AD-A111 062 ARMY RESEARCH INST OF ENVIRONMENTAL MEDICINE NATICK MA F/G 6/19
MEDICAL AND PERFORMANCE PROBLEMS OF ACUTE HIGH ALTITUDE-EXPOSUR--ETC(U)
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UNCLASSIFIED USARIEM-M-19/81 NL

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE	READ INSTRUCTIONS BEFORE COMPLETING FORM
1. REPORT NUMBER: M 19/81	2. GOVT ACCESSION NO.: AD-A111 062
3. RECIPIENT'S CATALOG NUMBER	
4. TITLE (and Subtitle): Medical and Performance Problems of Acute High Altitude-Exposure	5. TYPE OF REPORT & PERIOD COVERED
	6. PERFORMING ORG. REPORT NUMBER
7. AUTHOR(s): John T. Maher	8. CONTRACT OR GRANT NUMBER(s)
9. PERFORMING ORGANIZATION NAME AND ADDRESS: US Army Research Institute of Environmental Medicine, Natick, MA 01760	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS: 3E162777A879 CC 14183304126
11. CONTROLLING OFFICE NAME AND ADDRESS: US Army Medical Research & Development Command Fort Detrick Frederick, MD 21701	12. REPORT DATE: 11 Jul 81 13. NUMBER OF PAGES: 14
14. MONITORING AGENCY NAME & ADDRESS (if different from Controlling Office): Same as above	15. SECURITY CLASS. (of this report): unclassified 15a. DECLASSIFICATION/DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Distribution of this document is unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

N/A

18. SUPPLEMENTARY NOTES

N/A

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

acute mountain sickness, hypobaric hypoxia, acetazolamide, isocapnic-hypoxic sensitivity, aerobic work capacity, endurance performance

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

DD FORM 1 JAN 73 1473 EDITION OF 1 NOV 65 IS OBSOLETE

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MEDICAL AND PERFORMANCE PROBLEMS OF ACUTE HIGH-ALTITUDE EXPOSURE

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Of the numerous medical problems associated with acute exposure to high terrestrial elevations, of which this (Fig. 1) is but a partial list, the Army's research efforts have focused principally, though not exclusively, on the most common of the disorders, acute mountain sickness (AMS) or *soroche*. This self-limiting syndrome of unacclimatized individuals is characterized by headache, lassitude, insomnia, gastrointestinal symptoms and general malaise which usually become manifest within 4 to 8 hours after arrival, peak between 24 and 48 hours and gradually remit over 4 to 8 days. Experience at our Pikes Peak Laboratory (4,300 meters) indicates that approximately 60 percent of the soldiers so exposed experience symptoms severe enough to functionally incapacitate them as efficient combat troops. At altitudes higher than 4,300 meters one can expect a disproportionate increase in both the severity of symptoms and the number of individuals in whom they will occur.

Research efforts at our laboratory to prevent this illness have met with some success; we are now able to reduce symptom intensity at 4,300 meters by 85% through a combination of residence for 4 days at 1,600 meters plus the administration of 500 mg of acetazolamide b.i.d. for the last 2 days at 1,600 meters and the first 2 days at 4,300 meters (1). Since previous studies have

shown that staging or acetazolamide alone reduced symptoms by about 25%, the combined effect seems to be synergistic. The mechanisms operative with this combination of prophylactic measures are still to be determined.

Our early trials of acetazolamide in the amelioration of AMS were based on the realization that inhibition of renal carbonic anhydrase would result in an increased bicarbonate excretion and thereby mimic a major adaptive response to hypoxia. More recent work suggests that the beneficial effect of acetazolamide is not related to its ability to counter the respiratory alkalosis of altitude with a metabolic acidosis, thereby maintaining normal pH. The occurrence and severity of symptoms have been found consistently to correlate rather poorly with pH but quite well with CO_2 tension (2). Figure 2 is a scatter plot depicting the positive correlation, with a coefficient of .75, between blood P_{CO_2} and severity of headache in 24 untreated control subjects on their third day at 3,900 meters.

In chamber studies at our Institute, the role of hypocapnic alkalosis in the development of AMS was assessed by exposing subjects to simulated high altitude for 4 days with 3.8% CO_2 added to the chamber atmosphere to maintain normocapnia and comparing their responses to those of another group exposed without CO_2 supplementation (3). To achieve a comparable degree of alveolar hypoxia ($\sim$ 55 torr), it was necessary to subject the CO_2-treated group to a lower barometric pressure to offset the altitude-lowering effect of CO_2. Under such conditions, the severity of symptoms was significantly greater in the CO_2-treated normocapnic group than in the hypocapnic, alkalotic subjects.

A question, then, is *how* does acetazolamide exert its beneficial effect on symptomatology, if not by preventing the development of alkalosis? Furthermore, *why* does the development of hypocapnia appear to be an appropriate rather

than a maladaptive response to high altitude? Figure 3 depicts the sequence of events that I suggest may be causally related to the development of AMS. At high altitude, there is a rise in cerebrospinal fluid (CSF) pressure which is further increased with elevation of Pa_{CO_2}. Concurrently, there is an increase in cerebral blood flow (which is also positively related to the CO_2 tension by the autoregulatory mechanism), as well as increases in cerebral venous volume and pressure. Because brain tissue hydration is similarly elevated by hypoxia, whole brain volume increases. These considerations have led to the hypothesis that the increased volume or increased pressure, or both, within this semi-elastic system causes brain cell compression which, in turn, produces the symptoms of AMS (4). I suggest further that acetazolamide reduces symptoms of AMS by inhibiting CSF formation and that the lower the P_{CO_2}, the lower the CSF pressure and cerebral blood flow. This would be expected to reduce brain cell compression and illness.

Regarding efforts to pre-select or identify those individuals who are relatively resistant to the debilitating effects of altitude exposure, the best determinant that we have found thus far is the response to the isocapnic-hypoxic sensitivity test, i.e., the increase in ventilation induced by lowering the end-tidal oxygen tension to 45 torr while maintaining the end-tidal carbon dioxide tension constant. Twenty-four volunteers were studied in our hypobaric chamber at a simulated altitude of 4,300 meters (5). Figure 4 depicts the changes in mean symptom score and minute ventilation of the 5 most and 5 least ill subjects. The "well" group had a mean increase in ventilation of 3.3 $L/min/m^2$, while the "ill" group changed little from baseline during the first 6 hours. The mean isocapnic hypoxic sensitivity at sea level was 3.2 $L/min/m^2$ for the well group

versus 1.5 for the ill group, i.e., a ventilatory response more than double. We have also found the ventilatory response at sea level to the respiratory stimulant Doxapram® to be equally valuable in predicting susceptibility. Those individuals who relatively hyperventilate in response to Doxapram® also do well when subsequently exposed to high altitude, whereas those who relatively hypoventilate develop mountain sickness. The observation that individuals with high hypoxic drive appear better suited for sojourning at high altitude supports the findings described by Dr. Hu in the previous presentation and suggests that future efforts to augment peripheral chemoreceptor responsivity might be a rational approach to the prevention and treatment of AMS.

Let us change gears now and address briefly the performance problems associated with acute high-altitude exposure (Fig. 5), limiting consideration to the reduction in aerobic work capacity and endurance performance. The lowered oxygen tension at high altitude impairs those types of physical activities which are dependent upon sustained oxygen intake. Man's ability to perform muscular work is usually evaluated relative to his aerobic work capacity which can be measured as maximal oxygen uptake ($\dot{V}_{O_2}$ max). Figure 6 illustrates a relationship between altitude and aerobic work capacity, when expressed as a percent of $\dot{V}_{O_2}$ max at sea level. It can be seen that $\dot{V}_{O_2}$ max is not measurably altered by altitudes between sea level and $\sim$ 1500 meters. Above 1,500 meters, however, there is a linear decrease at the rate of 10% per 1,000 meters. At our laboratory atop Pikes Peak (4,300 m), $\dot{V}_{O_2}$ max is only 73% of that at sea level, a 27%

decrement (6). The reduction in $\dot{V}_{O_2}$ max that occurs with *acute* altitude exposure is attributable to a reduction in arterial oxygen content secondary to a fall in arterial oxygen saturation, whereas after several days at altitude (when oxygen content normalizes) reduced cardiac output during maximal exertion is the culprit which keeps $\dot{V}_{O_2}$ max depressed by reducing arterial oxygen transport.

Although aerobic work capacity is measured during maximal effort of relatively brief duration, the decreased aerobic capacity at high altitude is also reflected in more prolonged exercise of less severe intensity. However, unlike *maximal* work capacity which remains depressed for many weeks (and probably months) at altitude, *submaximal endurance* capacity improves dramatically within a short period of time. We have documented a 45% improvement in endurance time within 10 days at 4,300 meters (6) and a 60% improvement in 2 weeks (7) when subjects exercised to exhaustion at submaximal levels. Since submaximal systemic oxygen transport does not improve within this time frame, the improvement in endurance performance was attributed to favorable alterations in substrate availability, utilization, or both. Figure 7 depicts the concentrations of serum free fatty acids, glycerol and lactate and muscle (vastus lateralis) glycogen of 8 subjects at rest and following 30 minutes of exercise (85% $\dot{V}_{O_2}$ max) at sea level and after acute (2 hours) and chronic (18 days) exposure to 4,300 meters (8). The rate of glycogen depletion during exercise was significantly lower during chronic high-altitude exposure than at sea level or during acute exposure. Serum levels of glycerol and free fatty acids were significantly higher while lactate was markedly lower during chronic exposure to high altitude.

Endurance time has been shown by several investigators to be inversely related to the rate of muscle glycogen depletion. These and other more recent data support a shift to fat metabolism during sojourn at altitude with a resultant sparing of muscle glycogen and therefore enhanced endurance performance.

To summarize, ascent to high mountain areas produces striking and debilitating effects on the human body, the mechanisms of which are only beginning to be understood. Clearly, more basic understandings of the contributing causes of the altitude-induced disabilities - medical, physical and psychological - are critical to the development of methods for their effective management.

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MEDICAL PROBLEMS AT HIGH ALTITUDE

- ACUTE MOUNTAIN SICKNESS
- PULMONARY EDEMA
- NEUROLOGICAL COMPLICATIONS
- RETINAL HEMORRHAGE
- COLD INJURY
- ULTRA-VIOLET LIGHT INJURY
- CASUALTY EVACUATION

Figure 1

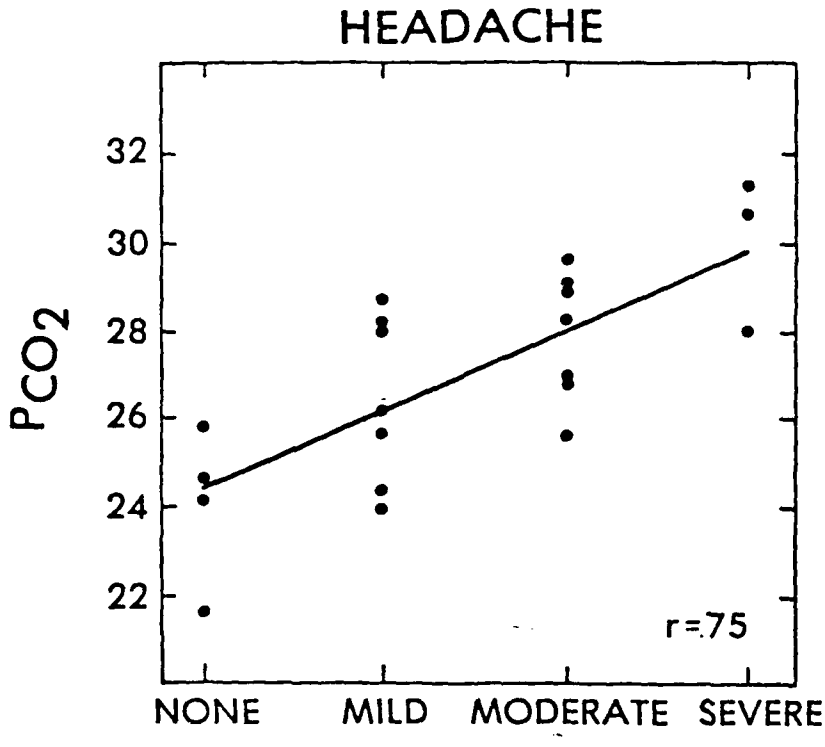


Figure 2. Relationship between blood carbon dioxide tension and severity of headache in 22 subjects on day 3 of altitude exposure. (From reference 2 . Reproduced by permission of the New England Journal of Medicine).

PATHOGENESIS OF ACUTE MOUNTAIN SICKNESS??

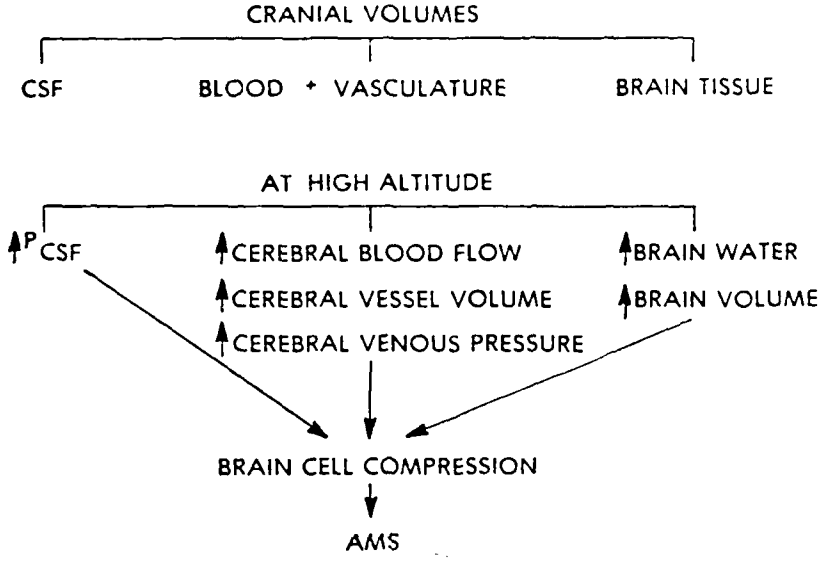


Figure 3

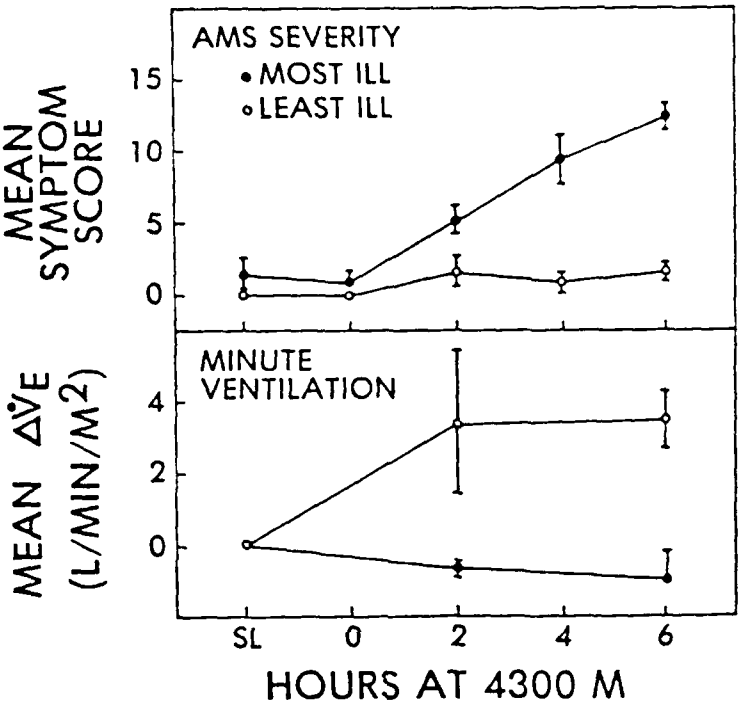


Figure 4. Mean (± SE) symptom score and change in ventilation of the 5 most ill and 5 least ill of 24 subjects at sea level (SL) and at a simulated altitude of 4,300 meters. (From reference 5 . Reproduced by permission of Aviation, Space and Environmental Medicine).

PERFORMANCE PROBLEMS AT HIGH ALTITUDE

PHYSICAL

- DECREASED WORK CAPACITY AND ENDURANCE PERFORMANCE

BEHAVIORAL

- DETERIORATION IN IMMEDIATE RECALL
- DECREASED VIGILANCE
- INCREASED ERRORS IN MENTAL ARITHMETIC
- PSYCHOMOTOR RETARDATION
- DECREASED ABILITY FOR CONCENTRATION
- IMPAIRMENT OF NIGHT AND PERIPHERAL VISION

Figure 5

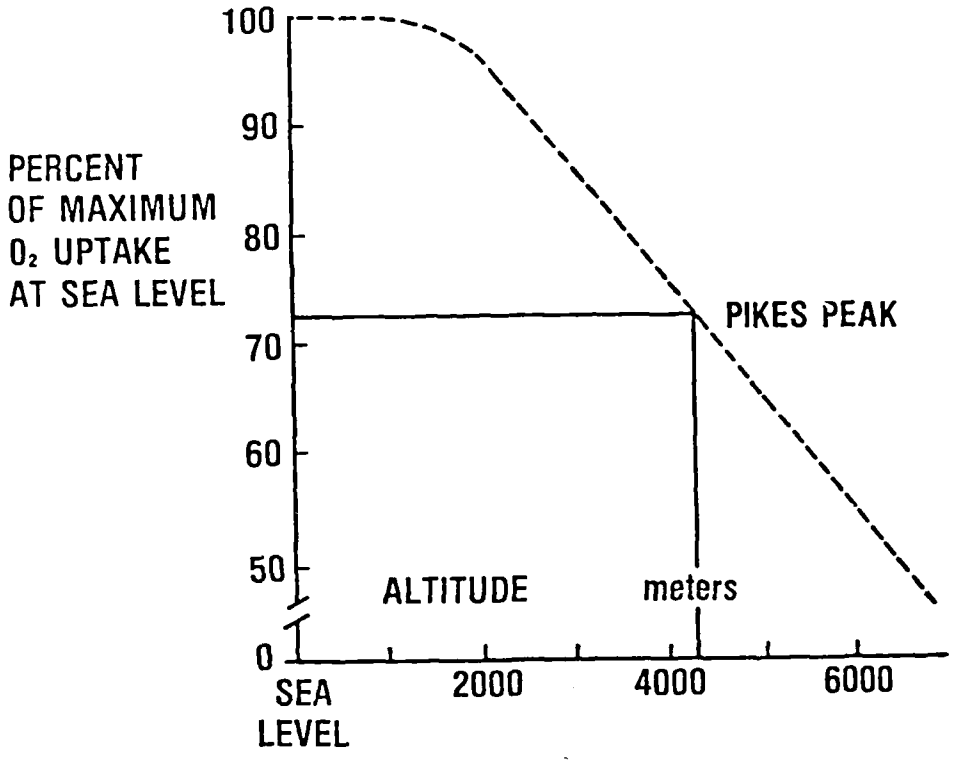


Figure 6. Relationship between altitude and aerobic work capacity.

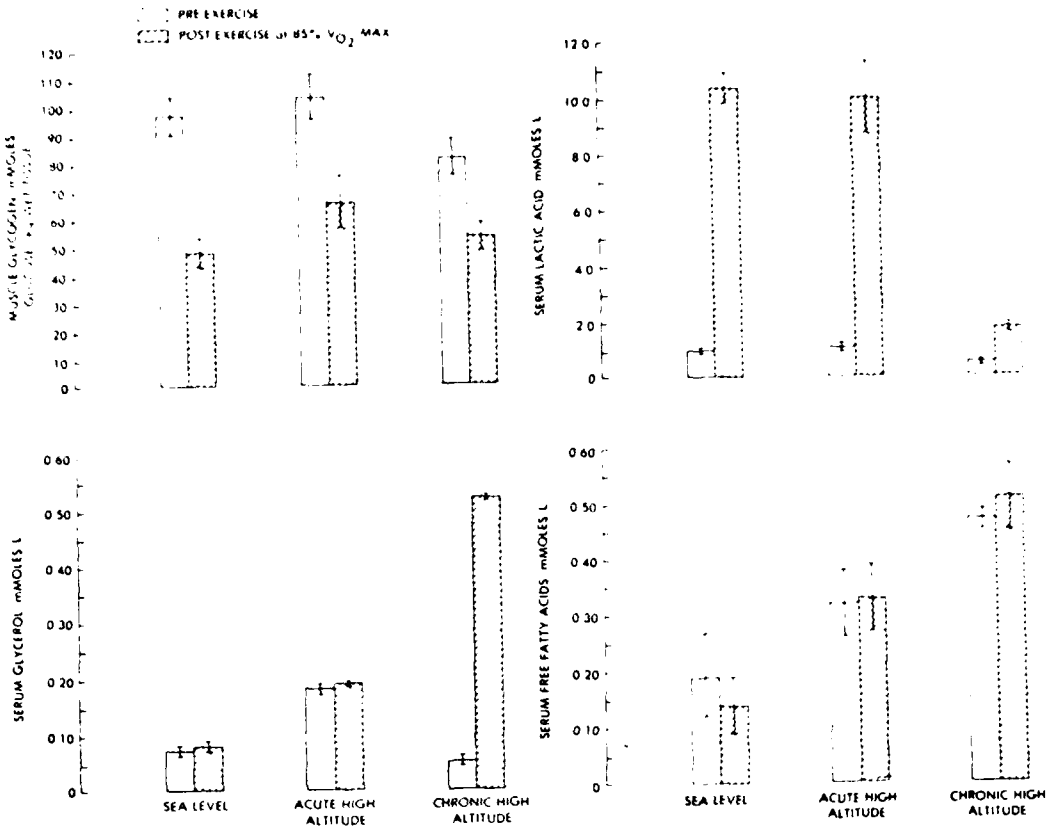
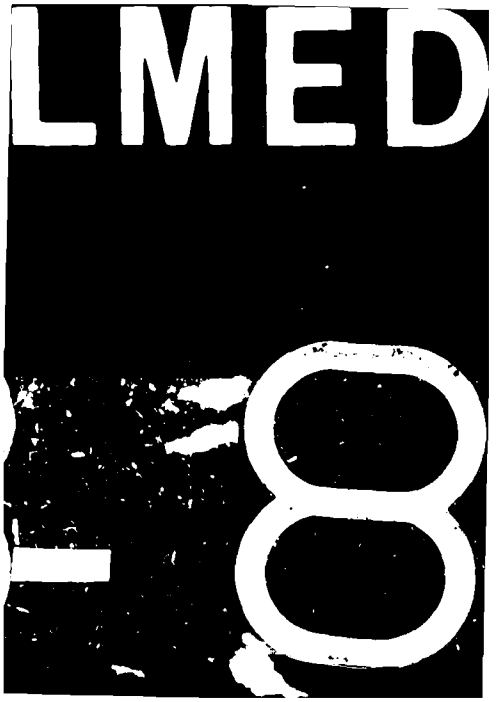


Figure 7. Mean concentrations (± SE) of serum free fatty acids, glycerol and lactate and muscle glycogen at rest and following 30 minutes of submaximal exercise.

The views, opinions, and/or findings contained in this report are those of the authors and should not be construed as an official Department of the Army position, policy, or decision, unless so designated by other official documentation.

Human subjects participated in this study after giving their free and informed voluntary consent. Investigators adhered to AR 70-25 and USAMRDC Regulation 70-25 on Use of Volunteers in Research.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