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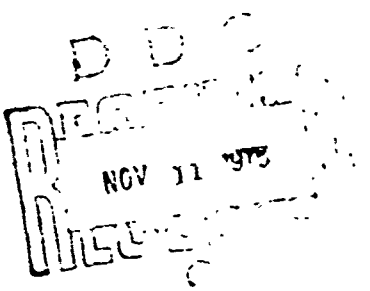

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INTRODUCTION

With the advent of submarine and aerospace research concerning environmental conditions in closed systems, the problem of carbon dioxide removal and man's ability to perform adequately in various levels of carbon dioxide has become paramount. Many studies utilizing acute elevation of carbon dioxide are available in the literature; however, owing to attendant difficulties, studies of chronic hypercapnia are less numerous. The following report will summarize some of the pertinent work done in the field of acute and chronic hypercapnia, utilizing physiologic, mental, and physical performance parameters in man as an aid to evaluation. A discussion will follow concerning acceptable carbon dioxide levels, both ideal and on a contingency basis, for manned space flight.

It is not within the scope of this paper to review completely the more sophisticated research aspects of hypercapnia and acid-base physiology, and for a detailed background the reader is referred to a series of articles by noted workers in the field (13, 18, 25, 30, 32, 35, 37, 58). In addition several articles reviewing manned experience in carbon dioxide are available (6, 29, 60).

Briefly, the body must maintain narrow limits of hydrogen ion concentration (H^-) for metabolic processes to be carried on normally. The pH (or H^- concentration) range judged to be acceptable for normal metabolic functions is from 7.35 to 7.44 with a mean of 7.40. To maintain these limits the partial pressure of carbon dioxide in the arterial blood ($P_{A_{CO_2}}$) is maintained at 40 mm. Hg (36 to 42 mm. Hg), while the total CO_2 (HCO_3^- + dissolved CO_2) ranges from 22-26 mEq./liter.

Four buffering mechanisms are utilized to keep the body fluids at a relatively constant pH when acid is either added or lost.

1. *Respiratory buffering.* The H^+ concentration is adjusted as the excess H^+ forms with HCO_3^- to form carbonic acid

(H_2CO_3). This then goes to CO_2 and H_2O so that for every molecule of CO_2 blown off through the lungs, one H^+ is removed in the form of water. Normally, the body rids itself of approximately 13,000 mEq. of volatile acids daily in this manner. During hypercapnia, this compensatory mechanism is effective in 5 to 30 minutes but seldom completely brings the pH back to normal.

2. *Extracellular buffering.* Excess H^+ combines with available buffers (HCO_3^-, proteins) in the extracellular fluid. This reaction is immediate but has limited buffering capabilities.

3. *Intracellular buffering.* Part of the excess H^+ diffuses into cells and is buffered by intracellular HCO_3^-, proteins. This reaction occurs in 2 to 4 hours.

4. *Renal acid excretion.* If an excess acid load is present chronically, the kidneys respond by putting out more hydrogen ion in the form of ammonium (NH_4^+) or titratable acidity (H^+ bound to phosphates). Also important is the ability of the kidney to conserve bicarbonate by reabsorbing more of the filtered HCO_3^-. On a normal diet, 40 to 80 mEq. of H^+ are excreted in a 24-hour period. With increasing acid loads as noted with marked hypercapnia, this figure is doubled or tripled for a 24-hour period. This parameter can be readily measured by carrying out a hydrogen ion balance study for 24 hours by measuring urinary NH_4^+, titratable acidity (T. A.), and bicarbonate. The total 24-hour H^+ excretion then becomes NH_4^+ + T. A. — HCO_3^-. This mechanism takes hours to days to become effective.

Utilizing the laws of mass action (addition of reagent to one side of an equation causes the reaction to shift to the other side) and the following formula, it becomes apparent what occurs physiologically when a man lives in a high carbon dioxide environment.

Lungs: Respiratory

$$CO_2 + H_2O \rightleftharpoons H_2CO_3 \rightleftharpoons H^+ + HCO_3^-$$
$$\Updownarrow \quad \Updownarrow$$
Kidneys

With increased levels of arterial CO_2 ($Paco_2$) in the blood, the equation is shifted to the right and there is an increase in H^+ and

in HCO_3^-. If the stimulus is strong enough (markedly elevated $Paco_2$'s), the respiratory (increased ventilation to blow off more CO_2), intracellular, and extracellular buffering systems will not be adequate. The kidney will then contribute by increasing the excretion of H^+ in the form of NH_4^+ and increasing the generation and reabsorption of HCO_3^- to buffer body fluids (26, 57). Clinically, then, we would see an elevated Pco_2, elevated respiratory minute volume, reduced pH, elevated serum HCO_3^- or total CO_2 and increased 24-hour hydrogen ion excretion. These are the main physiologic parameters to be followed and discussed in this paper along with the performance and psychomotor studies.

ACUTE STUDIES

Symptoms and physiology

Multiple acute studies are available for review and are summarized in table I. It should be noted that this review by no means covers all research in the field of hypercapnia. With one exception, no studies are reviewed with inspired Pco_2's higher than 41 mm. Hg (5.4%), although many are available (1, 2, 4, 8, 10, 53).

In 1922 Schneider and Truesdale (51) utilized 16 subjects to study the respiratory responses of normal men to varying levels of carbon dioxide. In all studies, the oxygen was adjusted to maintain normal levels of inspired oxygen. At an ambient partial pressure of carbon dioxide ($P_{I_{CO_2}}$) of 7 to 8 mm. Hg, a 24% increase (6.3 liters/min. up to 8.3 liters/min.) in respiratory minute volume was noted. There was no change in blood pressure, pulse, and respiratory rate. In a similar study carried out by Lindhard (33), a questionable increase was noted in respiratory rate although the alveolar partial pressure of carbon dioxide ($P_{A_{CO_2}}$) remained a normal 38 mm. Hg. Schaefer and co-workers (43) reported an excellent large-scale respiratory study utilizing 65 subjects breathing various gas mixtures for periods of 15 minutes. At a $P_{I_{CO_2}}$ of 11 mm. Hg, no significant changes were noted in the respiratory pattern including respiratory rate and tidal volume.

Working at the Scripps Clinic, Froeb (16) studied 32 subjects both resting and at mild exercise walking on a level treadmill at 2 miles per hour for 15 minutes. While at rest breathing a $P_{I_{CO_2}}$

TABLE I

Acute studies

P_{CO_2} (mm. Hg)	CO_2 (%)	Duration	Number subjects	Symptomatology and physiology	Performance	Ref.
7-8	1.0	17-32 min.	16-20	No change in blood pressure, pulse, respiratory rate. Small increase in tidal volume (V_T), 24% increase in respiratory minute volume ($\dot{V}$).		51
7-8	1.0	6 min.	3	Questionable increase respiratory rate (r.r.) $P_{A_{CO_2}}$ 38 mm. Hg.		33
11	1.5	15 min.	65	Asymptomatic, no dyspnea. No change r.r., V_T.		43
11	1.5	15 min.	25		No change flicker fusion frequency or alpha blocking.	42
12	1.9	15 min	32	No change resting expiratory minute volume ($\dot{V}_E$) from control approximately 5 liters/min. ↑ $\dot{V}_E$ over control with mild exercise.		16
15	2.0	6 min.	3	Small ↑ r.r. $P_{A_{CO_2}}$ 38 mm. Hg.		33
15	2.0	30 min.	9	Minimal metabolic acidemia in 30 minutes.		8

TABLE I (contd.)

P_{CO_2} (mm. Hg)	CO_2 (%)	Duration	Number subjects	Symptomatology and physiology	Performance	Ref.
15	2.0	12-32 min.	16	V_T ↑ ntrol 570 to 780 cc. rr. ↑ from control 12.7 to 14.8 breaths/min. $\dot{V}$ ↑ from control 6.7 to 11.3 liters/min. Minimal change blood pressure.		51
15	2.0	?	33	$\dot{V}$ ↑ approximately 2-3 liters/min. $P_{A_{CO_2}}$ ↑ 2-3 mm. Hg.		32
19	2.5	30 min.	12	Arterial pH from 7.44-7.39. $P_{A_{CO_2}}$ from 38.4 to 42.5 mm. Hg. No change cerebral blood flow.		36
21	3.0	17.32 min.	8-20	V_T ↑ from control 57? to 1,000 cc. r.r. ↑ from control 12.7 to 15.1 breaths/min. $\dot{V}$ ↑ from control 6.3 to 15.6 liters/min. $P_{A_{CO_2}}$ ↑ from control 38.4 to 42.0 mm. Hg.		51
21	3.0	1st 4 hours prolonged study	4	Subjects note ↑ r.r.	No performance degradation.	9
21	3.0	1st 4 hours prolonged study	7	Arterial pH from control 7.40-7.37. Subjects note ↑ r.r.	No performance degradation.	19
21-24	3.0-3.5	1-2 min.	37	Small loss in threshold of hearing.		17
25	3.3	15 min.	65	Marked CO_2 response variability. V_T ↑ 400-500 cc. over controls. $P_{A_{CO_2}}$ ↑ 3-5 mm. Hg over controls. No significant change r.r. noted.		43

TABLE I (contd.)

P_{CO_2} (mm. Hg)	CO_2 (%)	Duration	Number subjects	Symptomatology and physiology	Performance	Ref.
25	3.3	15	24	Respiratory parameters as above.	Questionably significant ↓ in flicker fusion frequency and ↑ alpha blocking.	42
26	3.4	15 min.	32	Resting $\dot{V}_E$ ↑ from control 7.5 liters/min. to 10-11 liters/min. Exercise $\dot{V}_E$ ↑ from control 15 liters/min. to 25 liters/min.		16
27	3.5	30 min.	11	Arterial pH from control 7.40 to 7.35. Arterial P_{CO_2} from control 39.4 to 44.7 mm. Hg. 10% ↑ cerebral blood flow.		36
30	4.0	17-32 min.	16-20	$\dot{V}$ ↑ from control 7 to 16 liters/min. $P_{A_{CO_2}}$ ↑ from control 38 to 45 mm. Hg.		51
38	5.0	16 min.	19	V_T from control 500 to 1,600 cc. $\dot{V}_E$ from control 10 to 28-32 liters/min. $P_{A_{CO_2}}$ ↑ from control 32 to 43 mm. Hg. 85% knew when CO_2 added.	No significant errors in multiple card sorting studies.	61
38	5.0	12 min.	13		Within 12 min., significant ↓ flicker fusion frequency.	56

TABLE I (contd.)

P_{CO_2} (mm. Hg)	CO_2 (%)	Duration	Number subjects	Symptomatology and physiology	Performance	Ref.
41	5.4	12 min.	24		Significant ↓ in flicker fusion frequency and alpha blocking.	42
41	5.4	15 min.	65	Vt ↑ from control 600 to 1,600 cc. r.r. ↑ from control 10 to 15 breaths/min. $P_{A_{CO_2}}$ ↑ 9 mm. Hg. V ↑ from control 10 to 19-20 liters/min.		43
53	7.0	40-90 min.	7	Arterial P_{CO_2} from control 39 to 53 mm. Hg. Arterial pH from control 7.42 to 7.31. Serum bicarbonate from control of 24.4 to 25.9 mEq./liter. Mild headaches and burning eyes.		4
76	10.0	15-25 min.	7	Restless, confused, progressive listlessness. Arterial pH from control 7.42 to 7.17. Arterial P_{CO_2} from control 39 to 78 mm. Hg. Serum bicarbonate from control 24.4 to 27.3 mEq./liter.		4

of 12 mm. Hg, no differences were noted in the expiratory minute volume ($\dot{V}_E$ liters/min.) when compared to air breathing control values. With light exercise, however, the minute ventilation increased from a control value of approximately 15 to 20 liters/min. when the subjects breathed the carbon dioxide mixture.

Many studies have been performed recording the effects of 15 mm. Hg inspired P_{CO_2}. Lindhard noted a small increase in respiratory rate with the $P_{A_{CO_2}}$ remaining at 38 mm. Hg. Schneider and Truesdale (51) recorded increases in respiratory minute volume from a control value of 6.7 to 11.3 liters/min. with an increase in tidal volume of approximately 200 cc. and an increase in the respiratory rate of 2 to 3 breaths per minute. Studies on 33 subjects by Lambertsen (32) recorded an increase of 2 to 3 liters/min. in respiratory minute volume and an overall increase in alveolar partial pressure of carbon dioxide of 2 to 3 mm. Hg. It is of interest that at levels of 15 mm. Hg, many subjects in these studies were unaware that they were breathing an abnormal gas mixture.

In 1927 Bronk and Gesell (5) and Schmidt (50) noted the vasodilator action of elevated levels of arterial carbon dioxide by showing increased cerebral blood flow in animals. Utilizing the nitrous oxide method, Kety and Schmidt (27) proved the relationship of increased arterial P_{CO_2} and increased cerebral blood flow in man. Sophisticated investigations by Patterson and co-workers (36) showed the threshold response of cerebral blood flow to elevated arterial carbon dioxide. Utilizing 7 patients and 5 normal volunteer subjects breathing a $P_{I_{CO_2}}$ of 19 mm. Hg (2.5%), the following was noted: Arterial pH declined from a control value of 7.44 to a value of 7.39; arterial P_{CO_2} rose from a level of 38.4 to 42.5 mm. Hg. No significant changes were noted in cerebral blood flow as measured by the nitrous oxide technic.

At an inspired P_{CO_2} of 21 mm. Hg more marked respiratory responses are noted. In twenty subjects (51), the respiratory minute volume increased by 9 liters/min. while the tidal volume was almost doubled. In the early phases of a chronic hypercapnia study (19), the mean change in arterial pH in 7 subjects decreased from a control value of 7.40 to 7.37 units. It is of interest to note that at an inspired P_{CO_2} of 21 mm. Hg, most subjects are aware

of an increased rate of breathing (9, 19). At this level, Gellhorn and Spiesman (17) have noted small losses in threshold of hearing at 128, 2048, and 4096 cps.

In a study referred to earlier, Schaefer (43) noted a marked variability to breathing carbon dioxide with P_{ICO_2}'s at 21 mm. Hg and above. He noted two distinct groups, one insensitive to moderate levels of CO_2 and the other group being sensitive by responding with greater respiratory rates and respiratory minute volume. At a P_{ICO_2} of 21 mm. Hg, a 3 to 5 mm. Hg increase of P_{ACO_2} was noted in conjunction with an increase in tidal volume ranging from 400 to 500 cc.

In another experiment (16) carried out at a P_{ICO_2} of 26 mm. Hg, the expiratory minute volume ($\dot{V}E$) increased from a control value of 7.5 to 10 or 11 liters/min. This was marked increased with moderate exercise from a control value of 15 up to 25 liters/min. No excessive problems were noted with this exercise program. In the second part of a cerebral blood flow study by Patterson et al. (36), subjects breathed a gas mixture with an inspired P_{CO_2} of 27 mm. Hg. At this level, mean arterial pH's changed from a control value of 7.40 to 7.35 accompanied by an increase in arterial P_{CO_2} from 39.4 to 44.7 mm. Hg. At a P_{ICO_2} of 27 mm. Hg, an increase in cerebral blood flow of 19% was first noted, thus placing the threshold of cerebrovascular dilation somewhere between P_{ICO_2} of 19 and 27 mm. Hg.

At a P_{ICO_2} of 30 mm. Hg, greater increases are noted in respiratory minute volume and alveolar partial pressure of carbon dioxide. An increase from a control value of 7 to 16 liters/min. was noted for the former and an increase of 5 to 6 mm. Hg for the latter (51).

In 1952 White and colleagues (61) reported studies done on 31 subjects at a P_{ICO_2} of 38 mm. Hg. In 42 instances out of the 50 man-exposures, the beginning of CO_2 breathing was subjectively noted by taste or smell. The remainder detected the increased CO_2 by increased respiratory response. About 50% of the subjects noted headaches and sweating in the experimental atmosphere. In this study the tidal volume increased from a mean control of approximately 500 cc. to a value of 1,600 cc. At the same time, the ventilation increased from control values of 10 liters/min. to 28 to 32 liters/min.

As reported by Altschule and Sulzbach (2), Price (37), and others, an increase in cardiac output is noted with elevated levels of inspired CO_2 if they are in the neighborhood of 45 to 50 mm. Hg. It is also reported that cardiac arrhythmias do not occur until the arterial P_{CO_2} is almost twice that of normal controls (37).

No discussion of acute hypercapnia studies would be complete without a brief review of some work by Brackett et al. (4). In this study seven volunteers tolerated $P_{I_{CO_2}}$ of 55 mm. Hg for 40 to 90 minutes and $P_{I_{CO_2}}$ of 76 mm. Hg for 15 to 25 minutes. Acid-base studies were performed to describe quantitatively how the body fluid pH is defended with acute increases in P_{CO_2}. Arterial P_{CO_2}'s showed an increase from a control value of 39 to 53 mm. Hg while breathing the first gas mixture and an increase to 78 mm. Hg during the second phase of the experiment. The pH of the serum went from a control of 7.42 down to 7.31 and finally 7.17. Analysis of data revealed modest buffering by endogenous bicarbonate stores with a linear relationship of H^+ concentration/P_{aCO_2}. It was found that for every millimeter of mercury increase in arterial P_{CO_2}, there was an increase in H^+ concentration of 0.77 nM. Similar studies carried out chronically in dogs (52) have shown this H^+/P_{aCO_2} relationship to increase only 0.33 nM. H^+ for every increment of 1 mm. P_{aCO_2}. The lower slope noted in the chronic dog studies is felt to be secondary to renal mechanisms and acid excretion which become operational after several days of hypercapnia.

Performance

A review of table I shows a paucity of performance studies to review in hypercapneic situations. In an attempt to quantitate the excitability of the central nervous system and other psychophysiologic parameters, Schaefer and Carey (46) utilized flicker fusion frequency and alpha blocking as noted on EEG. At an inspired P_{CO_2} of 11 mm. Hg, no significant changes were noted in 25 subjects tested.

Two different studies (9, 19) utilizing 11 subjects were carried out for prolonged periods of time at a $P_{I_{CO_2}}$ of 21 mm. Hg. No performance degradation was noted when studied in the acute phases. The Neptune Task System (20, 21) was utilized which

included test parameters of vigilance, arithmetic, tracking, memory, and problem solving.

At 25 mm. $P_{I_{CO_2}}$ (approximately 3.3%) questionably significant changes are first noted in studies of flicker fusion frequency and alpha blocking (46). At a $P_{I_{CO_2}}$ of 38 mm. Hg, Simonson and Winchell (56) reported a definite decrease in frequency of flicker fusion within 12 minutes after the subjects began breathing the experimental gas. The questionable significance of relating these findings to man's ability to perform a given task becomes apparent when reviewing a study by White et al. (61). Utilizing an identical $P_{I_{CO_2}}$ of 38 mm Hg, no significant errors were noted in 19 subjects performing numerous card-sorting tasks. These studies were carried out over a 16-minute period.

In an experiment similar to Simonson's, Schaefer and Carey (46) studied flicker fusion frequency and alpha blocking at an inspired P_{CO_2} of 41 mm. Hg. In this study the respiratory minute volume increased from 10 to a value of 20 liters/min. with an associated increase in $P_{A_{CO_2}}$ of 9 to 10 mm. Hg. Alpha blocking time was prolonged and flicker fusion frequency decreased. The authors concluded through hyperventilation studies that the changes were due to the elevated P_{CO_2} and not to the increased work of breathing.

CHRONIC STUDIES

Because of obvious problems concerned with studying the effects of elevated levels of inspired P_{CO_2} on normal man for prolonged periods, only a small number of studies are available for review. It should be pointed out that two of the longest studies (see text and table II) have been performed by the Russians, and details are quite incomplete concerning physiologic and performance data.

Reports of the American Medical Association in 1940 set acceptable safety limits for chronic exposure to carbon dioxide as not greater than 0.5% (3 to 4 mm. Hg) for a period longer than 8 hours. No performance or physiologic changes have been noted at these low levels.

TABLE II

Chronic studies

P_{CO_2} (mm. Hg)	CO_2 (%)	Duration	Number subjects	Symptomatology and physiology	Performance	Ref.
3.8	0.5	8 hr.		No symptoms. No physiologic change.	No performance degradation.	AMA-1940
7-8	1.0	30 days	2	pH unchanged. Minimal ↑ P_{ACO_2}, total CO_2.	No performance degradation.	62
11-12	1.5	42 days	21	No symptoms. Small ↑ V_T, $\dot{V}$, ↑ P_{ACO_2}, ↑ ketosteroid, minimal ↓ pH.	No performance degradation. Slight ↓ flicker fusion, ↑ alpha blocking.	14
15	2.0	30 days	2	Initial pH change from 7.41-.47 to 7.34-.38. ↑ P_{ACO_2} from 38.5-44 mm. Hg. $\dot{V}$ ↑ by 1.5 to 3.5 liters/min.	?	62
15	2.0	8 hr. daily	Brewery workers	Few symptoms. "Acclimatized."	No decrease in normal work.	24
21	3.0	4 days	8	↑ $\dot{V}$, ↑ ketosteroids, ↑ catecholamines, ↑ HCO_3, ↓ pH for 3 days.	No performance degradation.	9
21	3.0	5 days	7	pH from 7.40-7.36 to 7.40 by 4th day. Tolerated 1-hour exercise. No ↑ 24-hour hydrogen ion excretion.	No performance degradation.	19
23	3.0	3 days	2	↓ CO_2 sensitivity, ↑ P_{ACO_2}, ↑ $\dot{V}$.	—	15

TABLE II (contd.)

P_{CO_2} (mm. Hg)	CO_2 (%)	Duration	Number subjects	Symptomatology and physiology	Performance	Ref.
23	3.0	3-6 days	?	↓ pH compensated 3-4 days.	? impaired attentiveness performance. ? excitation-depression response.	39
38	Up to 5.25%	3-4 days	4-77	Expected changes of ↑ $\dot{V}$, ↑ V_T beginning ↑ cardiac rate. At $P_{I_{CO_2}}$ of 38-40 mm. Hg, $P_{A_{CO_2}}$ = 47-50 mm. Hg. Small ↓ pH.	Some ↓ performance. Judged able to carry on naval tasks .	7

Russian investigators (62) have recently reported a 2-man 30-day study with subjects living in a small chamber with an inspired P_{CO_2} of 7 to 8 mm. Hg. During this experiment the oxygen content of inspired air ranged from 19% to 22% at an average relative humidity of 50%. Physiologic parameters measured included total CO_2, alkaline reserve (Van Slyke), pH, and P_{CO_2} of the blood. Additional studies included alveolar partial pressure of gases and urinary pH, ammonia, bicarbonate, and titratable acidity. Over the 30-day period, a rise of 3 or 4 mEq./liter was noted in total CO_2 (17.9-22.3 mEq./liter and 20.5-23.7 mEq. liter). The blood pH (methods not described) was stated to have remained virtually unchanged while small increases were noted in urinary bicarbonate and ammonia. As expected, small increases were noted in alveolar P_{CO_2} (values not given) while pulmonary ventilation increased by an increment of 0.5 to 1.0 liters/min. Throughout the period of the experiment, frequent recordings of pulse rate, ECG, EEG, blood pressure, breathholding tests, temperature, and body weight were unaltered.

Performance studies were not reported in detail but included conditioned motor reflexes, outlining of geometric figures, and problem solving tasks. There were no changes when compared with controls. Expected changes were noted in cardiovascular function secondary to "deconditioning" (31, 34) or hypodynamia of living in a confined space.

A number of investigators (14, 40, 41, 44, 45) have reported results from a large study utilizing 21 subjects living in an atmosphere with an inspired P_{CO_2} of 11 to 12 mm. Hg. The volunteer subjects lived in this environment for 42 days with a 9-day control period before and after the experiment. A large number of physiologic, psychiatric, and psychomotor studies were performed and will be briefly reviewed.

Numerous measurements failed to show any change in oral temperature, body weight, blood pressure, and pulse (14). As expected, the respiratory minute volume was somewhat higher in the CO_2 atmosphere increasing from a control value of 6 liters/min., BTPS, to an experimental value of approximately 7.5 liters/min., while no change was seen in oxygen consumption. During this same period of time, the $P_{A_{CO_2}}$ rose from 38 to 41 mm. Hg (14).

After an initial increase the respiratory rate declined slowly during CO_2 exposure while the tidal volume increased (approximately 150 to 200 cc.) and remained elevated during the followup control period (47). Ventilatory response to breathing 5% (21 mm. Hg) CO_2 was significantly reduced after prolonged exposure to the carbon dioxide atmosphere but returned to initial values 3 to 4 weeks after the study.

Severinghaus et al. (54, 55) have shown that with increasing tidal volume there is an increase in alveolar dead space (nonperfused alveoli). Utilizing differences in alveolar-arterial CO_2 gradients, Schaefer et al. (47) estimated that there was a 4% increase in nonperfused alveoli associated with the increase in tidal volume in this study. This returned to control value 4 weeks after the study.

Several pH studies were carried out purporting to show a state of noncompensated metabolic acidosis for a period of 23 days (49). Studies were carried out on venous samples making them somewhat difficult to compare with other studies. Small changes in plasma calcium (48) were noted to correspond with changes in venous pH and pulmonary CO_2 excretion, possibly indicating a significant role of bone CO_2 stores in acclimatization to carbon dioxide. A very small increase was noted in serum phosphorus throughout the study while no significant changes were seen in sodium and H_2O balance.

Other blood parameters included no change in hematocrit, reticulocyte counts, and white blood cell counts while some decrease was seen in circulating eosinophils. This was probably secondary to an approximate twofold increase in ketosteroid excretion while in the experimental situation from a control of 6.8 mg./liter of urine to 12.4 mg./liter of urine.

Psychomotor and psychiatric studies were legion in number and the reader is referred to the reports by Fawcett and Newman (14) and Eron and Auld (12) for a more detailed review. Sensory and perceptual processes including dark adaptation, visual acuity and accommodation, depth perception, and pitch discrimination were not affected by the elevated levels of carbon dioxide (14). Psychomotor efficiency as measured by the Minnesota Manual

Dexterity Test, letter canceling tests, tests of mechanical ability, coordination, strength, problem solving, and memory did not exhibit any impairment in the experimental atmosphere.

Questionably significant decreases in flicker fusion frequency and increases in alpha blocking time were noted during the second and third weeks of exposure to CO_2 (42). This was interpreted by the author as showing a slight depression of the excitability of the nervous system.

In a second Russian study by Zharov (62) utilizing 2 subjects living in an atmosphere with an inspired P_{CO_2} of 15 mm. Hg, several changes were noted. For example, there was a greater increase in total carbon dioxide in the blood while the $P_{A_{CO_2}}$ rose from a control of 38-39 mm. to 43-46 mm. Hg. In both subjects during the first 15 to 20 days, a drop in blood pH from controls of 7.41-7.47 down to 7.34-7.38 was reported. The authors felt this indicated a period of noncompensated acidosis. Methods were not given for these determinations. Slight EEG changes are reported and it was stated that there was "much more functional tension" and a marked deterioration in ability to perform exercise. No comment is made concerning problem solving, geometric tracing, or any other psychomotor studies.

Although no controlled studies have been performed, Hunter (24), in his book on occupational hazards, discusses brewery employees who worked 8 hours daily in fermentation vats with carbon dioxide levels approximating 15 mm. Hg. Evidently, no decreases have been noted in normal work efficiency presumably secondary to adaptation to the environment.

Several chronic hypercapnia studies have been performed at levels from 21 to 23 mm. Hg P_{CO_2}. Cutler and co-workers (9) successfully exposed 8 subjects to an inspired carbon dioxide partial pressure of 21 mm. Hg in an atmosphere of 700 mm. Hg total pressure and 200 mm. Hg total pressure. Exposure to carbon dioxide lasted 4 days in each case and the response as measured by respiratory, metabolic, and psychomotor studies was the same at each pressure. Inspiratory minute volume increased from control values of 6.3 to 9.9 liters/min. in elevated CO_2 while the $P_{A_{CO_2}}$ increased from 40.6 to 44.3 mm. Hg. A one-third increase was

noted in tidal volume which accounts for the higher inspiratory minute volumes noted. No significant changes were seen in oxygen consumption. Venous blood pH from the brachial vein decreased from 7.39 to 7.33 returning to control values by the third day probably secondary to metabolic compensation. Irrespective of dietary changes there was an effect of carbon dioxide on 24-hour excretions of epinephrine, norepinephrine, 17-hydroxycorticosteroids and corticosterone-like hormones (59). Increased excretion rates were noted for all hormones measured except 17-hydroxycorticosteroids. The author felt that perhaps a 4-day exposure was not long enough to show changes in the latter.

Utilizing the Neptune Task System (20, 21), performance testing included a vigilance task, arithmetic encoding, compensatory tracking, short-term memory, and problem solving. No performance deterioration was noted during this study and operator efficiency was maintained at a remarkably even level.

A second experiment at 21 mm. Pco_2 with a total pressure of 700 mm. Hg was carried out by Glatte et al. (19). Seven subjects were studied for 15 days, 5 days in elevated carbon dioxide bracketed by two 5-day control periods. Physiologic changes were definite and quite similar to those described by Cutler's group. In addition to the usual respiratory measurements, daily arterial pH, Pco_2 and hydrogen ion balance experiments were carried out. A moderate exercise program was also instituted using workloads of 100 w. at 60 r.p.m. for one hour.

An increase of 3 to 4 mm. Hg was seen in alveolar and arterial Pco_2's. Arterial (actually capillary ear bloods) pH dropped initially from control values of 7.40 down to 7.37 units and then reattained near normal values by the third to fourth day as adaptation took place. Despite the relatively high levels of P_{Ico_2}, there was no significant increase in the ammonium excretion or the overall 24-hour hydrogen ion excretion. While on a fixed diet, no significant changes were noted in urine or serum calcium and phosphorus levels. Urinary hydroxyproline studies were carried out on the urine samples as a guide to collagen tissue turnover and to provide an insight into any aberrant bone metabolism brought about in the elevated carbon dioxide (11, 23, 38). Analysis of these data have failed to show abnormalities other than those expected in confinement studies.

Moderate exercise studies were carried out without apparent problems. In conjunct on with the exercise, certain psychomotor tasks (encoding and reactio:: time) showed no changes. The Neptune Task System was again utilized to test performance along with letter canceling and geometric tracing. Statistical analysis of these data fails to show any change from the control periods. In addition, no trends or changes are noted when the acute phase of the experiment is compared with the chronic phase.

Schaefer (39) reports experiences in 3- to 6-day studies at a CO_2 concentration of 3% ($P_{I_{CO_2}}$ of 23 mm. Hg). It was noted that the alveolar CO_2 tension was raised 2 to 3 mm. Hg and the subjects developed a definite decrease in responsiveness to 5% levels of carbon dioxide. Initial decreases in serum pH were returned to normal after 3 or 4 days. In contrast to other studies, the author reports definite decrease in attentiveness as measured by letter canceling tests and changes in other psychomotor parameters such as hand steadiness and chronaxie measurements. A definite biphasic reaction to CO_2, that is a period of excitation followed by depression, was also noted. Similar findings have not been reported in other studies. Unfortunately, complete data concerning the above studies by Schaefer have not been translated from German, and it has been necessary to utilize various incomplete references to the study.

In a paper devoted to the physiology of abnormal gas environments, Fenn (15) reports a study consisting of 2 subjects confined in 23 mm. Hg P_{CO_2} for 3 days. No note was made concerning blood or psychomotor studies. A definite decrease in sensitivity to carbon dioxide was noted as judged by the rate of ventilation and alveolar carbon dioxide tension.

In the experiments with a carbon dioxide partial pressure of 21 to 23 mm. Hg, almost all subjects were quite aware of an increased respiratory rate. This was not marked enough to interfere with normal daily functions. Other than mild dyspnea, symptomatology was mainly limited to mild to moderate frontal headaches lasting from 2 to 24 hours following the onset of CO_2 exposure.

Finally, Consolazio et al. (7) performed a number of studies over 3- to 4-day periods with CO_2 buildup and varying levels of

oxygen tension. Exposures in atmospheres with carbon dioxide concentrations up to 38 mm. Hg (5%) did not seriously impair the physical condition and efficiency of the subjects as measured by biochemical, physiologic, and psychologic tests. As expected, respiratory rate, respiratory minute volume, and tidal volume increased markedly with the high CO_2 levels. Alveolar P_{CO_2}'s increased from 40 mm. Hg to 46-49 mm. Hg with parallel increases in total CO_2. There was no significant effect upon visual and auditory parameters. Similarly, no changes were noted in paper and pencil test scores. The eye-hand coordination tests showed a slight decline in most cases. The hand dynamometer scores dropped from 3% to 10% in well-practiced subjects. Mild increases in body sway were thought to be secondary to the heavy breathing. A similar situation was noted with hand-arm steadiness tests. Despite some of the mild changes seen in the various performance tests, the authors felt that all personnel were quite able to carry on any usual Naval tasks.

DISCUSSION AND SUMMARY

From the foregoing review of pertinent acute and chronic studies dealing with varying levels of carbon dioxide, table III has been constructed to predict expected physiologic and performance changes. Note that up to approximately 6 mm. Hg inspired P_{CO_2}, no symptomatic, physiologic, or performance differences are expected. Studies performed at 7 to 8 mm. Hg carbon dioxide have shown only minor respiratory changes including slight increases (up to 24%) in respiratory minute volume and minimal alveolar P_{CO_2} differences. No significant pH changes are recorded as endogenous buffers are effectively utilized. After 10 to 15 days, respiratory parameters all returned to control values except the slightly elevated $P_{A_{CO_2}}$. No performance changes have been noted at this level and include measurements of problem solving, mild exercise, and psychomotor studies

Short- and long-term studies carried out at carbon dioxide partial pressures of 8 to 13 mm. Hg have revealed increasing but still minimal physiologic shifts. Subjects are asymptomatic with small increases in respiratory minute volume, tidal volume, and $P_{A_{CO_2}}$. Questionable changes in central nervous system "excitability" have been noted and are probably of little importance

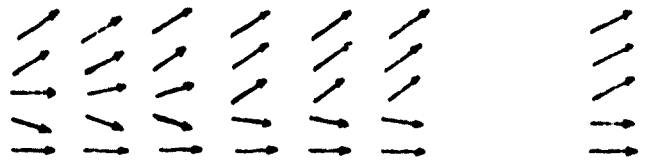
TABLE III

ACUTE AND CHRONIC EFFECTS OF HYPERCAPNIA

Ambient P_{CO_2} mm Hg		4 Hrs	1 Day	2 Day	3 Day	4 Day	5 Day	---------- 30 Day
4-6	Lung: r.m.v. t.v. P_{ACO_2}	No						
	Blood: Total CO_2 pH		Physiologic,					
	Kidney: 24 Hr H^+ excretion							
	Central Nervous System:			Symptomatic				
	Symptoms:							
	Performance:						Performance	
7-8	Lung: r.m.v. t.v. P_{ACO_2}	→	→	→	→	→	→	→
	Blood: Total CO_2 pH	→	→	→	→	→	→	→
	Kidney: 24 Hr H^+ excretion	→	→	→	→	→	→	→
	Central Nervous System:	No Changes						
	Symptoms:	Few aware of any symptomatology						
	Performance:	No degradation ----------						

8-13

- Lung: r.m.v., t.v., $P_{A_{CO_2}}$
- Blood: Total CO_2, pH
- Kidney: 24 Hr H^+ excretion
- Central Nervous System: Beginning questionable change flicker fusion frequency.
- Symptoms: No symptoms
- Performance: No degradation

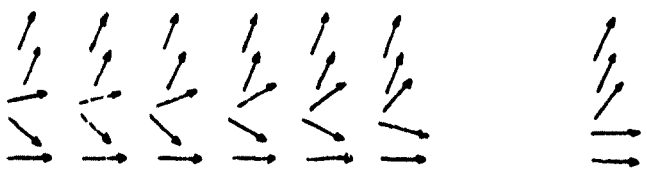


14-15

- Lung: r.m.v., t.v., $P_{A_{CO_2}}$
- Blood: Total CO_2, pH
- Kidney: 24 Hr H^+ excretion
- Central Nervous System: Minor EEG changes
- Symptoms: Few symptoms. Some aware of increased rate and depth of breathing.
- Performance: Probably no performance degradation----------

19-21

- Lung: r.m.v., t.v., $P_{A_{CO_2}}$
- Blood: Total CO_2, pH
- Kidney: 24 Hr H^+ excretion
- Central Nervous System: Nearing threshold for cerebral blood flow changes.
- Symptoms: Aware of increased rate & depth of breathing.
- Performance: Most studies do not show performance degradation.



(e.g., decreased flicker fusion frequency). Extensive psychomotor testing has failed to reveal significant change. Exercise studies performed at 12 mm. Hg $P_{I_{CO_2}}$ showed a rather marked increase in ventilation over controls as opposed to only minor differences in the resting state.

At 14 to 15 mm. Hg ambient P_{CO_2}, more prominent changes are seen in both respiratory and metabolic parameters. Pulmonary changes include an increase in the $P_{A_{CO_2}}$ of 2 to 3 mm. Hg with a 200 cc. increase in tidal volume and a small increase in respiratory rate. One long-term study has shown initial decreases in serum pH which becomes compensated during the experiment. At these levels of $P_{I_{CO_2}}$, some subjects become aware of increased rate and depth of breathing while others do not. No definite changes have been reported in performance studies; however, the Russian experience was incompletely reported.

Increased respiratory minute volume, $P_{A_{CO_2}}$ (3 to 4 mm. Hg) and tidal volume are noted at $P_{I_{CO_2}}$'s of 21 mm Hg. Definite small decreases are noted in pH which becomes compensated in 3 to 4 days. Increased excretion rates are noted for ketosteroids, 17-hydroxycorticosteroids, and catecholamines while no changes are noted in 24-hour hydrogen ion excretion. Most studies measuring performance have failed to note any differences when control experiments are compared with those carried out in high carbon dioxide levels.

The review of the foregoing studies of manned experience with elevated levels of carbon dioxide enable one to set realistic tolerance limits. These limits are briefly outlined.

Certainly, no difficulties would be encountered up to 6 mm. Hg ambient P_{CO_2} as no physiologic or performance changes are noted. In view of this it would seem proper that no problems would develop with very long exposure (greater than 30 days).

Experience has shown us that $P_{I_{CO_2}}$'s of 7 to 8 mm. Hg are quite acceptable for periods up to 30 days. Here, small changes in respiratory measurements are seen while other parameters are stable. A similar situation is seen with 11 to 12 mm. Hg ambient P_{CO_2} as was shown by the 42-day study, "Operation Hideout" (14).

As one approaches 15 mm. Hg ambient P_{CO_2}, changes are seen not only in respiratory parameters but also acid-base status. Performance studies are acceptable at this level for short periods. It would seem proper, therefore, to establish 15 mm. Hg ambient P_{CO_2} as the maximum tolerable level in spacecraft standards and, further, that this level should not be a design point, but should be an upper limit for relatively short exposures.

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