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ON THE VALIDITY OF CSF (H+) AS A MEDIATOR OF MAN'S VENTILATORY --ETC(U)
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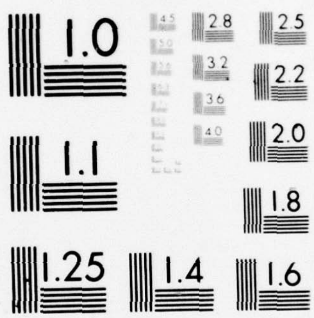

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"On the Validity of CSF [H+] as a Mediator of Man's Ventilatory Adaptation to Hypoxia."

FINAL TECHNICAL REPORT
January 29, 1976

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The central questions of this report were concerned with testing widely held theories concerning the mechanisms regulating the acid-base status of cerebrospinal fluid (CSF) and the role of this acid-base status as a mediator of ventilatory acclimatization to chronic hypobaric hypoxia (high altitudes). We have tested the regulation of CSF pH in healthy men, ponies while awake and dogs while anesthetized during 10 hours to 3 weeks of hypoxia and/or hypocapnia and found consistently that CSF pH is imperfectly regulated and that this (continued)

20. Abstract (continued)

regulation depends critically on concomitant changes in the blood, and that the acid-base status of this fluid played no positive role as a mediator of ventilatory acclimatization. These data challenged established theories and has reopened the broad question of the chemical regulation of breathing in chronic states of hypoxic or acid-base derangement.

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ABSTRACT

The central questions of this report were concerned with testing widely held theories concerning the mechanisms regulating the acid-base status of cerebrospinal fluid (CSF) and the role of this acid-base status as a mediator of ventilatory acclimatization to chronic hypobaric hypoxia (high altitudes). We have tested the regulation of CSF pH in healthy men, ponies while awake and dogs while anesthetized during 10 hours to 3 weeks of hypoxia and/or hypocapnia and found consistently that CSF pH is imperfectly regulated, that this regulation depends critically on concomitant changes in the blood, and that the acid-base status of this fluid played no positive role as a mediator of ventilatory acclimatization. These data challenged established theories and has reopened the broad question of the chemical regulation of breathing in chronic states of hypoxia or acid-base derangement.

In conducting the research described in this report, the investigator adhered to the "Guide for Laboratory Animal Facilities and Care", as promulgated by the Committee on the Guide for Laboratory Animal, Resources, National Academy of Sciences-National Research Council and all protocols for human research were approved by local committee.

A. The Problem.

The central question in this research was: "What factors mediate ventilatory acclimatization to the chronic hypoxia of high altitude in man?"

B. Background.

When man is exposed to hypoxia, one observes an initial hyperventilation which continues to increase over a 2 to 3 week period. The hyperventilation becomes quite severe, particularly during prolonged work at high altitude, and is an essential adaptation in the sojourner for maintaining adequate O_2 transport.

What mechanisms mediate this ventilatory acclimatization. It cannot be explained by concomitant changes in arterial blood pH or P_{O_2}, both of which rise during acclimatization, therefore presenting a decreasing stimulus level to peripheral chemoreceptors. In 1963, Severinghaus and co-workers[1], proposed the concept--based on a single study of 4 human sojourners at high altitude--that this acclimatization was mediated by a combination of hypoxic peripheral chemoreceptor drive plus a [H+] stimulus level at the medullary level which was diminished in magnitude during acute hypoxic exposure, but returned toward normal with prolonged exposure. This hypothesis has gained wide acceptance and has been applied to explain ventilatory acclimatization in a variety of chronic clinical conditions. This postulate is critically dependent upon the operation of local mechanisms at the blood:CSF and/or brain:CSF barriers which promote a precise regulation of CSF pH.

Our work was designed to test the validity of this dual chemoreceptor hypothesis in general and specifically, to examine the premise of a local regulation of CSF pH. Two key studies[2,3] were completed prior to the initiation of this contract and these data formed the basis for our testing of the hypothesis.

C. Summary of Approach, Results, Discussion and Conclusion.

Please note: All pertinent details of our work completed under Contract DAMD17-74C-4020 (1973-'75) are contained in five publications, four of which are attached.

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[1]Severinghaus, J.W., et al. "Respiratory control at high altitudes suggesting active transport regulation of CSF pH." J. Appl. Physiol., 18:1155-1166, 1963.

[2]Dempsey, J.A., H.V. Forster, N. Gledhill and G.A. doPico. "Effects of moderate hypoxemia and hypocapnia on CSF [H+] and ventilation in man." J. of Appl. Physiol., 38(4):665-674, April, 1975.

[3]Dempsey, J.A., H.V. Forster, and G.A. doPico. "Ventilatory acclimatization to moderate hypoxemia in man: the role of spinal fluid [H+]." J. Clin. Invest., 53(4):1091-1100, April, 1974.

1. Orr, J.A., G.E. Bisgard, H.V. Forster, D.D. Buss, J.A. Dempsey and J.A. Will. "Cerebrospinal fluid alkalosis during high altitude sojourn in unanesthetized ponies." <u>Resp. Physiol.</u>, 25:23-37, 1975.

2. Forster, H.V., J.A. Dempsey and L.W. Chosy. "Incomplete compensation of CSF [H+] in man during acclimatization to high altitude (4,300 m)." <u>J. Appl. Physiol.</u>, 38(6):1067-1072, June, 1975.

3. Forster, H.V., R.J. Soto, J.A. Dempsey and M.J. Hosko. "Effect of sojourn at 4,300 m altitude on electroencephalogram and visual evoked response." <u>J. of Appl. Physiol.</u>, 39(1):109-113, July, 1975.

4. Pelligrino, D.A. and J.A. Dempsey. "Dependence of CSF on plasma bicarbonate during hypocapnia and hypoxemic hypocapnia." <u>Resp. Physiol.</u> (In Press, 1976.)

5. Dempsey, J.A. and H.V. Forster. Cerebrospinal fluid alkalosis in chronic hypoxia: implications." (Presented before the Krogh Centenary Symposium, Srinigar, India, 1974, Proceedings. (In Press.)

The following narrative represents a summary of our work.

a. <u>Approach</u>. In essence two types of studies were completed in three species. First, to provide the necessary descriptive data--healthy man and ponies were studied while awake during 2 to 6 week exposures to varying severi[illegible] of hypobaric hypoxia (altitudes of 3200 to 4300 m). The major effor[illegible] was to obtain detailed time-course information on the changes in b[illegible]d CSF acid-base status during the acclimatization process. A total [illegible]5 men and 30 ponies were used in these studies. A technical key to these studies was our unique method of acid-base measurements for CSF, which is described in detail.[2,3] Secondly--based on these descriptive data--an extensive study was conducted in about 100 anesthetized, paralyzed dogs subjected to 7 to 14 hours of various combinations of hypoxia and/or hypocapnia. These studies were designed to test specifically the importance of changes in blood [HCO_3^-] on the regulation of CSF pH.

b. <u>Results</u>.

1. Changes in arterial blood gases and pH at 3100-4300 m showed that in man ventilatory acclimatization is a continuous process over a minimum 2 week period and that it is complete in $\sim$ 3 days in awake ponies. The physiologic responses of the pony, together with the relative ease of studying such animals while awake, makes this animal an ideal model for studies of high altitude adaptation.

2. pH compensation in blood was quite good (66-75% compensation) with bicarbonate excretion by the kidney accounting for a significant portion of this compensation even within the first few hours of exposure to high altitude.

3. CSF pH compensation was identical to that in arterial blood and remained significantly alkaline--to sea-level control values--with up to 5 weeks sojourn at high altitude. Severity of chronic hypoxia--up to 4300 m--did not provide any better compensation of CSF pH.

4. With regard to mediation of ventilatory acclimatization, the data revealed that all three conventional chemoreceptor stimuli--arterial P_{O_2} and pH and CSF pH--changed in a direction which would make them a negative rather than positive force in explaining ventilatory acclimatization. Changes in the EEG and evoked stimulus response during acclimatization strongly suggested that hypoxia induced a progressive change in CNS function, possibly compatible with an increased source of stimulus for ventilatory acclimatization.

5. The dog studies showed that plasma bicarbonate regulation was critical to the regulation of CSF $[HCO_3^-]$ and pH. A significant "local" control of CSF pH was detected only under conditions of rather severe hypoxemia and hypocapnia, which would only be encountered in man under highly non-physiologic conditions.

c. Conclusions and Recommendations.

These results are in contradiction with generally accepted theory in two key ways:

1. We found no evidence for specific mechanisms which would operate independently of drops in blood HCO_3^- in the regulation of CSF HCO_3^- during hypocapnia.

2. As a result of this non-specific regulation, the maintained alkalinity in CSF pH during acclimatization rules out brain ECF pH as an important mediator of ventilatory acclimatization.

We propose, then, that some very potent stimulus of "extra-chemoreceptor" origin must play a major mediator role in ventilatory acclimatization to chronic hypoxia or chronic acid-base disturbances of respiratory origin. It is recommended that studies of chemical mechanisms in ventilatory control recognize thisdistinct possibility of other CNS-related factors in the control of breathing. We intend to pursue this work in two areas: 1) an investigation of potential mediators in brain tissue--including intracellular pH and turnover of brain neurotransmitters; and 2) an *in vivo* assay of unknown factors in brain ECF which may influence respiration.