and behavioral responses is much smaller particularly when the exposure is for a prolonged period of time, e.g., a week or longer. Moreover, many of the studies reported in the literature were done to answer problems in aviation medicine (4). Consequently, the exposure period was short, the subjects were usually above average mentally and physically, and the tasks performed quite different from those performed by the infantry soldier. In addition, there has been relatively little progress since 1950 in our understanding of the psychological effects of hypoxia (7). With this background, it was clear that there was a great need for a study of the effects of high terrestrial elevations on the ability of soldiers to perform their duties when they were abruptly moved up to high elevations from near sea level.

In the summer of 1966, ARIEM scientists had an opportunity to study Army troops in a small maneuver at near sea level in North Carolina and subsequently at high elevations in Colorado. These troops (approximately 120 soldiers) were transported as rapidly as possible by air and then bus from Fort Bragg, North Carolina, to Denver, Colorado, and thence to an area near Mt. Evans, Colorado. Two biomedical observers were assigned to each unit of approximately ten men for the entire five days of maneuvering in both North Carolina and in Colorado. The data which

were collected included (1) periodic reports by soldiers as to symptoms of illness, (2) reports on quality of performance of each soldier by the officer in charge of the unit and by the medical observers attached to the unit, (3) hourly reports by the observers on the activity level in four categories – sleeping or lying down, non-strenuous activity (sitting, standing, messing, etc.), strenuous activity, walking at an easy pace, (walking on level or gradual slope down hill, etc.), very strenuous activity (climbing or rapid descent or running, etc.), and (4) observers' diaries of critical events. Post maneuver interviews with the officer and/or senior non-commissioned officer in each unit as well as with the attached biomedical observers yielded further information.

The long form symptom questionnaire was to be answered by each soldier twice daily – once each morning and evening. The short form questionnaire was to be answered every four hours when the soldiers were not sleeping. Needless to say, weather conditions, long sustained and difficult movement, and darkness were among the reasons that these data were not always obtained as planned. Nevertheless, the results are consistent in that those symptoms most frequently mentioned in the literature are in general those most frequently responded to in the questionnaire. Moreover, responses to the longer questionnaire were consistent with those given to the short form and yielded additional information as well. A selection of responses to the two questionnaires which illustrates these points is given in Table 1. The items from the short form questionnaire are those with the more daily responses. In general, the highest proportion of responses occurred on either Days 1 or 2 at high elevation after which they decreased. Since the subjects arrived on Day 1 after an overnight of travel, fatigue may have affected Day 1 responses considerably. In reviewing the items on each questionnaire, it was noted that the increased specificity of some questions asked may have reduced the proportion of soldiers responding to those questions as, for example, item 2 of Table 1. Finally, there was an indication that the symptoms were persistent over a number of hours for the individual rather than erratic or transient.

Observers' reports of critical events and noteworthy occurrences as well as interview data did yield some important observations. On the first day at high elevation differences in performance of troops as compared to sea level became apparent. In a number of units, columns became strung out over many hundreds of yards. For example, by the first afternoon, one observer attached to a unit which was headed up the side of a mountain reported that average lateral and vertical movement

TABLE 1. Proportion of Reports Indicating Symptoms Experienced Some Time During the Day

	Days					Approximate No. of Questionnaires Answered Daily
	1	2	3	4	5	
1. Headache (No. of + responses) (No. of questionnaires answered)						
Sea Level	.08	.14	.21	.13	.12	200
High Elevation	.56	.56	.45	.44	.33	200
2. Ache or Pain in Forehead						
Sea Level	.03	.04	.10	.03	.04	100
High Elevation	.30	.30	.22	.16	.11	100
3. Sick to Stomach						
Sea Level	.03	.03	.02	.02	.04	200
High Elevation	.26	.22	.09	.15	.13	200
4. Feel Unusually Sick to Stomach						
Sea Level	.01	.02	.03	.03	.02	100
High Elevation	.20	.13	.10	.07	.06	100
5. Short of Breath						
Sea Level	.17	.11	.14	.10	.13	200
High Elevation	.73	.60	.68	.68	.55	200
6. Have You Been Short of Breath When Walking?						
Sea Level	.10	.14	.09	.09	.08	100
High Elevation	.52	.55	.56	.52	.50	100
7. Dizzy						
Sea Level	.03	.04	.07	.04	.02	200
High Elevation	.50	.35	.26	.22	.15	200
8. Felt Unusually Dizzy						
Sea Level	.00	.02	.02	.00	.01	100
High Elevation	.44	.27	.15	.09	.05	100
9. Generally Sick						
Sea Level	.04	.05	.04	.04	.04	200
High Elevation	.24	.22	.12	.17	.11	200
10. Feel Unusually Bad						
Sea Level	.03	.01	.01	.02	.03	100
High Elevation	.24	.14	.05	.09	.03	100
11. Noted Heart Pounding						
Sea Level	.01	.03	.01	.00	.01	100
High Elevation	.31	.15	.13	.05	.05	100
12. Difficulty Sleeping						
Sea Level	.01	.10	.06	.02	.07	100
High Elevation	.21	.21	.16	.16	.13	100

distance between rests on steep inclines was quite small, probably 50 and 10 feet respectively. Many men stopped frequently, gasping for breath, whereas other flopped wearily to the ground. Despite superb motivation some were unable to keep up with the majority of the unit. In spite of excellent leadership all units had difficulty and a number failed to attain planned objectives. Significantly, the biomedical observers with eight days of acclimatization and the umpires with five days acclimatization were able to move

much more rapidly and steadily than the newly arrived troops during the first few days of the maneuver. By Day 5, the troops were moving reasonably well; however, in the opinion of experienced experts of mountain warfare they still would be at a marked disadvantage in moving when compared by highly acclimatized mountain troops.

It was apparent on the first day that there is no real substitute for experience in the mountains. Those with experience, used traversing techniques, short steps, and a steady pace which proved more effective than methods used by the less knowledgeable individuals who tended to follow steeper and more direct routing. Moreover, leaders with mountain experience were better able to keep their units together.

Although the decrease in temperature with altitude is well known, the wide and rapid fluctuations in temperature, humidity, solar radiation, and wind were a new, unusual and stressful experience for the participants. Such abrupt changes may affect cover, concealment, and mobility. Moreover, in the mountains, radio communication can be extremely unreliable. The lack of water; the unavailability of trees for concealment, shelter, fuel, splints or litters; the heavy loads; and the freezing temperatures even in midsummer, add to the discomfort and problems of living.

Although the area of maneuver, particularly at high elevation, was selected so that some groups traversed a more difficult route than others (and this was verified by the reports on levels of activity) it was not possible to relate these data to reports of symptoms, illness, or quality of performance and accomplishment. In a similar manner, the different experiences of observers and units made it impossible to compare performance ratings of individual soldiers across groups or to relate the ratings to other measures mentioned above. It should be noted that evacuation of medical casualties at high elevation proved to be a formidable problem, particularly when a helicopter was not available or could not be used.

There were, however, a number of important findings for any future study conducted in the field. First and foremost was the difficulty in obtaining meaningful observational data for comparison across individuals and groups. Although this was recognized as a critical problem prior to the initiation of the study, it proved so important and formidable that it is unlikely that any future study would be designed in a similar manner. One is forced to conclude that it would be preferable to sacrifice some fidelity and realism in the military maneuver in order to obtain reliable measures on a periodic basis at predesignated test locations. Such a design would

in part overcome the problem of missing data, with the resultant possibility of selective and biased sampling. Since judgments of even preacclimatized observers may be affected under the environmental stresses involved, or the observers may not have the skill or detachment to draw correct conclusions, more objective testing procedures are also to be preferred. This points up a second important finding of this study, the need for behavioral and performance type tests having relevance to the types of performance expected of the soldier. Recently, more attention has been given to this problem and some progress has been made on improved tests and rationale for measuring a soldier's performance (1, 5, 6). However, attempts to measure group performance remain woefully inadequate. Finally, on the basis of this first study, one may conclude that there are numerous factors in addition to hypoxia which affect the performance of soldiers at high elevation. For example, weather and terrain may be critical and particular to the time and location. Consequently, in a field study, it may be impossible to draw any conclusions concerning the effects of a single variable.

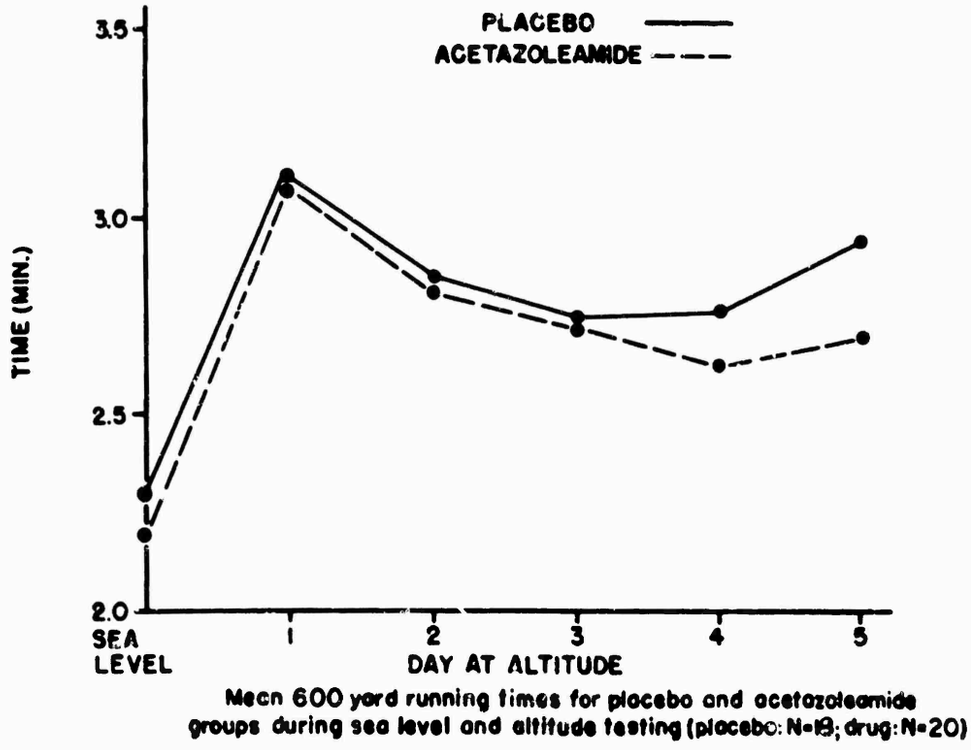
On the more positive side, it should be pointed out that for the first time we have some experience with the types of problems soldiers may face at high elevations based on a sizeable group of men. Moreover, the maneuver did provide a framework of experience for ARIEM scientists and increased their interest in conducting laboratory research on the effects of hypoxia on behavior and performance.

In association with the field maneuver a controlled field study was conducted to determine the effectiveness of acetazoleamide in helping to alleviate or prevent acute mountain sickness. A number of performance measures were taken by the behavioral scientists to evaluate the effects of the drug as well as the effects of high elevation on performance. Visual measurements were obtained on visual acuity, depth discrimination, vertical and lateral phoria, and critical flicker-fusion threshold. A test of intellectual performance was also given at sea level and several times at high elevation. In addition, the effect of acute exposure to altitude on time estimation was studied. Finally, a battery of physical performance tests were given at sea level and for five days at high elevation.

The results showed no statistical evidence for an effect of either drug or high elevation on visual performance. A similar finding applied to the measures of intellectual performance (3). The study of time estimation showed a slowing of subjective time at high elevation, i.e., subjects under estimated time intervals at altitude compared to time intervals at sea level (2). There was no effect on time estimation attributable to the drug.

There were eight tests used in the physical performance battery: 600 yard run; shuttle run; hand grip, bend-twist and touch; leg lifts, softball throw; balance; and pull ups. There was no statistical evidence for a difference between the drug and placebo groups on any of the events. Only the 600 yard run and the shuttle run showed a statistically significant drop in performance from sea level. The shuttle run performance returned to sea level control values by the third day at high elevation while the mean time to run 600 yards never approached the sea level value during the five days that measurements were taken at high elevation (Figure 1).

As a result of this study, it was concluded that the primary effect of exposure to high elevation is on tests of endurance, e.g., the 600 yard run. Moreover, it was concluded that the experience of subjective time is altered as a result of exposure to high elevation although it might be emphasized that isolation, weather conditions, and other variables associated with high elevation may be as important as hypoxia in altering one's estimate of the passage of time. Nevertheless, any effect on perception (whether of time, auditory localization, visual distance, etc.) may have important implications since a soldier frequently uses such perceptions in making decisions.



Mean 600 yard running times for placebo and acetazoleamide groups during sea level and altitude testing (placebo: N=19; drug: N=20)

Figure 1.

Although the intellectual tests, visual tests, and six of the eight physical performance tests were not sensitive to the effects of exposure to high elevation, it is entirely possible that the elevation, 12,800 feet, was marginal for observing effects on the performance of such tasks. However, as a result of the experience gained in this study, a number of ARIEM investigators are concentrating on improving the precision, sensitivity and reliability of such measures of performance for use in studying the effects of hypoxia and/or drugs on behavior.

During the summer of 1967 a Behavioral Sciences Laboratory team, led by Miss Joyce House, in collaboration with the Army Medical Research and Nutrition Laboratory, studied the effects of two different drugs and/or high elevations on the performance of soldiers. For this study it was possible to construct tests to give in the field. Members of the laboratory had collected an extensive file on military performance and had reviewed the pertinent literature. On the basis of this background plans were made for constructing a set of field tests which were believed to measure behavioral factors critical to a soldier's combat performance. As finally designed, the performance course included the events listed on Table 2. The course was set up at Seattle, Washington for

TABLE 2. Events Comprising the Performance Course

Performance	Score	Probable Factor Measured
1. run 75 yards	time	speed
2. shoot a Crossman CO_2 single shot pistol six times at a standard rifle target 25 feet away.	time to shoot accuracy	steadiness eye-hand coordination
3. listen to a tape recorded message twice and then write down as much of message as retained immediately.	accuracy	short term memory
4. run 75 yards	time	speed
5. presented 14 pictures to the soldier and he identified the pictures presented as either an enemy or friend.	reaction time accuracy	perceptual speed and accuracy
6. throw six grenades at a target 70 feet away.	accuracy	specific military psychomotor skill
7. identify hand signal given by observer.	accuracy	visual perception
8. run 75 yards.	time	speed
9. shoot a Crossman CO_2 single shot pistol at one of three targets 25 feet away depending on the hand signal identified (shoot a total of six shots).	time to shoot	steadiness eye-hand coordination
10. transmit message received at the first station (see event 3)	accuracy	longer term memory

measurements at near sea level and on top of Pike's Peak for measurements at high elevation. Five days of intensive pretraining were used in an attempt to bring all subjects to an asymptotic level of performance prior to the beginning of the study. In addition, measurements were made on each soldier at sea level both before and after five days of exposure on Pike's Peak.

Although the data collection was completed this summer, the data are still being analyzed. Nevertheless, several observations can be made concerning the performance course. First, the preliminary training did not achieve asymptotic levels of performance on all tasks when the environmental conditions were comparable. There was some improvement on some of the tasks during the entire study. Secondly, the performance course did measure skills related to military tasks, but it did not measure endurance. The performance course used is too short and the duration of time of performance on the course (i.e., 5-10 minutes) needs to be extended – at least doubled. Apparently, performance sustained for a considerable period of time is most sensitive to stress such as that involved in exposure to hypoxia. In spite of these shortcomings, we feel we have a promising start and in the future can improve considerably on our performance measures. Still lacking, however, is any satisfactory measure of the overall performance of a group of soldiers.

As a result of our experience in conducting studies at high terrestrial elevations, we have plans for future studies. Among the more important areas needing research are the effects of high elevation on (1) the performance of groups of trained soldiers, (2) the intellectual and decision making capabilities of men, (3) perceptual capabilities of men. Inasmuch as some drugs may alleviate or prevent the worst aspects of acute mountain sickness, their effects on man's performance should be studied under normal and hypoxic conditions. Finally, every effort should be made to design and use tasks and tests based on the accumulated knowledge of the behavioral sciences, yet having specifiable relationships to tasks the soldier must perform under combat conditions. The latter requirement may never be met, yet any progress in this direction will make our research efforts more meaningful to the military as well as to the larger scientific community.

Finally, I would like to mention that Dr. Martin Gerben of our Laboratory has accumulated considerable information on the effects of hypoxia on the voluntary running behavior of rats. Under certain conditions, he has also been able partially to reverse decrements in running behavior associated with hypoxia. For example, the addition of 5% CO_2 to the atmosphere, while reducing activity under normoxic conditions, increased activity under hy-

poxic conditions. Motivational conditions such as food deprivation and hypothalamic electrical stimulation, while increasing activity to some extent under normoxic conditions, increase activity to an even greater extent during hypoxic conditions. Thus, it appears that the relationship between the above-mentioned variables and oxygen level is interactive.

As a result of these animal studies, it has been proposed that a fruitful area for human research might involve studying voluntary work-rest cyclic behavior under conditions of relatively low motivation. This may be more representative of a soldier's performance and also be more sensitive to the effects of hypoxia and other relevant variables than are tests of maximum performance.

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GENERAL DISCUSSION

DR. ROY: I was very touched by what Major Evans said, because whatever we are doing in the basic sciences it is really to see that at the end we can help our soldiers who are stationed at high altitude. We have covered a lot of fields in maneuvers and field exercises but I am probably the only one present here who faces the real problems of soldiers being kept at high altitude. One such major problem I would like to emphasize is that of solitude. It is difficult to believe that soldiers posted at high pickets (at 18,000 to 20,000 feet) look through their binoculars at the opposite camp – the Chinese troops changing guard – for their only source of relaxation during three months of the year. Solitude is something we have not thought of. We tend to think soldiers or troops are always posted in relatively large groups, but that need not be true. Sometimes only three or four persons are at a post. Because these places are not readily accessible, one may not even get mail regularly. Sometimes one is cut off for six to eight weeks at a time. Whatever research we do at any height, we should be aware that there is a problem of solitude. If you want to do actual maneuvers, organize so that solitude is a part, and see their reactions.

DR. FINE: It seems as though there is an important message which is going to pass us by unless it is brought out. It is the apparent underlying philosophy of all of the research and all of the papers I have heard that all individuals are the same, physiologically and psychologically. To me, this basic philosophy is one which is hindering rather than facilitating effective research in this area.

Current research in most areas of psychology and some areas of physiology and biochemistry indicates that there are systematic

differences between individuals in their functioning. In listening to Dr. Roy and Dr. Evans, and in personal conversation with Colonel Bernstein, these individual differences were brought up as important real problems. Some people do well, others do poorly. In my own research, looking at some of the data from ARIEM studies, for example, one finds such things as older people doing more poorly on a 60-yard run; cigarette smokers doing more poorly on the same run; people who are hypochondriacs seemingly not effected by acetazoleamide, etc. I think these are the more basic things which, if we refer to the basic psychological literature dealing with individual differences in perception, etc., and to our knowledge of individual differences in physiology and biochemistry, are going to bring out some of the more pertinent findings. These findings, I believe, will facilitate the prediction of decrements in performance and changes in behavior at altitude. This approach is not consistent with one which assumes that everybody is the same, an approach which I do not think is going to get us anywhere.

DR. McFARLAND: It was emphasized. I made a point of it in concluding my paper, saying that this is an important aspect of selection; that we would have to try to get methods and means of selecting people who will do well at high altitude, both physiologically and psychologically. Prediction is a very great undeveloped area.

MAJ. EVANS: I should like to mention a study on that. In the first study we did on Pikes Peak, we had normal values for bicycle riding, throwing of medicine balls and jumping up in the air, MMPI's, and cardiac output, and about 40 other variables (age, weight, etc.) which we tried to use in correlating with the various changes in both behavior and physiology that took place at high altitude. None of the 40 variables we tried yielded any predictive values, with the exception of a slight relationship with anxiety and MMPI. About a year ago, we tried breath-holding as a predictor. We had noted what seemed to be a correlation with breath-holding. Unfortunately, we were unable to replicate these results. So, I do not think it is out of ignorance of this problem nor a lack of interest. It is just a total lack of success so far in identifying characteristics of those people who will be sensitive to the mountain and those who will not.

DR. WEINSTEIN: I think besides Dr. McFarland's having brought this out, one of the themes emphasized at these meetings (starting with Dr. Roy's paper) was the wide individual variability in response to high altitude, and in response to environmental stress. I do not think any of us, either panelists or people here as guests would have made the statement that one should ignore

individual variability. One often ends up pooling data; but when one does this, one is always aware of the exceptions. One of the great areas of integration between physiology and behavior will come when we try to relate the physiological variables to the behavioral variables, taking account of individual variations.

You might find a man who does respond behaviorally to high altitude. He shows a great decrement in performance. What is his oxygen saturation, his PO_2, his PH, his response to CO_2? How does he differ from a person showing no behavioral decrement? It is going to be in these differences, between the responders and non-responders, between people who show a great decrement and those who do not, that we are very likely to find great leverage in working with the effects of altitude. I think most of the panelists have brought this out in their discussions.

DR. McFARLAND: It has been pointed out that we have not forgotten about Sir Francis Galton. I think if Claude Bernard were alive today he would be very pleased at the attempt to measure the performance of individuals in relation to the internal environment. It was he, you will recall, who first pointed out that the condition of the free life is related to the constancy of the internal environment and it was my professor, Sir Joseph Barcroft who said "Freedom for what?". It is freedom for intellectual activity and for the higher nervous centers to develop, and without this constancy in internal environment, whether it be oxygen, temperature or PH or other, unless the body can operate within those ranges, certainly cerebral functions, mental functions cannot operate properly.

The program this afternoon has brought out some of the attempts to relate these measurements, and although we have made a beginning, there is much to be accomplished. To me, as one who has been interested in this field, I mention these original experiments in 1927 and 1928 at Cambridge. Since that time it has been one of my major interests, and to find so many outstanding scientists doing such outstanding work as we have reported here is indeed a wonderful day for me, as I am sure it is for Dr. Hurtado.

CLOSING REMARKS

DR. HURTADO:

It is my opinion that this has been a very pleasant and stimulating meeting. We have learned a great deal. Some questions have been answered but many others still remain to be answered in the future.

I think one of the outstanding characteristics of this meeting has been to point out that high altitude is a field of integrated physiology. There are many organs, many systems, and many functions and chemical adjustments, all related to each other for optimum operation.

Before concluding, I should like to express the thought which I believe belongs to all my Peruvian colleagues here. In the past year we have had the opportunity and the pleasure of having many investigators from this country in Peru using the facilities we have there. In our country the high altitude is very near the coast; it is very easy to go up and to come down again to sea level. We have the permanent population at high altitude, and I always feel in the study of these people there is a great deal of information to interpret for an understanding of acclimatization.

I hope in the future we will have the same happy opportunity to see many of you down there. Thank you very much.

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13. ABSTRACT

The proceedings, as the title suggests, deal with some of the biomedical problems which result specifically from exposure to the low ambient oxygen tensions which prevail at high terrestrial elevations. The most important quantitatively are: acute mountain sickness, high altitude pulmonary edema, performance decrements and behavioral disturbances. One section concerns itself with the nature of the acclimatization processes.

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Anoxia	6.9		6			
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Behavior	7	7				
Stress (Psychology)			9			
Measurement			8			
Psychological Tests	7					
Time perception			6.9			
Oxygen		6				
Carbon dioxide		6				
Sensory mechanisms	7		9			
Mental processes	7		9			
Cardiac output				7		
Exercise				6		
Endocrine glands	7					
Autonomic nervous system					6	
Cardiovascular system					7	
Performance	7		7			
Tissue	7					
Respiration					7	7
Pulmonary edema	7					
Pulmonary circulation	7					
Subjective	0					
Testing	7					
Acetazolamide						6
Benzolamide						6
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