EFFECTS OF SHORT-TERM CARBON DIOXIDE EXPOSURE ON BACKGROUND EEG AND EVOKED POTENTIALS IN MAN

by

Peter Crown

A Thesis Submitted to the Faculty of the

DEPARTMENT OF PSYCHOLOGY

In Partial Fulfillment of the Requirements
For the Degree of

MASTER OF ARTS

In the Graduate College

THE UNIVERSITY OF ARIZONA

1 9 6 9

STATEMENT BY AUTHOR

This thesis has been submitted in partial fulfillment of requirements for an advanced degree at The University of Arizona and is deposited in the University Library to be made available to borrowers under rules of the Library.

Brief quotations from this thesis are allowable without special permission, provided that accurate acknowledgment of source is made. Requests for permission for extended quotation from or reproduction of this manuscript in whole or in part may be granted by the head of the major department or the Dean of the Graduate College when in his judgment the proposed use of the material is in the interests of scholarship. In all other instances, however, permission must be obtained from the author.

SIGNED: Peter Brown

APPROVAL BY THESIS DIRECTOR

This thesis has been approved on the date shown below:

Robert W. Lansing

R. W. LANSING
Professor of Psychology

7-12-68

Date

ACKNOWLEDGMENTS

Acknowledgment is made to Dr. Robert W. Lansing, Thesis Director, for directing this project and for his many helpful suggestions and contributions given during each stage of its completion, and to Dr. Neil R. Bartlett and Dr. Jack E. Capehart, the other two members of the thesis committee, for their suggestions in the preparation of the manuscript.

This project was partially supported by an Institutional Grant from the National Aeronautics and Space Administration.

TABLE OF CONTENTS

LIST OF ILLUSTRATIONS

ABSTRACT

The purpose of this study was to investigate the effects of short-term exposure to 5% carbon dioxide (CO_2) on respiratory and central nervous system (CNS) activity in man, and to investigate the relationship between these effects.

Eight normal college students breathed 5% CO_2 in air for 4-minute trials. There was an air control for each CO_2 trial. Electroencephalograms (EEG) were obtained from occipital and central monopolar electrodes and were recorded on magnetic tape. Visual evoked potentials (VEPs) to stroboscopic flashes were obtained from minute $2\frac{1}{2}$-$3\frac{1}{2}$. Respiratory volume was monitored with a pneumotachograph. Partial pressure of alveolar CO_2 ($pACO_2$) of end tidal samples was measured with an infra-red medical CO_2 analyzer.

During CO_2 inhalation there was a significant decrease in the mean integrated energy of the central EEG, particularly in the 16-24 Hz. band. Occipital EEG energy was not significantly decreased, and was even slightly increased in the 8-12 Hz. band. Occipital alpha frequency increased during photostimulation during air control trials, but did not change during CO_2 trials. These results rule out a general activation effect. They were interpreted as a local excitatory response in the central region.

There was a significant correlation across subjects (.79) between the energy decrease in the central recording (16-24 Hz. band) and increase in estimated arterial CO_2. No correlation was found between changes in EEG and respiratory minute volume. Therefore, the central EEG response cannot be explained on the basis of increased sensory input related to ventilation, nor does it appear to be coordinated with the brain-stem systems which regulate respiration. No consistent changes in occipital VEPs were noted for the group. Late potentials were enhanced in the instance of 3 individuals, while in the 4 others no change or decrease was observed.

INTRODUCTION

An increase in the partial pressure of arterial CO_2 ($pACO_2$) is well known to be an adequate stimulus for an increased ventilatory response. As such a stimulus, CO_2 may be defined as "a regulating factor of ventilation, depending on the properties of the blood connected with CO_2, acting directly on the respiratory centers (central chemoreceptors) or upon the arterial chemoreceptors" (Dejours, 1958).

Increased $pACO_2$ also affects the central nervous system (CNS) activity as reflected in the electroencephalograms (EEG), but there is disagreement as to whether the effects are inhibitory or excitatory, what region or regions of the brain are affected, and how these changes are related to behavioral changes. (For a complete discussion of these problems see Wyke, 1963.) Also, there is little known about the relationship between the respiratory response and the EEG response to elevated level of arterial CO_2. Dell (1958) states that both a decrease in partial pressure of O_2 and an increase in partial pressure of CO_2 stimulate the mesencephalic portion of the reticular formation as well as stimulating the classical respiratory centers of the medulla. He concludes that ventilation and the craving

for air are mediated first at the bulbar level, and then if needed, at the mesencephalic level.

Many questions remain unanswered. It has not been demonstrated whether the ventilatory response occurs before, after, or at the same time as the EEG response. Also, sensitivity to CO_2 as reflected in respiratory measures has been shown to differ between individuals (Schaefer, 1949; Harter, 1967), but these differences have not been related to individual differences in the EEG response.

The purpose of this study was to investigate the effects of short-term exposure to 5% CO_2 on respiration and on the EEG in man, and to investigate the relationship between these effects. Background EEG and visual evoked potentials (VEP) were recorded from central and occipital areas. Respiratory response was defined in terms of increased minute volume. Transient exposure to a low CO_2 level (5%) was the independent variable. Short durations were employed to avoid the many changes which accompany long-term exposure or exposure to high CO_2 levels.

Originally it was hoped that this technique could be used to aid in the study of the relationship between the EEG and VEP. It was thought that CO_2 would regulate the EEG by affecting cerebral physiology, and this, in turn, would affect the evoked potential.

METHOD

Subjects and Experimental Conditions

Five male and 3 female college students with no history of respiratory disease served as subjects (Ss). Four trials of 4-minute 30-second duration were administered to each S. Air was administered during trials 1 and 4, CO_2 during trials 2 and 3. Air was administered to one male S for all 4 trials as a control.

Data were taken in late afternoon or early evening when the laboratory was quiet. A radio supplied soft background music. A 3-minute recovery period was given after each trial to permit S's CO_2 level to return to baseline. Each session lasted about 45 minutes.

Each trial began with a 30-second air control period. Then S was switched from breathing air to the closed breathing system. He then breathed through the system for 4 minutes. Sixty-four stroboscopic flashes were presented from minute $2\frac{1}{2}$-$3\frac{1}{2}$.

Apparatus and Data Recording Procedure

The EEG, respiratory volume, and end-tidal CO_2 were simultaneously recorded on a Grass Inkwriter throughout the experimental and control trials. The EEG and VEP were

obtained from central and occipital monopolar electrodes. The occipital electrode was located 3 cm. above and to the right of the inion. The central electrode was positioned 3 cm. below the vertex on the right side. A reference electrode was located on the right ear, a ground electrode on the left ear. Brain potentials were amplified with Grass EEG pre-amplifiers and taped on a Hewlett Packard Model 3900 FM tape system. The taped EEG was played later through a Krohn-Hite Model 330B Band-Pass Filter and integrated on a Grass Model UI-1E integrator. Four broad bands (Q = 5) were used with center frequencies 5, 10, and 20 Hz. The filter was calibrated in the laboratory before retrieval and integration.

Alpha frequency was determined by selecting 6 samples of 10 waves from each 30-second period. The samples were measured in mm. and converted to cycles per second.

Evoked potentials were obtained by summing 64 intervals of 0.5 second duration on a Fabritek 1052 signal averager. A Grass PS-2 Photostimulator set at intensity 16 provided the flashes. The stimulator was mounted 12" from S's eyes, which were kept closed for the duration of the trials. The interflash interval was varied randomly between 0.75 seconds and 1.25 seconds to avoid synchronizing EEG alpha rhythm and the flash. A square wave pulse synchronous with the flash was recorded on tape so evoked potentials could be averaged off-line on the averager.

Arterial CO_2 tension was estimated by analyzing end-tidal samples on line with a Beckman infra-red CO_2 analyzer. Known gas mixtures were used to calibrate the apparatus and generate calibration curves, which later were used to convert pen deflections to percentage CO_2. Percentage CO_2 was then converted to $pACO_2$ by the formula:

$pACO_2$ = % expired CO_2/100 (barometric pressure - 47)

The volume of each breath was determined with a Grass pneumotachograph. Minute volume was obtained on-line from a breath-by-breath integration of the output of the pneumotachograph by the Grass integrator.

During the trials S was in a reclining position, wore a noseclip, and breathed through a mouthpiece. The apparatus was arranged so that S could breathe room air, or from one of the two Douglas bags containing air and the CO_2-air mixture. The apparatus and a sample of the ink-writer record are shown in Figure 1.

Care was taken to keep S from knowing which gas he was breathing, but it was possible for S to determine this from his increased breathing rate under CO_2 and from the taste of the CO_2 mixture. (Five percent CO_2 in air is not a tasteless mixture. It was described by the Ss as having a dry, acrid taste and feeling.)

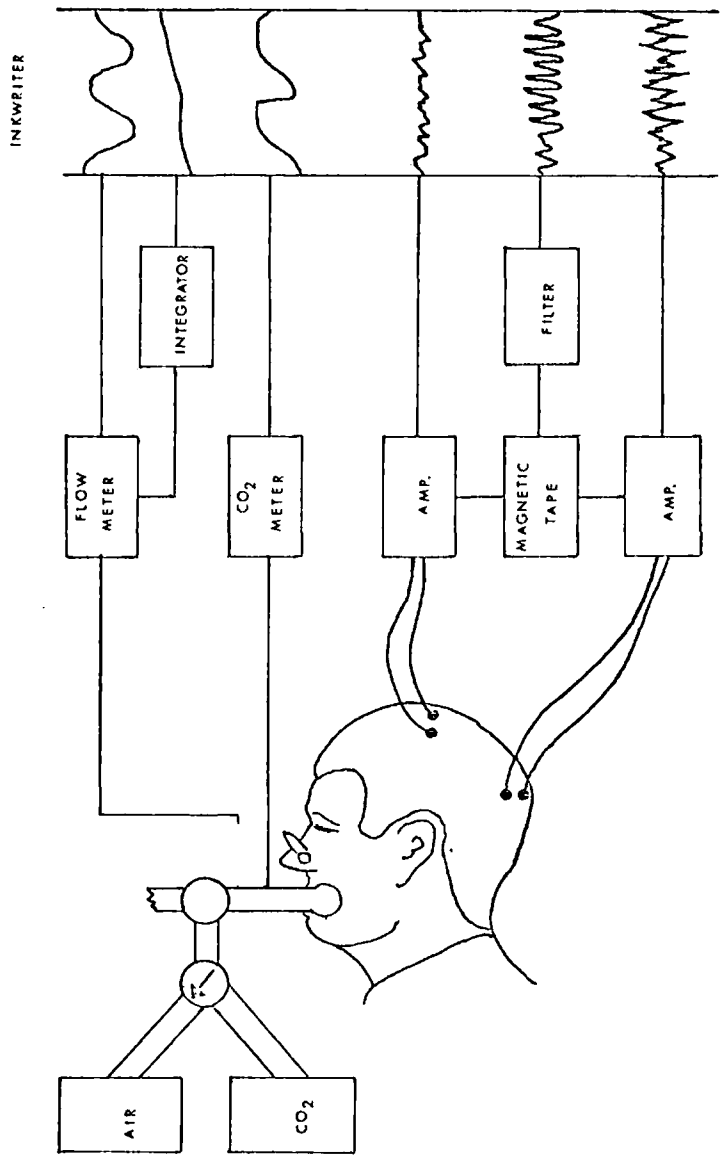

Fig. 1. Experimental Apparatus and Sample of the Inkwriter Record.

RESULTS

The group means (N = 7) for respiratory measures are shown in Figure 2. The $pACO_2$ reaches an asymptote at minute 2, but the minute volume continues to increase to the end of the trial. Under the air condition $pACO_2$ and minute volume remain unchanged. These changes have been well established in physiological literature (White, et al., 1952).

The mean integrated energy (MIE) of background EEG is the integration of specified time epochs. The MIE for all conditions is shown in Figure 3. In each pair of histograms the air condition is a baseline or 100%, and the CO_2 conditions are expressed as a percentage of the appropriate air control. There is a decrease in energy under CO_2 for all frequencies in the central region. The decrease was significant at the .05 level for the 3-40 Hz. and 16-24 Hz. bands by a matched pairs t-test. The decrease in the alpha band (8-12 Hz.) was at the .06 level. There were no significant decreases in the occipital leads. No change at all was noted in the 16-24 Hz. band, and in the alpha band there was even a slight increase under the CO_2 condition.

A comparison of EEG and respiratory changes is made in Figure 4. An attempt was made to analyze the first

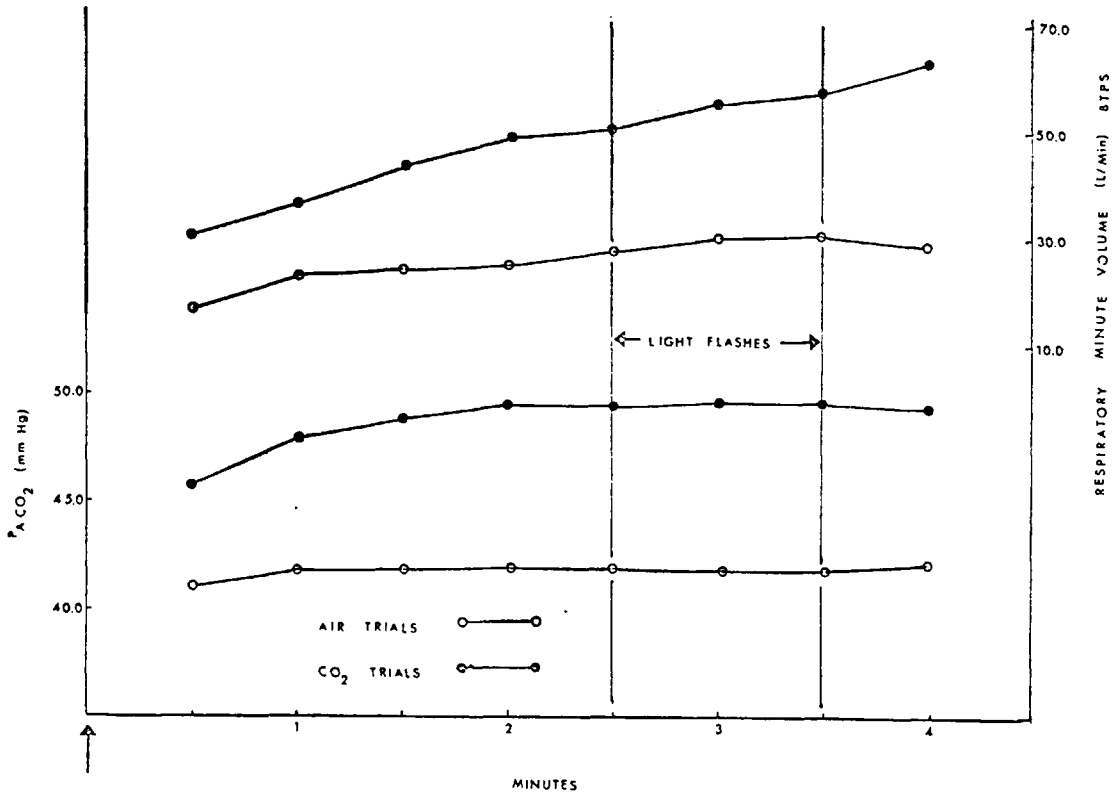

Fig. 2. Group Means (N = 7) of Respiratory Measures.

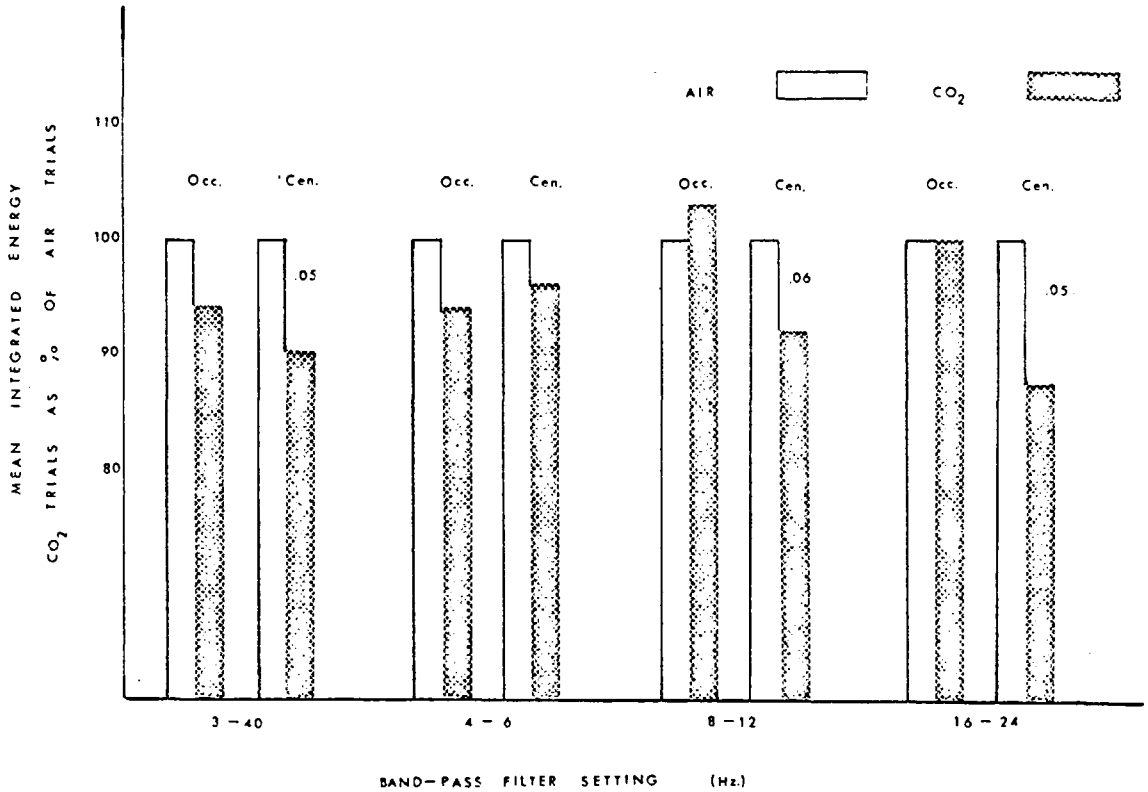

Fig. 3. Mean Integrated Energy (MIE) of Background EEG.

The EEG changes under CO_2 are expressed as percentages of air control trials.

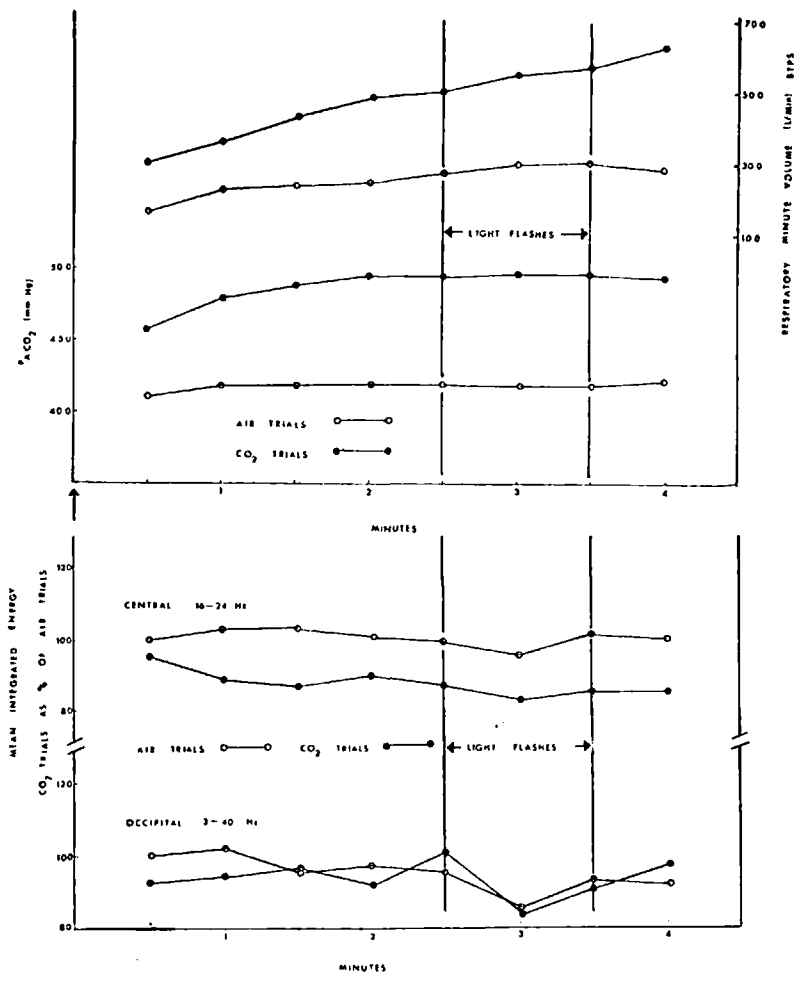

Fig. 4. Comparison of EEG and Respiratory Changes with Time.

40 seconds of these data by 10-second intervals. All Ss showed great variability and no consistent trends were noted. The EEG changes are expressed as percentages of an air control. The period of photic stimulation is shown to take place between minute $2\frac{1}{2}$ and $3\frac{1}{2}$. The primary function of the photic stimulation was to obtain VEPs, but it served also as an activating stimulus. Occipital alpha frequencies under air and CO_2 conditions were, for the most part, the same. The one important difference was that the increase in alpha frequency during photic stimulation was twice as great in the air condition. This suggests that CO_2 was not producing a general activation, as alpha frequency would be higher under CO_2 than air were this the case.

It was thought that the decrease in energy in the central area may have been due to increased sensory input related to the increase in ventilation. A correlation between respiratory minute volume and EEG changes was performed but no relationship was found. There was, however, a significant correlation (.79) between the energy decrease in the central recording (16-24 Hz. band) and increase in estimated $pACO_2$. Thus, EEG changes were more closely related to blood CO_2 levels than to respiratory changes.

The latencies of prominent evoked potential peaks were measured. No consistent changes for the group nor for individuals were found. The areas of these components were

found with a planimeter but again there were no consistent changes.

It was expected that late potentials would be enhanced selectively while early potentials would be reduced under the CO_2 condition, a finding reported by W. Grey Walter (1964). There was such an enhancement in 3 cases, while the other 4 showed either no change or decreased. Figure 5 illustrates some of these changes. Subjects BF and AB show enhanced late potentials under the CO_2 condition. Subject GW shows a decrease while GI shows no change.

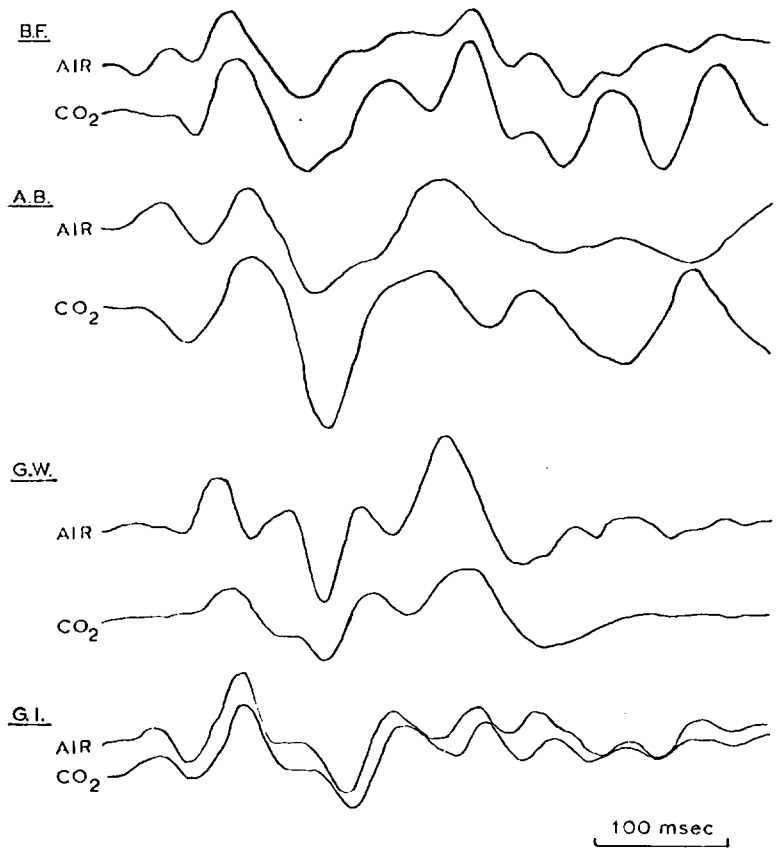

Fig. 5. Visual Evoked Potentials.

Subjects BF and AB show enhancement of late potentials under CO_2, GW a reduction, and GI no change.

DISCUSSION

These data suggest that the effects of 5% CO_2 on the brain over short periods are localized more in the central than in the occipital region. Ivanov (1962) reported that cats and dogs given 2.5-4.5% CO_2 show a decrease in slow components, increased frequency, and desynchronization that begins in the frontal region and spreads later to the occipital and parietal areas. Likewise, Dell (1958) has found central activation in cats. These animal studies are similar to the findings in the present study, the main difference being that the effect seems to be more localized in man.

The decrease in MIE in the central region, notably in the 16-24 Hz. band, was interpreted as a local excitatory response, resulting primarily from the change in blood and tissue state brought about by CO_2. Potentials in this frequency range (beta rhythm) typify the spontaneous activity of the central region, and a blocking or reduction in voltage accompanies increased activity. EEG changes were not thought to be a result of increased sensory afference resulting from increased respiratory work because there was no correlation between EEG and respiratory changes, although sensory inputs from the lungs and carotid sinus

could be involved. Certainly, some of the Ss' feelings of distress are centered on the somatic sensory region of the brain associated with the thoracic area.

It is conceivable that the EEG changes were a result of the physical discomfort of breathing the CO_2 mixture, fear, or other emotional responses to the situation. However, if factors of this nature were operating, one would predict a generalized activation response. This is ruled out for several reasons. One is that the occipital EEG was little affected by the CO_2 conditions, and alpha activity actually increased under CO_2. Second, occipital alpha frequency during CO_2 trials was about the same or slower than during air trials. Third, during sensory activation by photic stimulation occipital alpha frequency was found to be slower during CO_2 trials than it was for air.

Finally, one would predict that evoked potentials would be affected by a generalized change in activation level (Haider, Spong, and Lindsley, 1964; Spong, Haider, and Lindsley, 1965). No consistent changes in latency or amplitude (amplitude inferred from areas under the curve) were noted.

The time course of the changes noted would be of interest. However, when data from the first 30 seconds were analyzed by 10-second intervals, it was found that

the EEG changes were highly variable between Ss and no definite time course was noted.

It is difficult to compare data from this study with that of others, there being so little similarity in variables used; CO_2%, duration of breathing gas mixtures, method of EEG analysis and other variables are usually different and frequently are not described at all.

Gibbs, Williams, and Gibbs (1940) did not specify electrode placement nor the CO_2 level used, but reported CO_2 levels from internal jugular vein samples to be around 54 volume %. This CO_2 increase shifted the EEG to the fast side of the spectrum with a decrease in total energy. This agrees with the energy decrease found in the present study. It is possible that there was also a frequency shift that went undetected by the band-pass filter method employed herein. Gibbs, Williams, and Gibbs report, for instance, that the 19 per-second peak shifts to 20 per-second under CO_2. This shift may have occurred in the present study but, of course, would not be detected with the 16-24 band-pass setting.

The slight increase in occipital alpha under CO_2 was also found in a breath-holding study of Ivanova (1964). He found that the decreased alpha amplitude and the frequent alpha blocking seen in the first 15 seconds of breath-holding was followed by an enhancement of alpha, amplitude surpassing base level. Schaefer and Carey (1954)

also found that alpha blocking time increased with CO_2 concentrations of 3.3% or more. Schaefer (1949) found an increase in alpha activity in Ss breathing 2% CO_2. The number of waves in a train increased with time; one to two minutes later alpha waves came continuously rather than in bursts. Schaefer also reports a "preponderant discontinuation of potential production" which is taken to mean a decrease in background EEG, a finding supported by the present study.

There is an interesting parallel to this in the respiratory changes that accompany changes in wakefulness. When one falls asleep the respiratory minute volume decreases while the $pACO_2$ increases, or in other words, the threshold of CO_2 sensitivity increases. Ingvar and Bülow (1963) noted that the alpha bursts which occur while someone is going to sleep are accompanied by respiratory increases. They suggest the possibility of a functional linkage between those brain-stem centers controlling wakefulness and those involved in respiratory regulation. Such a linkage may be inferred in the present study in that CO_2 increased alpha amplitude slightly.

In summary then, short-term exposure to CO_2 sufficient to elevate blood CO_2 level about 10 mm. Hg and moderately affect ventilation seems to produce regional rather than generalized changes in EEG. Neither the time

course nor extent of EEG change is closely related to ventilatory change produced by CO_2. The relationship between blood CO_2 and degree of EEG change suggests that the EEG may be a useful index of CNS sensitivity to CO_2. The reactivity of higher centers may not be predicted by measuring CO_2 sensitivity using breathing measures.

REFERENCES

Brazier, M. A. B. The physiological effects of carbon dioxide on the activity of the central nervous system in man. Medicine, 1943, 4, 205-221.

Dejours, P. Étude du stimulus gaz carbonique de la ventilation chez l'homme. Journal de Physiologie, 1958, 50, 239-243.

_____. Chemoreflexes in breathing. Physiological Reviews, 1962, 42, 335-358.

Dell, P. Humoral effects on the brain stem reticular formations. In Reticular Formation of the Brain, H. H. Jaspers (ed.). Boston: Little, Brown and Company, 1958.

Gibbs, F. A., Williams, D., and Gibbs, E. L. Modification of the cortical frequency spectrum by changes in CO_2, blood sugar, and O_2. Journal of Neurophysiology, 1940, 3, 49-58.

Haider, M., Spong, P., and Lindsley, D. Attention, vigilance, and cortical evoked-potentials in humans. Science, 1964, 145, 180-182.

Harter, R. Effects of carbon dioxide on the alpha frequency and reaction time in humans. Electroencephalography and Clinical Neurophysiology, 1967, 23, 561-563.

Ingvar, D. H. and Bülow, K. B. Respiratory regulation in sleep. Annals of the New York Academy of Sciences, 1963, 109, 870-881.

Ivanov, Y. N. Changes in electrical activity of different brain regions in dogs and cats exposed to carbon dioxide. Sechenov Physiological Journal of the USSR, 1962, 48, 13-18.

Ivanova, M. P. The latency period of motor responses and alpha-rhythm depression during muscular exercise, hyperventilation, and breath-holding. Sechenov Physiological Journal of the USSR, 1964, 690-696.

Jasper, H. Diffuse projection systems: The integration — action of the thalamic reticular system. Electroencephalography and Clinical Neurophysiology, 1949, 1, 405-420.

Meyer, J. S., Sakamoto, K., Akiyama, M., Yoshida, K., and Yoshitake, S. Monitoring cerebral blood flow, metabolism and EEG. Electroencephalography and Clinical Neurophysiology, 1967, 23, 497-508.

Proctor, C. M. and Thompson, J. P. A new compilation and graph of carbon dioxide exposure data. The Boeing Company, 1963, 1-19.

Schaefer, K. E. Der Einfluss eines langdauerenden Aufenhaltes in 3% CO_2 auf die Hirnaktionsströme. Pflügers Archiv gesamete Physiologie, 1949, 251, 726-740.

Schaefer, C. E. and Carey, C. R. Influence of exposure to various carbon dioxide concentrations on flicker fusion frequency and alpha blocking. Medical Research Laboratory, Report No. 251, August 27, 1954.

Spong, P., Haider, M., and Lindsley, D. Selective attentiveness and cortical evoked responses to visual and auditory stimuli. Science, 1965, 148, 395-397.

Walter, W. G. The convergence and interaction of visual, auditory, and tactile responses in human nonspecific cortex. Annals of the New York Academy of Sciences, 1964, 109, 320-361.

White, C. S., Humm, J. H., Armstrong, E. D., and Lundgren, P. V. Human tolerance to acute exposure to carbon dioxide report No. 1: Six per cent carbon dioxide in air and in oxygen. Journal of Aviation Medicine, 1952, 23, 439-455.

Wyke, B. Brain Function and Metabolic Disorders. London: Butterworths, 1963, pp. 161-163.