# CARBON DIOXIDE TOLERANCE STUDIES

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## FOREWORD

This work was done in the Environmental Systems Branch under AF task No. 793002 and NASA contract No. T-41829-G. The study was accomplished during 1966, and the paper was submitted for publication on 14 June 1967.

The cardiotachometer used in this study was constructed in the Biomedical Engineering Branch.

This report has been reviewed and is approved.

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## ABSTRACT

Seven normal volunteers were exposed to an environment of 21 mm. Hg $CO_2$ (3%) for a 5-day experimental period bracketed by two 5-day control periods. Measurements included daily serum and urine electrolytes, blood gas studies, and net acid excretion studies. Also included were detailed investigations of respiratory physiology, exercise response, and psychomotor performance. All subjects tolerated the experimental atmosphere with no undue problems. Arterial and alveolar $P_{CO_2}$'s increased 3 to 4 mm. Hg with a mild reduction in arterial pH from 7.40 to 7.37. Arterial pH values returned to near control values by the fourth day. No increases were noted in net acid excretion. Exercise was tolerated remarkably well.

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## I. INTRODUCTION

With the advent of submarine and aerospace research, the problems of carbon dioxide removal and man's ability to perform adequately in varying levels of carbon dioxide have become paramount. Numerous studies have been carried out in man with acutely elevated levels of carbon dioxide (2, 4, 6, 20, 25). Owing to obvious problems, studies of man in chronically elevated carbon dioxide environments are less numerous.

Problems of importance to the aerospace investigator in studying chronic hypercapnia pertain mainly to respiratory, acid-base, and psychomotor performance parameters. A brief résumé of manned experience in chronically elevated levels of carbon dioxide is presented in table I. These studies comprise the sum total of chronic $CO_2$ exposure utilizing normal man as test subjects. Several of these studies by Schaefer and coworkers (38, 44, 45, 47) have been carried out in submarine environments with one of 42 days' duration being conducted at 12 mm. Hg ambient $P_{CO_2}$ (1.5%). Many of the aspects of this study were excellent; however, methodology was not adequately described and some of the data (acid-base changes) disagree with most reports in the literature. A very extensive psychomotor program of testing failed to reveal any performance degradation. Earlier studies by this group at levels of 21 to 23 mm. Hg ambient $P_{CO_2}$ (3%) showed some changes in psychomotor performance (39). These changes are questioned at this time as no adequate controls were available, and there was no knowledge of possible contaminant buildup which could have greatly influenced the results. A 4-day study by Cutler and associates (5) at the same level of carbon dioxide failed to reveal any performance degradation. Two other studies have been conducted by the Russians, who reported them in a very incomplete manner (59). Thus, owing to the paucity of chronic data available, the need for more comprehensive carbon dioxide investigations is obvious.

TABLE I

*Chronic hypercapnia studies*

| $CO_2$ (%) | $P_{CO_2}$ | Duration (days) | Investigator | |
|---|---|---|---|---|
| 1.0 | 7-8 | 30 | Russia | (59) |
| 1.5 | 11-12 | 43 | U.S. Navy | (8) |
| 2.0 | 15 | 30 | Russia | (59) |
| 3.0 | 21 | 5 | U.S. Air Force | (5) |
| 4.0 | 31 | 5 | U.S. Air Force | (14) |
| 5.3 | 38 | 3-4 | U.S. Navy | (3) |

The following study was designed to provide additional data in this area by determining the effects of 21 mm. Hg ambient $P_{CO_2}$ on normal man. An effort was made to assess acid-base metabolism with the best available methodology, which will be reported in detail. The opportunity was also taken to study psychomotor performance. In addition, exercise studies were carried out with simultaneous simple reaction control and memory tasks to give some insight into psychomotor performance with exercise.

## II. SUMMARY

Seven normal male volunteers have successfully lived for a period of 5 days in a space cabin simulator with an ambient $P_{CO_2}$ of 21 mm. Hg (3% $CO_2$ at sea level). Physiologic studies indicated that the atmosphere was only

a mild challenge to acid-base adaptive mechanisms. Induced respiratory acidosis was almost completely compensated by the fourth to fifth day. No subject showed evidence of a prolonged uncompensated acidosis. Minute ventilation was increased approximately 2.5 liters/min. along with a 3 to 4 mm. Hg elevation in arterial and alveolar $P_{CO_2}$. This was easily tolerated. No abnormalities were noted in pulmonary function testing. There was no suggestion of abnormalities of mineral metabolism. Serum and urine calcium and phosphorus remained normal. Hydroxyproline studies failed to denote abnormal parathyroid activity. A full hour of moderate exercise was carried out several times during the study. These exercise periods were always completed and tolerated well. Repetitive psychomotor and psychologic testing was done daily. No decrements were noted in any of these studies and would indicate that the $CO_2$ atmosphere had no adverse effects. It was concluded that a 5-day exposure to 3% $CO_2$ was easily adapted to and failed to adversely affect moderate exercise ability, psychomotor performance, or mineral metabolism.

## III. MATERIALS AND METHODS

### Study format

All 7 subjects were normal airmen volunteers selected from the Lackland AFB Basic Training Facility. They were selected after an interview with the principal investigator and review of past records. Table II lists the subjects' vital statistics. The study was originally planned for 8 subjects; however, during the control period of the first study, 1 subject with acute tonsillitis had to be removed from the chamber.

After selection, the subjects underwent a detailed history, physical examination, posteroanterior and lateral chest x-rays, and 12-lead electrocardiogram. Before final selection, all candidates had a detailed survey of blood and urine chemistries. Metabolic and acid-base determinations are listed in table III. Table IV lists liver function, hematology, and renal studies performed.

These studies were conducted in a 4-man space simulator altitude chamber at the USAF School of Aerospace Medicine. Carbon dioxide was monitored by a Beckman LB-1 infrared $CO_2$ analyzer; oxygen, by a Beckman F-3 analyzer; and nitrogen, by a Med-Science nitralyzer 300 AR. Calibration of all instruments was carried out every 12 hours by use of standards verified by gas chromatography. Readings were taken every 15 minutes. Table V lists the average environmental conditions during both phases of this study, which was broken down into substudies I and II.

The volunteer subjects in the two groups were studied for 15 days while living in the space simulator. The study plan was outlined as follows: control, 5 days; experimental, 5 days; and recovery, 5 days.

TABLE II

*Vital statistics of subjects*

| Initials | Subject No | Age | Height (in.) | Weight (lb.) | Surface area ($m.^2$) | Education |
|---|---|---|---|---|---|---|
| D. H. | 1 | 19 | 71 | 198 | 2.11 | High school graduate |
| R. L. | 2 | 21 | 71 | 158 | 1.91 | 2 years of college |
| C. O. | 3 | 19 | 71 | 160 | 1.92 | 1½ years of college |
| T. A. | 4 | 18 | 64 | 129 | 1.62 | High school graduate |
| A. C. | 5 | 19 | 71½ | 161 | 1.94 | 2 years of college |
| D. K. | 6 | 19 | 73 | 155 | 1.92 | High school graduate |
| K. S. | 7 | 23 | 71½ | 186 | 2.05 | College graduate |

TABLE III

*Metabolic studies*

| | |
|---|---|
| Blood | |
| a. Venous Na, K, Cl, $CO_2$, Ca, Mg, P, creatinine | Daily |
| b. "Arterialized" $P_{CO_2}$, pH on capillary blood | |
| Urine | |
| a. Na, K, Cl, Ca, Mg, P, creatinine | 24-hr. excretion |
| b. $NH_4^+$, $HCO_3^-$, titratable acidity, pH | |
| c. 24-hour hydrogen ion excretion | |
| $NH_4^+ + T.A. - HCO_3^- = 24\ H^+$ excretion | |

TABLE IV

*Miscellaneous studies*

Liver function
- Bilirubin
  - Direct
  - Indirect
- SGOT
- SGPT
- Alkaline phosphatase
- Total protein
- Serum protein electrophoretic study

Hematology
- Hemoglobin
- Hematocrit
- Red blood cell count
- Red cell morphology
- White blood cell count with differential
- Reticulocyte count

Renal
- BUN
- Serum creatinine
- Urine creatinine
- Creatinine clearance
- Renal sediment exam
- Urine culture

To assure a seal on the chamber, the entire study was carried out at a total pressure of 700 mm. Hg. During the control phases of the study the partial pressure of carbon dioxide ($P_{CO_2}$) was nominal, while during the experimental phase the ambient $P_{CO_2}$ was maintained at 21 mm. Hg. Because of the known stimulatory effect the elevated $P_{CO_2}$ has on respiratory minute volume, the partial pressure of oxygen ($P_{O_2}$) was reduced during the experimental phase of the study in order to maintain normal alveolar $P_{O_2}$'s (9). In this manner, the only experimental variable was elevated carbon dioxide.

The transition from low to high $CO_2$ partial pressures occurred over a 6-hour period from 0200 to 0800 hours while the subjects were sleeping. The subjects were not told when the carbon dioxide was increased.

To insure a stable, steady-state excretion of hydrogen ion and electrolytes, the subjects ate a prepared liquid diet (SMBP-D-10) which contained approximately 2,600 calories and was adequate in carbohydrates, fats, and protein. The diet also provided approximately 100 mEq. NaCl per day and 30 mEq. $K^+$ per day.

Figure 1 is a schedule of the daily activities throughout the test. On the 6 days of exercise studies, psychomotor testing hours were changed. Two exercise studies were performed in the morning and two immediately after lunch. Exercise was completed by 1500 hours.

**Blood studies**

Free-flowing venous blood samples were drawn from antecubital veins daily during the fasting period. Determinations included $Na^+$, $K^+$, $Cl^-$, total $CO_2$, $Ca^{++}$, $Mg^{++}$, P, and creatinine. Serum $Na^+$, $K^+$, creatinine, and phosphate were determined using automated technics (11, 16, 56). A Cotlove titrator was utilized for serum chlorides, and total $CO_2$ was determined by the automated method of Skeggs (52). Initially, samples were split and total $CO_2$ was compared with this procedure carried out in the classic Van Slyke manometric

TABLE V

*Environmental conditions (period means)*

| Conditions | Study I | | | Study II | | |
|---|---|---|---|---|---|---|
| | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 |
| Total pressure (mm. Hg) | 696.2 | 699.6 | 699.2 | 699.3 | 699.9 | 699.7 |
| $P_{O_2}$ (mm. Hg) | 157.4 | 136.1 | 156.7 | 157.0 | 136.2 | 156.3 |
| $P_{CO_2}$ (mm. Hg) | 4.4 | 21.4 | 1.6 | 2.1 | 21.4 | 1.3 |
| $P_{N_2}$ (mm. Hg) | 540.5 | 535.6 | 543.2 | 546.4 | 544.4 | 549.7 |
| Temperature (° C.) | 22.7 | 23.2 | 23.3 | 22.9 | 22.1 | 22.9 |
| Relative humidity (%) | 48.3 | 46.7 | 47.6 | 49.7 | 53.7 | 52.0 |

| | SUBJECT #1 | SUBJECT #2 | SUBJECT #3 | SUBJECT #4 |
|---|---|---|---|---|
| 0730 | ----------Basal Respiratory Studies---------- | | | |
| 0800 | ----------EKG---------- | | | |
| 0830 | ----------Blood Studies---------- | | | |
| | ----------Liquid Diet---------- | | | |
| 0900 | Psychomotor Testing | | | |
| 0930 | | Psychomotor Testing | | |
| 1000 | | | Psychomotor Testing | |
| 1030 | | | | Psychomotor Testing |
| 1100 | ----------Hygiene---------- | | | |
| 1200 | ----------Liquid Diet---------- | | | |
| 1300 | | | | |
| 1400 | Psychomotor Testing | | | |
| 1430 | | Psychomotor Testing | | |
| 1500 | | | Psychomotor Testing | |
| 1530 | | | | Psychomotor Testing |
| 1600 | | | | |
| 1700 | ----------Liquid Diet---------- | | | |
| 1800 | | | | |
| 1900 | Psychomotor Testing | | | |
| 1930 | | Psychomotor Testing | | |
| 2000 | | | Psychomotor Testing | |
| 2030 | | | | Psychomotor Testing |
| 2100 | | | | |
| 2200 | ---------- Liquid Diet---------- | | | |
| 2300 | ----------Sleep---------- | | | |

FIGURE 1

*Daily activities schedule.*

method. The automated technic varied approximately ± 1.0 mEq./liter from the classic method. Calcium and magnesium were determined by methods developed in-house on the Perkin-Elmer atomic absorption spectrophotometer.

On selected days hematologic studies were performed on oxalated blood by standard technics. These determinations included microhematocrit, hemoglobin, red blood cell count, white blood cell count and differential, smear for cell morphology, and a reticulocyte count. As shown in table IV, liver function studies were also carried out periodically during the study. Direct and indirect bilirubin was measured by the method of Malloy and Evelyn (28), and SGOT and SGPT enzymes by the Sigma-Frankel technic (50). Alkaline phosphatase determinations were carried out by an automated modification of the King-Armstrong method (22). Total protein and electrophoresis were determined using the Spinco paper electrophoresis method. Finally, in the miscellaneous category, blood sugar was determined by the method of Hoffman (18) and blood urea nitrogen by the automated method of Skeggs (51).

To assess arterial acid-base parameters, blood was collected from the ear lobes of the subjects. The capillary bed was "arterialized" by heating the ear lobe to approximately 45° C. A deep puncture was then made with a No. 11 Bard-Parker blade on a modified handle. Free-flowing "arterialized" blood was collected anaerobically in heparinized capillary tubes (60 µl.) containing a small metal filing, sealed with clay and mixed with a magnet. These samples were then placed on ice, and pH and $P_{CO_2}$ determinations were carried out in duplicate on the Radiometer AME-1 Astrup machine (19) within 30 minutes of collection. The efficacy of capillary ear blood equating with arterial blood is well supported in the literature (12, 13, 27), as long as the sample is from a properly heated capillary bed and is free-flowing.

### Urine studies

Urine specimens (24-hour) were collected daily in constantly refrigerated bottles containing thymol and a layer of mineral oil. Urine $Na^+$, $K^+$, $Cl^-$, phosphate, $Ca^{++}$, $Mg^{++}$, and total $CO_2$ ($HCO_3^-$) were carried out by the methods described. Urine pH was determined with the Astrup AME-1 pH machine; titratable acidity (T. A.) was calculated using blood and urine pH and phosphate by the method described by Pitts (33). Urinary ammonium ($NH_4^+$) was determined by the automated method of Logsdon (26). All urine variables were reported in milliequivalents excreted per 24 hours. In this manner, 24-hour hydrogen ion ($H^+$) excretions could be calculated utilizing the following equation:

$$NH_4^+ + \text{T. A.} - HCO_3^- = \text{24-hr. } H^+ \text{ excretion (36).}$$

In addition to the above studies, all subjects underwent a urine culture before selection to rule out the possibility of a urinary tract infection with urea-splitting organisms which would affect the urinary ammonium excretion. Careful urine sediment examinations were done at selected intervals and daily 24-hour urine protein excretion was approximated utilizing standard technics. Table VI lists the normal values for this laboratory and the standard deviation of determinations carried out. As the subjects were on a diet containing very little hydroxyproline, 24-hour urine specimens were evaluated for this amino acid to give some insight into mineral metabolism and parathyroid activity (7, 21, 23). Hydroxyprolines were determined by an automated modification of Woessner's technic (58).

### Basal cardiopulmonary studies

Table VII lists the cardiac and respiratory studies carried out during the test and the frequency of determinations. Basal respiratory studies were carried out with the subjects fasting and recumbent after a 9-hour sleep period. Expiratory minute volume was calculated from a 4-minute collection in a Douglas bag with volumes measured in a Tissot spirometer. Respiratory rate was sensed by a pressure transducer and recorded on a Sanborn recorder. End tidal air (alveolar air) was collected daily using the Rahn sampler technic. Samples of alveolar air, expired air, and cabin atmosphere

## TABLE VI

*Laboratory methods*

| Test | Procedure | S.D. | Equipment |
|---|---|---|---|
| Calcium | Technics developed in-house. | ± .36 mg./100 ml. | Atomic absorption spectrophotometer |
| BUN | Skeggs, L. T. (51). | ± .49 mg./100 ml. | AutoAnalyzer |
| Creatinine | Modification of Folin-Wu technic (16, p. 506). | ± .08 mg./100 ml. | AutoAnalyzer |
| P | Modification of Fiske and Subbarow Method (11). | ± .19 mg./100 ml. | AutoAnalyzer |
| Na | AutoAnalyzer method N-20A Technicon Laboratory. | ± 1.36 mEq./liter | AutoAnalyzer |
| K | *Ibid.* | ± .11 mEq./liter | AutoAnalyzer |
| Cl | Cotlove titrator. | ± 1.08 mEq./liter | Cotlove titrator |
| Total protein | Biuret (modified). | ± .06 gm./100 ml. | Model B spectrophotometer |
| Mg | Technics developed in-house. | ± .15 mg./100 ml. | Atomic absorption spectrophotometer |
| Electrophoresis | Spinco paper eletcrophoresis instruction manual. | ± .11 gm. albumin | Spinco |
| | | ± .05 gm. $a_1$ globulin | |
| | | ± .05 gm. $a_2$ globulin | |
| | | ± .07 gm. B globulin | |
| | | ± .66 gm. G globulin | |
| | | ± .13 A/G ratio | |
| Bilirubin | Malloy and Evelyn (28). | ± .11 mg./100 ml. | Model B spectrophotometer |
| Glucose | Modification of Hoffman technic (18). | ± 2.59 mg./100 ml. | AutoAnalyzer |
| Alkaline phosphatase | Modification of King-Armstrong technic (22). | ± 1.42 units/100 ml. King-Armstrong | AutoAnalyzer |
| SGOT and SGPT | Sigma-Frankel technic (50). | ± 1.68 S. F. units. | Sigma reagents Model B spectrophotometer |

were collected in syringes lubricated with saturated LiCl. Oxygen and carbon dioxide fractions were determined by the Beckman E-2 oxygen analyzer and the Liston-Becker-1 or 15A infrared carbon dioxide analyzer. From the above determinations, tidal volume, $O_2$ consumption, $CO_2$ production, and respiratory minute ventilation could be determined. These are reported in BTPS values. Maximum breathing capacity (MBC), vital capacity (VC), and timed vital capacity (TVC) were determined utilizing standard methods. On the days that the basal respiratory studies were performed, a 12-lead ECG was also done.

**Exercise studies**

Each subject was exercised twice during each control and experimental period. Exercise was carried out for 1 hour on a Collins bicycle ergometer with a 100-watt load at 60 r.p.m. Exercise periods were widely separated to protect against the effects of conditioning, as no preconditioning program was feasible. During the experimental period, subjects exercised the first day (acute hypercapnia) and the last day (chronic hypercapnia) in high $CO_2$. Table VIII lists the time sequences and number of determinations made including pulse response, minute ventilation, $O_2$ consumption, and $CO_2$ production. The pulse rate was continuously monitored by a cardiotachometer, which received its signal from a Sanborn electrocardiogram and recorded heart rate on a beat-to-beat basis from the R-R interval. Miniature Beckman electrodes were positioned on the chest in such a manner to give a maximum positive QRS deflection and insure adequate cardiotachometer recordings. Expired air volumes were recorded with a Franz-Mueller gas meter collecting 0.6% of the expired air in a rubber bag. A Hans-Rudolph low resistant one-way valve was utilized for gas collection. Expired fractions of $O_2$ and $CO_2$ were measured by methods described earlier. From the above data, it was possible to calculate minute ventilation, $O_2$ consumption, and $CO_2$ production.

**Psychomotor testing**

All subjects underwent repetitive testing of several types throughout the study. Before the collection of data, subjects were trained for a time sufficient to insure familiarity with the tasks.

An electronically automated series of tasks were carried out three times daily for 30-minute periods (37). Six tasks are involved in this series of measurements. Arithmetic problems presented in two parts necessitate addition, multiplication, and memory. Pitch, roll, and yaw maneuvers were a simple vigilance task. Satellite tracking measured hand steadiness and compensatory tracking maneuvers. A short-term memory task was included after monitoring and counting flashing lights for 1-minute periods. Another problem-solving task was utilized in reactor control testing, and finally auditory monitoring was

TABLE VII

*Basal cardiopulmonary studies*

| | Cont. 1 | | Exp. | | Cont. 2 | |
|---|---|---|---|---|---|---|
| | Day 2 | 4 | 2 | 4 | 2 | 4 |
| Minute ventilation ($\dot{V}_E$) | X | X | X | X | X | X |
| $O_2$ consumption ($\dot{V}O_2$) | X | X | X | X | X | X |
| $CO_2$ production ($\dot{V}CO_2$) | X | X | X | X | X | X |
| Maximum breathing capacity (MBC) | X | X | X | X | X | X |
| Vital capacity (VC) | X | X | X | X | X | X |
| Timed vital capacity (TVC) | X | X | X | X | X | X |
| 12-Lead ECG | X | X | X | X | X | X |

tested utilizing Morse Code and the proper letter response.

Repetitive psychologic measurements including six tests were carried out daily for 3-minute periods. These tests were so designed that it was impossible to complete the task in the time allotted. They included flexibility of closure (finding 4-letter words in rows of letters), aiming (quantitating hand steadiness), visualization, and number facility utilizing arithmetic addition. Measurements were also made concerning speed of closure (canceling letters in a row of letters) and speed of perception.

In addition to the psychomotor tests described, other tasks were programmed into the bicycle exercise aspects of the study. Each subject rode the bicycle for a 1-hour period twice during control, experimental, and recovery periods. For the last 25 minutes of each bicycle ride, the subjects were given tasks of simple vigilance (light on or off) and a more complex auditory memory task dealing with combinations of letters and numbers.

## IV. RESULTS

As shown by an analysis of variance (54), there was little difference between the two groups in response to elevated carbon dioxide. Because of these findings the results will be reported from the pooled data on the 7 subjects.

### Acid-base studies

Table IX summarizes the period means for each subject with respect to urinary and blood acid-base parameters. It should be understood that each figure represents a mean of five determinations and does not adequately reflect day-by-day trends. As noted earlier, all urinary studies are recorded as milliequivalents per 24 hours so that daily hydrogen ion excretion patterns could be assessed. Inspection of table XI shows the largest changes in arterial pH occur during the acute exposure to carbon dioxide. On the first 2 days of exposure the most marked pH reduction was from 7.40 to 7.35 in subject 2. For all 7 subjects, the overall mean decrease in pH acutely was from 7.40 to 7.37. In the recovery period, the hydrogen ion concentration of the arterialized blood returned to normal. More pertinent daily hydrogen ion changes will be more adequately appraised in tables X and XI. With exposure to the elevated carbon dioxide atmosphere, a moderate increase (approximately 3 to 4 mm. Hg) was seen in the arterialized capillary $P_{CO_2}$'s. Alveolar gas samples collect-

TABLE VIII

*1-Hour exercise protocol*

| Time (min.) | 1-Min. pulse | Minute ventilation ($\dot{V}_E$) | $O_2$ consumption ($\dot{V}_{O_2}$) | $CO_2$ production ($\dot{V}_{CO_2}$) | Psychomotor |
|---|---|---|---|---|---|
| Resting | X | X | X | X | |
| 5 | X | | | | |
| 10 | | | | | |
| 15 | X | X | X | X | |
| 20 | | | | | |
| 25 | X | | | | |
| 30 | | | | | |
| 35 | X | X | X | X | |
| 40 | | | | | |
| 45 | X | | | | X |
| 50 | | | | | |
| 55 | X | X | X | X | |
| 60 | X | | | | |

## TABLE IX

*Acid-base studies (period means)*

| Subject No. | Urine | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | $NH_4^+$ (mEq./24 hr.) | | | T. A. (mEq./24 hr.) | | | $HCO_3$ (mEq./24 hr.) | | | $H^+$ (mEq./24 hr.) | | | $Cl^-$ (mEq./24 hr.) | | |
| | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 |
| 1 | 21 | 20 | 19 | 49 | 44 | 34 | 5.1 | 2.6 | 1.2 | 69 | 61 | 52 | 74 | 41 | 20 |
| 2 | 24 | 24 | 19 | 44 | 45 | 38 | 10.8 | 7.7 | 10.3 | 58 | 61 | 46 | 75 | 79 | 60 |
| 3 | 18 | 16 | 12 | 46 | 38 | 31 | 7.2 | 4.2 | 3.4 | 57 | 49 | 32 | 70 | 58 | 22 |
| 4 | 24 | 22 | 18 | 39 | 31 | 26 | 5.0 | 9.3 | 11.6 | 59 | 46 | 33 | 92 | 80 | 80 |
| 5 | 25 | 27 | 20 | 52 | 55 | 44 | 6.5 | 9.2 | 10.0 | 71 | 73 | 54 | 76 | 94 | 70 |
| 6 | 24 | 22 | 15 | 45 | 44 | 34 | 3.7 | 8.7 | 9.5 | 65 | 57 | 39 | 73 | 96 | 61 |
| 7 | 15 | 12 | 9 | 43 | 35 | 28 | 7.3 | 7.7 | 12.2 | 50 | 39 | 32 | 84 | 78 | 72 |
| Mean | 21.4 | 20.5 | 16.1 | 45.5 | 41.6 | 33.0 | 6.5 | 7.1 | 8.3 | 61 | 55 | 42 | 78 | 75 | 56 |

| Subject No. | Blood | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | pH (arterial) | | | $Pco_2$ (mm. Hg) | | | Total $CO_2$ (mEq./liter) | | | Cl (mEq./liter) | | |
| | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 |
| 1 | 7.40 | 7.37 | 7.41 | 39.7 | 43.3 | 41.1 | 26.5 | 26.3 | 26.2 | 105.0 | 102.2 | 100.2 |
| 2 | 7.40 | 7.37 | 7.41 | 40.7 | 43.6 | 41.2 | 27.2 | 27.6 | 27.2 | 102.5 | 102.5 | 102.0 |
| 3 | 7.40 | 7.38 | 7.40 | 42.4 | 44.9 | 43.3 | 27.8 | 28.2 | 26.9 | 102.5 | 101.0 | 101.0 |
| 4 | 7.39 | 7.36 | 7.40 | 41.0 | 45.2 | 44.0 | 27.3 | 29.1 | 29.2 | 104.5 | 99.5 | 100.9 |
| 5 | 7.41 | 7.38 | 7.40 | 38.7 | 43.0 | 43.0 | 28.3 | 29.6 | 29.4 | 105.5 | 102.3 | 102.4 |
| 6 | 7.38 | 7.38 | 7.39 | 43.0 | 46.8 | 45.2 | 29.4 | 33.1 | 31.5 | 104.7 | 99.5 | 99.9 |
| 7 | 7.40 | 7.38 | 7.39 | 40.7 | 46.8 | 43.2 | 30.0 | 32.3 | 30.8 | 103.5 | 100.3 | 102.2 |
| Mean | 7.40 | 7.38 | 7.40 | 40.8 | 44.9 | 43.0 | 28.1 | 29.5 | 28.7 | 104.5 | 101.3 | 100.8 |

## TABLE X

*Acid-base studies (daily means)*

| | | Cont. 1 | | | | | Exp. | | | | | Cont. 2 | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | Day 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 | 4 | 5 |
| $Pco_2$ (mm. Hg) | Study I | 38.3 | — | 43.0 | — | 41.0 | 41.7 | 42.3 | | 41.7 | 43.0 | 40.7 | 43.0 | 43.3 | 41.7 | 40.7 |
| | Study II | 41.3 | — | 41.3 | — | 40.0 | 45.8 | 4 ..3 | 46.8 | 46.8 | 48.0 | 44.8 | 43.8 | 43.5 | 43.8 | 43.5 |
| | Mean | 40.0 | — | 42.0 | — | 40.4 | 44.0 | 41.7 | | 44.6 | 46.0 | 43.0 | 43.4 | 43.4 | 42.9 | 42.3 |
| Arterial pH | Study I | — | — | 7.40 | — | 7.39 | 7.36 | 7.37 | 7.37 | 7.39 | 7.39 | 7.40 | 7.40 | 7.40 | — | — |
| | Study II | — | — | 7.39 | — | 7.40 | 7.37 | 7.37 | 7.37 | 7.38 | 7.38 | 7.38 | 7.40 | 7.40 | — | — |
| | Mean | — | — | 7.39 | — | 7.40 | 7.37 | 7.37 | 7.37 | 7.38 | 7.38 | 7.39 | 7.40 | 7.40 | — | — |
| Total $CO_2$ (mEq./liter) | Study I | 25.7 | — | 28.0 | — | 27.8 | 26.2 | 24.3 | 27.8 | 28.2 | 30.3 | 27.7 | 27.8 | 26.8 | 27.7 | 24.0 |
| | Study II | 27.5 | 30.2 | 28.6 | — | 28.6 | 31.1 | 32.2 | 30.6 | 32.0 | 29.3 | 31.1 | 31.2 | 28.4 | | 28.4 |
| | Mean | 26.7 | 29.3 | 28.2 | — | 28.2 | 29.0 | 28.8 | 29.4 | 30.0 | 29.7 | 29.6 | 29.7 | 27.7 | | 26.5 |
| Plasma Cl− (mEq./liter) | Study I | — | — | 104.2 | — | 102.5 | 102.0 | — | 101.2 | — | 103.0 | 99.8 | 102.5 | 100.2 | — | — |
| | Study II | — | — | 105.1 | — | 105.5 | 101.4 | — | 101.3 | — | 101.4 | 100.5 | 100.2 | 101.5 | — | — |
| | Mean | — | — | 104.7 | — | 104.2 | 101.5 | — | 101.2 | — | 102.1 | 100.2 | 101.1 | 100.9 | — | — |
| Urine $NH_4$+ (mEq./24 hr.) | Study I | 21.0 | 21.0 | 19.0 | 22.0 | 20.0 | 23.0 | 19.0 | 21.0 | 20.0 | 17.0 | 15.0 | 16.0 | 18.0 | 17.0 | 17.0 |
| | Study II | 22.0 | 20.0 | 22.0 | 23.0 | 23.0 | 23.0 | 22.0 | 21.0 | 20.0 | 18.0 | 15.0 | 15.0 | 16.0 | 17.0 | 15.0 |
| | Mean | 22.0 | 21.0 | 21.0 | 22.0 | 22.0 | 23.0 | 21.0 | 21.0 | 20.0 | 18.0 | 15.0 | 16.0 | 17.0 | 17.0 | 16.0 |
| Urine T. A. (mEq./24 hr.) | Study I | 49.0 | 61.0 | 44.0 | 38.0 | 40.0 | 49.0 | 40.0 | 44.0 | 39.0 | 38.0 | 23.0 | 35.0 | 38.0 | 33.0 | 43.0 |
| | Study II | 55.0 | 41.0 | 45.0 | 37.0 | 46.0 | 45.0 | 36.0 | 39.0 | 48.0 | 39.0 | 28.0 | 34.0 | 35.0 | 33.0 | 36.0 |
| | Mean | 53.0 | 50.0 | 44.0 | 37.0 | 43.0 | 46.0 | 38.0 | 41.0 | 44.0 | 39.0 | 26.0 | 34.0 | 36.0 | 33.0 | 39.0 |
| Urine $HCO_3$− (mEq./liter) | Study I | 4.6 | 5.2 | 9.8 | 11.4 | 7.4 | 4.7 | 5.7 | 4.0 | 5.3 | 4.4 | 11.1 | 2.2 | 2.8 | 6.5 | 2.3 |
| | Study II | 4.5 | 3.3 | 6.9 | 7.5 | 5.9 | 6.7 | 12.5 | 13.1 | 3.7 | 7.7 | 12.6 | 11.0 | 9.4 | 11.0 | 10.2 |
| | Mean | 4.5 | 4.1 | 8.2 | 9.2 | 6.5 | 5.8 | 9.6 | 9.2 | 4.4 | 6.3 | 11.9 | 7.2 | 6.6 | 9.1 | 6.8 |
| H+ excretion (mEq./24 hr.) | Study I | 66.0 | 77.0 | 61.0 | 49.0 | 53.0 | 67.0 | 53.0 | 62.0 | 51.0 | 52.0 | 27.0 | 49.0 | 53.0 | 44.0 | 49.0 |
| | Study II | 73.0 | 59.0 | 60.0 | 52.0 | 63.0 | 60.0 | 46.0 | 50.0 | 64.0 | 50.0 | 39.0 | 38.0 | 41.0 | 39.0 | 41.0 |
| | Mean | 70.0 | 66.0 | 61.0 | 51.0 | 58.0 | 63.0 | 49.0 | 55.0 | 58.0 | 51.0 | 34.0 | 43.0 | 46.0 | 41.0 | 44.0 |

ed during the study confirmed these observations. A small but definite increase was seen in serum total $CO_2$ ($HCO_3^-$) with the exposure to the experimental atmosphere. The mean increase over the experimental period was 1.5 mEq./liter. With the mild increase in total $CO_2$, an expected decrease was seen in the serum chloride of approximately 3 mEq./liter. The mild reduction in serum chloride was not marked enough to determine a definite associated chloruresis.

As shown in table IX, the two main renal acidifying parameters ($NH_4^+$ and T. A.) were unchanged from the first control period through the experimental period. Mean 24-hour $NH_4^+$ excretion during control and experimental periods was 21.4 mEq./24 hours and 20.5 mEq./24 hours, while titratable acidity excretion was stable at 45.5 and 41.6 mEq./24 hours, respectively. As expected, small increases in urinary bicarbonate were noted in both experimental and recovery periods. No significant changes were noted in 24-hour hydrogen ion excretion from control to experimental periods. A definitely significant change was noted in the recovery period with a reduction in hydrogen ion excretion. This overall change was secondary to decreased $NH_4^+$ and T. A. excretions and an increase in bicarbonate in the urine.

To represent more fully day-by-day trends, pertinent acid-base parameters are recorded in table X as *daily* means for flight I and flight II. Note that the increase in $P_{aCO_2}$ is quite prompt on the first day as is the reduction in arterial (capillary) pH. The alveolar $P_{CO_2}$ remains fairly constant through the experimental period, while small increases are noted in serum total $CO_2$. Commensurate with the increases in serum total $CO_2$, arterial pH's returned to near control levels by the fifth day in elevated carbon dioxide. Table XI illustrates individual day-by-day changes in arterial pH. Again, note the prompt but small reduction in arterial pH on day 1 of the experimental period with a gradual return to near control values by the fifth day in high carbon dioxide. It is noteworthy that at no time did the arterial pH deviate outside the accepted normal range.

Figure 2 graphically portrays the prompt rise in $P_{CO_2}$ and fall in arterial pH. The initial reduction in arterial pH is gradually returned to near control values by the fifth day as serum bicarbonate stores increase.

Table XII lists the period means (five determinations) of urine and serum electrolytes for each subject during the control and experimental periods. No significant changes are noted in any of the serum parameters in-

TABLE XI

*Daily arterial pH determinations*

| Subject No. | Cont. 1 | | Exp. | | | | | Cont. 2 | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Day 3 | 5 | 1 | 2 | 3 | 4 | 5 | 1 | 2 | 3 |
| 1 | 7.39 | 7.40 | 7.37 | 7.37 | 7.36 | 7.39 | 7.38 | 7.42 | 7.41 | 7.38 |
| 2 | 7.39 | 7.40 | 7.35 | 7.37 | 7.38 | 7.39 | 7.39 | 7.39 | 7.39 | 7.40 |
| 3 | 7.42 | 7.38 | 7.37 | 7.35 | 7.37 | 7.40 | 7.39 | 7.42 | 7.40 | 7.40 |
| 4 | 7.37 | 7.41 | 7.37 | 7.36 | 7.36 | 7.36 | 7.36 | 7.38 | 7.40 | 7.41 |
| 5 | 7.42 | 7.40 | 7.37 | 7.39 | 7.38 | 7.37 | 7.38 | 7.38 | 7.40 | 7.41 |
| 6 | 7.37 | 7.39 | 7.37 | 7.38 | 7.38 | 7.38 | 7.37 | 7.38 | 7.40 | 7.39 |
| 7 | 7.39 | 7.41 | 7.39 | 7.39 | 7.37 | 7.38 | 7.38 | 7.39 | 7.40 | 7.40 |
| Mean | 7.39 | 7.40 | 7.37 | 7.37 | 7.37 | 7.38 | 7.38 | 7.39 | 7.40 | 7.40 |
| S.D. | ± .02 | ± .01 | ± .01 | ± .02 | ± .01 | ± .02 | ± .01 | ± .02 | ± .02 | ± .01 |

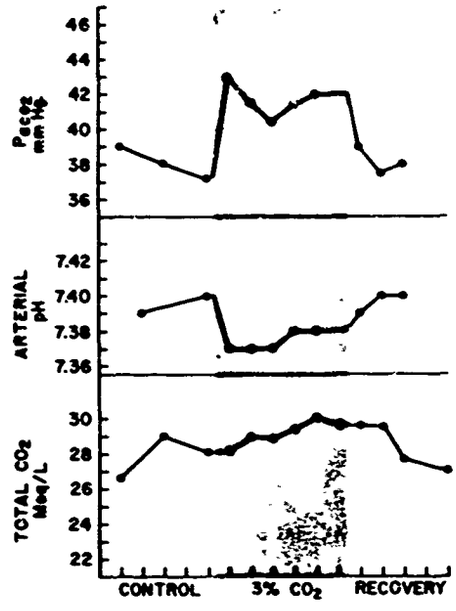


FIGURE 2

*Acid-base studies (mean of 7 subjects).*

cluding serum $Na^+$, $K^+$, and $Ca^{++}$, and P. All values are well within the normal range. Most subjects show little variation in electrolyte excretion patterns throughout the study. Blood sugar, blood urea nitrogen, and serum creatinine determinations were all within normal limits and did not reveal any developing trends.

### Liver function studies

Pertinent liver function studies were followed throughout the experiment at appropriate intervals. As shown in table XIII, there were no abnormal values recorded with respect to bilirubin and protein metabolism. SGOT, SGPT. and alkaline phosphatase determinations were also normal and no developing trends were noted.

### Hematology studies

Red blood cell counts, hemoglobin, hematocrit, and reticulocyte counts are recorded in table XIV. There is a mild reduction in all subjects with respect to hematology parameters. This is felt to be secondary to blood loss during the study as approximately one unit of blood was taken from each subject over the 15-day period. Note the significant increase in the reticulocyte count of subject 7, which

TABLE XII

*Electrolyte studies (period means)*

| Subject No. | Urine | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Na (mEq./24 hr.) | | | K (mEq./24 hr.) | | | Ca (mEq./24 hr.) | | | $PO_4$ (mEq./24 hr.) | | |
| | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 |
| 1 | 81 | 34 | 24 | 65 | 53 | 32 | 88 | 83 | 107 | 74 | 61 | 45 |
| 2 | 89 | 86 | 72 | 82 | 65 | 66 | 67 | 88 | 77 | 78 | 77 | 66 |
| 3 | 153 | 85 | 82 | 93 | 103 | 52 | 95 | 104 | 141 | 60 | 65 | 63 |
| 4 | 100 | 93 | 89 | 79 | 87 | 77 | 30 | 63 | 85 | 66 | 64 | 68 |
| 5 | 92 | 110 | 67 | 108 | 120 | 103 | 87 | 120 | 160 | 88 | 92 | 80 |
| 6 | 71 | 113 | 72 | 90 | 98 | 85 | 124 | 165 | 162 | 74 | 78 | 70 |
| 7 | 76 | 60 | 32 | 93 | 103 | 81 | 131 | 123 | 92 | 78 | 60 | 44 |
| Mean | 84 | 83 | 63 | 86 | 88 | 78 | 90 | 107 | 117 | 74 | 71 | 61 |

| Subject No. | Plasma | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Na (mEq./liter) | | | K (mEq./liter) | | | Ca (mEq./liter) | | | $PO_4$ (mEq./liter) | | |
| | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 | Cont. 1 | Exp. | Cont. 2 |
| 1 | 137 | 140 | 138 | 4.8 | 4.7 | 5.0 | 10.4 | 10.1 | 10.6 | 3.9 | 4.0 | 4.1 |
| 2 | 136 | 139 | 139 | 5.2 | 5.0 | 5.0 | 10.1 | 10.1 | 10.0 | 4.2 | 4.4 | 4.3 |
| 3 | 137 | 139 | 137 | 5.0 | 4.9 | 4.8 | 10.2 | 10.0 | 10.0 | 3.3 | 3.3 | 3.4 |
| 4 | 135 | 135 | 133 | 4.7 | 4.9 | 4.3 | 10.8 | 9.9 | 10.1 | 3.8 | 4.2 | 4.6 |
| 5 | 139 | 141 | 135 | 4.4 | 4.8 | 4.6 | 10.6 | 10.4 | 10.4 | 3.7 | 3.8 | 4.1 |
| 6 | 140 | 139 | 137 | 5.0 | 4.9 | 4.7 | 9.9 | 10.0 | 10.1 | 3.8 | 3.8 | 4.0 |
| 7 | 140 | 140 | 137 | 4.9 | 4.8 | 4.7 | 10.3 | 10.2 | 10.1 | 3.5 | 4.3 | 4.0 |
| Mean | 138 | 139 | 137 | 4.9 | 4.9 | 4.7 | 10.3 | 10.1 | 10.2 | 3.7 | 4.0 | 4.1 |

## TABLE XIII

*Liver function studies*

| Subject No. | Bilirubin direct (mg. %) | | | | | | Bilirubin indirect (mg. %) | | | | | | Total protein (gm. %) | | | | | | Albumin (gm. %) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cont. 1 | | Exp. | | Cont. 2 | | Cont. 1 | | Exp. | | Cont. 2 | | Cont. 1 | | Exp. | | Cont. 2 | | Cont. 1 | | Exp. | | Cont. 2 | |
| | Day 1 | 5 | 3 | 5 | 1 | 5 | 1 | 5 | 3 | 5 | 1 | 5 | 1 | 5 | 3 | 5 | 1 | 5 | 1 | 5 | 3 | 5 | 1 | 5 |
| 1 | .27 | .21 | .16 | .11 | .08 | .15 | .68 | .43 | .72 | .68 | .68 | .98 | 8.0 | 7.9 | 7.7 | 7.3 | 7.5 | 7.0 | 5.2 | 4.8 | 5.0 | 4.4 | 5.0 | 4.2 |
| 2 | .14 | .19 | .16 | .12 | .06 | .10 | .27 | .31 | .38 | .38 | .67 | .49 | 7.4 | 7.4 | 7.7 | 7.3 | 7.4 | 7.2 | 4.9 | 4.8 | 5.0 | 4.5 | 4.5 | 4.7 |
| 3 | .14 | .14 | .08 | .07 | .15 | .60 | .31 | .56 | .30 | .75 | .91 | .60 | 7.5 | 7.1 | 7.4 | 7.2 | 7.0 | 7.0 | 5.0 | 4.7 | 4.8 | 4.3 | 4.5 | 4.3 |
| 4 | .20 | .13 | .07 | .18 | .17 | .05 | .35 | .39 | .39 | .42 | .32 | .29 | 7.1 | 7.4 | 7.0 | 7.3 | 7.8 | 7.3 | 4.4 | 4.6 | 4.3 | 4.5 | 4.8 | 4.8 |
| 5 | .06 | .52 | .21 | .12 | .51 | .05 | .93 | .82 | .74 | .76 | 1.23 | .40 | 7.7 | 7.8 | 7.3 | 7.3 | 7.6 | 7.2 | 4.8 | 4.9 | 4.7 | 4.8 | 4.6 | 4.6 |
| 6 | .20 | .13 | .16 | .18 | .08 | .14 | .36 | .51 | .62 | .42 | .60 | .20 | 7.1 | 7.5 | 7.3 | 7.5 | 7.0 | 6.8 | 4.4 | 4.4 | 4.5 | 4.7 | 4.4 | 4.3 |
| 7 | .20 | .19 | .20 | .18 | .17 | .23 | .63 | .74 | .20 | .70 | .51 | .76 | 7.4 | 7.2 | 7.0 | 7.2 | 7.1 | 7.2 | 5.1 | 4.5 | 4.6 | 4.9 | 4.8 | 4.5 |

| Subject No. | SGOT (S-F units) | | | | | | SGPT (S-F units) | | | | | | Alkaline phosphatase (K. A. units) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cont. 1 | | Exp. | | Cont. 2 | | Cont. 1 | | Exp. | | Cont. 2 | | Cont. 1 | | Exp. | | Cont. 2 | |
| | Day 1 | 5 | 3 | 5 | 1 | 5 | 1 | 5 | 3 | 5 | 1 | 5 | 1 | 5 | 3 | 5 | 1 | 5 |
| 1 | 24 | 47 | 20 | 17 | 17 | 17 | 15 | 16 | 16 | 11 | 14 | 11 | 14.1 | 14.1 | 11.5 | 11.7 | 10.4 | 10.8 |
| 2 | 17 | 12 | 16 | 14 | 12 | 17 | 15 | 9 | 12 | 9 | 11 | 15 | 7.8 | 7.8 | 8.8 | 8.7 | 8.5 | 8.7 |
| 3 | 17 | 17 | 18 | 19 | 14 | 14 | 16 | 18 | 19 | 19 | 13 | 12 | 7.6 | 6.5 | 7.5 | 7.6 | 6.6 | 7.1 |
| 4 | 22 | 24 | 24 | 30 | — | — | 16 | 20 | 20 | 28 | — | — | 10.9 | 8.9 | 10.9 | 9.9 | 10.0 | 8.5 |
| 5 | 32 | 22 | 19 | 19 | 19 | 20 | 26 | 19 | 19 | 16 | 18 | 18 | 7.9 | 6.3 | 6.5 | — | 6.9 | 6.1 |
| 6 | 20 | 23 | 22 | 22 | 24 | 22 | 17 | 18 | 15 | 20 | 19 | 21 | 10.1 | 7.6 | 8.9 | 8.7 | 8.9 | 7.8 |
| 7 | 20 | 20 | 22 | 23 | 22 | 23 | 19 | 19 | 24 | 26 | 26 | 30 | 4.8 | 5.2 | 5.7 | 5.2 | 5.6 | 5.2 |

was out of proportion to the blood loss. This was felt to be compatible with a chronic hemolytic process. Careful re-evaluation of blood smears and repeat physical examination indicated spherocytes on the peripheral blood smear and a barely palpable spleen dip. Consultation with the Hematology Section of Wilford Hall USAF Hospital confirmed the diagnosis of a chronic hemolytic process secondary to congenital spherocytic hemolytic anemia. With the exception of subject 7, all blood smears, white blood cell counts, and differential counts were normal during control and experimental phases.

### Respiratory studies

Tables XV and XVI include studies of oxygen uptake ($\dot{V}O_2$), carbon dioxide production ($\dot{V}CO_2$), minute ventilation ($V_E$), and various pulmonary function studies. Individual oxygen uptake and carbon dioxide production studies indicate a change in the R ($\dot{V}CO_2/\dot{V}O_2$) value relationships largely secondary to a decrease in carbon dioxide production. As the subjects were not trained in breathing technics, these figures are questionable and bear further investigation. As expected, there is a mild but definite increase in the resting minute ventilation of approximately 2.5 liters/min.

The table of pulmonary function studies is self-explanatory. Most values are quite normal with no apparent trends brought out by the increased carbon dioxide other than mild increases in calculated tidal volume. Again, some values of tidal volume (subjects 4 and 7) are difficult to interpret and probably secondary to not having subjects adequately trained in using respiratory equipment. There does not appear to be any change in maximum breathing capacity, tidal capacity, and timed vital capacity.

TABLE XIV

*Hematology studies*

| Subject No. | Red blood cell count ($10^6$/ml.) | | | | | Hemoglobin (gm. %) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cont. 1 | | Exp. | Cont. 2 | | Cont. 1 | | Exp. | Cont. 2 | |
| | A | B | | A | B | A | B | | A | B |
| 1 | 5.27 | 5 30 | 5.13 | — | 5.07 | 14.9 | 15.1 | 14.6 | — | 13.5 |
| 2 | 5.09 | 4.54 | 5.42 | — | 4.75 | 14.3 | 14.5 | 15.1 | — | 14.2 |
| 3 | 5.33 | 5.22 | 5.09 | — | 4.69 | 15.4 | 15.1 | 15.2 | — | 14.6 |
| 4 | 4.86 | 5.07 | 4.41 | 3.45 | 5.22 | 14.1 | 14.5 | 15.2 | 14.2 | 14.2 |
| 5 | 4.12 | 4.85 | 4.34 | 5.22 | 4.18 | 14.6 | 14.3 | 13.8 | 14.1 | 13.1 |
| 6 | 5.02 | 4.30 | 4.53 | 4.73 | 4.86 | 14.8 | 13.9 | 15.0 | 13.9 | 14.2 |
| 7 | 4.71 | 4.86 | 4.88 | 4.89 | 3.72 | 14.7 | 12.7 | 13.9 | 12.6 | 13.0 |

| Subject No. | Hematocrit (%) | | | | | Reticulocyte count (%) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Cont. 1 | | Exp. | Cont. 2 | | Cont. 1 | | Exp. | Cont. 2 | |
| | A | B | | A | B | A | B | | A | B |
| 1 | 55 | 43 | 46 | — | 38 | 0.5 | 0.9 | 0.5 | — | 0.5 |
| 2 | 43 | 47 | 44 | — | 40 | 0.7 | 0.6 | 0.4 | — | .04 |
| 3 | 48 | 49 | 44 | — | 45 | 0.5 | 0.4 | 0.4 | — | 0.6 |
| 4 | 41 | 44 | 44 | 43 | 41 | 1.4 | 0.8 | 0.9 | 0.7 | 1.7 |
| 5 | 41 | 43 | 44 | 45 | 42 | 0.8 | 0.8 | 0.5 | 1.2 | 0.8 |
| 6 | 44 | 40 | 46 | 44 | 41 | 1.0 | 0.7 | 1.2 | 1.3 | 1.7 |
| 7 | 42 | 38 | 40 | 38 | 39 | 1.3 | 2.0 | 4.5 | 5.9 | 5.8 |

### Exercise studies

Exercise data were collected on 6 of the 7 subjects during this study. Data from subject 4 were deleted. This subject was of quite small stature (5 ft. 4 in.; 129 lb.) and had great difficulty riding the bike as the seat could not be adjusted to a low enough level for him. As a result of this, every bike ride was a maximum effort for him as he lost all mechanical advantage. After a short time interval on the bike, it was apparent that a maximum effort was involved as heart rates were 180 beats/min. or above and minute ventilation was extraordinarily high.

With the exception of subject 4, all subjects were able to tolerate the 1-hour bike ride quite well. Subjectively, all felt well at the end of the exercise period and even suggested that if necessary, they could go for a longer period of time.

Table XVII lists means for all 6 subjects during the exercise studies. Measurements listed include minute ventilation, oxygen uptake ($\dot{V}O_2$), and carbon dioxide production ($\dot{V}CO_2$). Note the increase of 5 to 6 liters/min. in resting minute ventilation with almost no change in $\dot{V}O_2$ and $\dot{V}CO_2$. With the onset of exercise a rather marked increase in minute ventilation of 20 to 25 liters/min. from control states is accompanied by a mild but definite increase in $\dot{V}O_2$.

Table XVIII outlines the exercise pulse response in beats per minute. Again, there is little change in the resting pulse rate from the control phase, while a definite increase in pulse rate is seen in the experimental period during exercise. Generally, the pulse rates in the last 5-day recovery period are all higher than in the first control period. Finally, a steady, moderate workload is mirrored by the fact that the pulses remain relatively stable after approximately 15 minutes of exercise. The last 30 minutes of exercise were accompanied by psychomotor testing.

### Psychomotor testing

The Neptune psychomotor testing, repetitive psychologic measurements, and exercise psychomotor parameters were tested statistically by an analysis of variance. A statistical analysis was carried out on all 7 subjects (including subject 4 who was actually working under a maximum workload). A review of all psychomotor and psychologic studies failed to reveal any significant changes or trends when compared to control states. From the foregoing, it is concluded that the ambient 3% $CO_2$ atmosphere did not reveal any detectable performance changes in the variables measured.

Subjectively, the men felt the atmosphere was quite tolerable and in no way interfered with reading, working, or the usual daily activities. This is supported by a study of the daily diaries which they kept. The only symptoms which were related to the atmosphere were mild-to-moderate frontal headaches, throbbing in nature but not severe enough to interfere with normal activities. These headaches occurred in 4 of the 7 subjects and were during the first 2 days of $CO_2$ exposure. Three of the subjects felt that the headache was prominent enough so that an analgesic was requested. A 32-mg. capsule of dextropropoxyphene adequately relieved distress. A general physical examination during the period of headaches failed to reveal any abnormalities. Results from a neurologic examination and funduscopy were normal. No recurrence of headache was noted after the first 2 days of exposure to the experimental atmosphere. There were no complaints of headaches during the recovery period.

## V. DISCUSSION

The main points brought out by this study relate to the relatively mild challenge presented by an atmosphere with an ambient $P_{CO_2}$ of 21 mm. Hg (3%). This is particularly true when reviewing the mild physiologic changes occurring in acid-base metabolism. As shown in figure 2, an increase in $P_{aCO_2}$ of only 3 to 4 mm. Hg was achieved. Such a small change was accompanied by a minimal reduction in the arterial pH of the blood from a control value of 7.40 down to 7.37, a figure well within the accepted normal range. As expected and shown in other studies (2, 49), an initial in-

## TABLE XV

*Basal respiratory studies*

| Subject No. | Basal $O_2$ consumption (liters/min., BTPS) | | | | | | Basal $CO_2$ production (liters/min., BTPS) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cont. 1 | | Exp. | | Cont. 2 | | Cont. 1 | | Exp. | | Cont. 2 | |
| | A | B | A | B | A | B | A | B | A | B | A | B |
| 1 | .358 | .354 | .377 | .320 | .401 | .572 | .334 | .350 | .249 | .208 | .235 | .353 |
| 2 | .243 | .288 | .311 | .300 | .309 | .586 | .180 | .274 | .228 | .248 | .257 | .447 |
| 3 | .314 | .331 | .407 | .291 | .281 | .379 | .236 | .281 | .262 | .234 | .209 | .299 |
| 4 | .693 | .487 | .533 | .532 | .441 | .438 | .589 | .468 | .390 | .461 | .527 | .391 |
| 5 | .767 | .582 | .231 | .314 | .662 | .552 | .502 | .484 | .164 | .241 | .490 | .481 |
| 6 | .517 | .319 | .294 | .320 | .226 | .395 | .397 | .295 | .240 | .252 | .261 | .370 |
| 7 | .524 | .410 | .362 | .454 | .429 | .579 | .387 | .372 | .265 | .337 | .382 | .454 |

| Subject No. | RQ ($\dot{V}co_2/\dot{V}o_2$) | | | | | | Minute ventilation (liters/min., BTPS) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cont. 1 | | Exp. | | Cont. 2 | | Cont. 1 | | Exp. | | Cont. 2 | |
| | A | B | A | B | A | B | A | B | A | B | A | B |
| 1 | .93 | .99 | .66 | .65 | .59 | .62 | 11.1 | 10.1 | 11.1 | 9.3 | 7.6 | 10.5 |
| 2 | .76 | .95 | .73 | .83 | .83 | .76 | 5.8 | 8.1 | 10.1 | 10.3 | 7.7 | 7.4 |
| 3 | .75 | .85 | .64 | .81 | .74 | .75 | 6.8 | 7.1 | 11.0 | 9.3 | 6.1 | 8.5 |
| 4 | .85 | .96 | .73 | .87 | 1.19 | .89 | 14.8 | 12.5 | 17.4 | 18.8 | 11.2 | 9.5 |
| 5 | .65 | .83 | .71 | .77 | .74 | .87 | 13.4 | 12.1 | 7.1 | 11.4 | 10.1 | 12.5 |
| 6 | .77 | .92 | .82 | .79 | 1.16 | .94 | 10.2 | 7.4 | 9.8 | 10.0 | 6.7 | 8.7 |
| 7 | .74 | .91 | .73 | .74 | .89 | .78 | 8.6 | 8.2 | 8.9 | 11.3 | 9.5 | 10.3 |

## TABLE XVI

*Pulmonary function studies*

| Subject No. | Calculated tidal volume (liters) | | | | | | Maximum breathing capacity (liters/min., BTPS) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cont. 1 | | Exp. | | Cont. 2 | | Cont. 1 | | Exp. | | Cont. 2 | |
| | A | B | A | B | A | B | A | B | A | B | A | B |
| 1 | .854 | .546 | .717 | .580 | .629 | .760 | 181.0 | 174.4 | 179.0 | 176.2 | 171.9 | 176.3 |
| 2 | .453 | .611 | .523 | .683 | .540 | .836 | 170.6 | 187.6 | 183.7 | 180.0 | 172.6 | 177.0 |
| 3 | .455 | .517 | .666 | .572 | .422 | .613 | 185.1 | 158.0 | 175.4 | 166.5 | 135.6 | 130.4 |
| 4 | 1.033 | .820 | 1.202 | 1.298 | 1.347 | .867 | 173.2 | 169.5 | 167.1 | 163.5 | 166.6 | 155.9 |
| 5 | .891 | 1.009 | .463 | .738 | .729 | 1.018 | 182.3 | 161.3 | 161.4 | 164.0 | 163.3 | 164.9 |
| 6 | .796 | .534 | .638 | .798 | .578 | .656 | 152.9 | 132.8 | 172.7 | 169.3 | 165.2 | 127.3 |
| 7 | .860 | .959 | .954 | 1.285 | 1.363 | 1.416 | 173.6 | 186.8 | 180.8 | 181.6 | 182.1 | 189.5 |

| Subject No. | Vital capacity (liters, BTPS) | | | | | | 1-Sec. vital capacity (% of total) | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Cont. 1 | | Exp. | | Cont. 2 | | Cont. 1 | | Exp. | | Cont. 2 | |
| | A | B | A | B | A | B | A | B | A | B | A | B |
| 1 | 5.477 | 6.094 | 5.752 | 5.631 | 5.362 | 5.800 | 85 | 84 | 85 | 69 | 73 | 80 |
| 2 | 5.067 | 5.503 | 5.453 | 5.444 | 5.308 | 5.489 | 89 | 90 | 89 | 90 | 92 | 90 |
| 3 | 5.860 | 5.720 | 5.849 | 5.764 | 5.930 | 5.819 | 87 | 86 | 89 | 88 | 88 | 89 |
| 4 | 4.701 | 4.861 | 4.840 | 4.840 | 4.637 | 4.729 | 87 | — | 90 | 92 | 90 | 92 |
| 5 | 5.398 | 5.295 | 5.752 | 5.691 | 5.578 | 5.530 | 86 | 74 | 85 | 89 | 89 | 86 |
| 6 | 6.246 | 6.068 | 6.282 | 6.186 | 6.048 | 6.104 | 83 | 86 | 85 | 85 | 89 | 87 |
| 7 | 6.519 | 6.671 | 6.744 | 6.851 | 6.541 | 6.691 | 71 | 75 | 74 | 73 | 74 | 74 |

crease of approximately 1 mEq./liter in total $CO_2$ ($HCO_3^-$) was seen acutely. Although the increased acid load, brought on by the elevation of ambient carbon dioxide was minimal, there is still some compensation from the renal conservation of bicarbonate which is controlled by changes in the $P_{CO_2}$ (35). By the fifth experimental day, the serum total $CO_2$ ($HCO_3^-$) had increased approximately 2 mEq./liter and the arterial pH had returned to near control levels, thus indicating partial acid-base adaptation to this environment.

Chronic studies carried out by Schwartz et al. (49) and Sullivan and Dorman (55) in animals have shown a definite increase in net hydrogen ion excretion under high ambient carbon dioxide levels (7% and 10%). With the mild stimulus of this 3% experimental atmosphere, very little was seen with respect to renal changes. It is apparent that no significant change (or, more appropriately, increase) was seen in the excretion of urinary $NH_4^+$, titratable acidity, and net hydrogen ion excretion ($NH_4^+$ + T. A. — $HCO^{3-}$). A marked and statistically significant reduction of $NH_4^+$, T. A., and net hydrogen ion excretion is seen in the followup control period. This is not surprising as a bicarbonate diuresis and subsequent increase in urine pH are seen in the first days of the recovery period. It has been shown by other investigators (32) that an increase in urine pH will definitely decrease the excretion of ammonium and titratable acidity owing to distal tubular changes. The bicarbonate diuresis was expected upon removal from the carbon dioxide atmosphere with reduction in arterial $P_{CO_2}$ as the kidneys "dumped" the excessive bicarbonate buffers (32).

Studies by Schaefer et al. (39, 46) and Stanmeyer et al. (53) in man at 1.5% $CO_2$ and animals at 15% $CO_2$ have raised the question of abnormalities of calcium metabolism and parathyroid function. As our study was too short to carry out a calcium balance, we elected instead to investigate urinary hydroxyproline excretion. This amino acid is almost exclusively tied up in collagen tissue and bone and is believed to be a good indicator of parathyroid activity (7, 21). Past investigators have shown definite hydroxyproline abnormalities with parathormone injection, hyperparathyroidism, calcium infusion, and other states (17, 21, 23, 30).

## TABLE XVII

*1-Hour exercise-respiratory studies (period means of 6 subjects)*

| | | Cont. 1 | | Exp. | | Cont. 2 | |
|---|---|---|---|---|---|---|---|
| | | A | B | A | B | A | B |
| $\dot{V}_E$ | (liters/min., STPD) | | | | | | |
| | Resting | 14.9 | 13.5 | 19.1 | 17.6 | 12.0 | 10.6 |
| | 15-20 min. | 41.5 | 41.6 | 66.7 | 62.7 | 40.4 | 38.2 |
| | 35-40 min. | 41.7 | 43.3 | 67.4 | 65.0 | 40.0 | 38.3 |
| | 50-55 min. | 40.7 | 43.2 | 69.6 | 64.4 | 39.8 | 38.9 |
| $\dot{V}_{O_2}$ | (liters/min., STPD) | | | | | | |
| | Resting | 0.312 | 0.343 | 0.353 | 0.333 | 0.313 | 0.340 |
| | 15-20 min. | 1.364 | 1.491 | 1.597 | 1.576 | 1.304 | 1.394 |
| | 35-40 min. | 1.383 | 1.395 | 1.647 | 1.538 | 1.317 | 1.417 |
| | 50-55 min. | 1.390 | 1.432 | 1.697 | 1.640 | 1.250 | 1.352 |
| $\dot{V}_{CO_2}$ | (liters/min., STPD) | | | | | | |
| | Resting | 0.347 | 0.353 | 0.320 | 0.262 | 0.297 | 0.290 |
| | 15-20 min. | 1.480 | 1.390 | 1.377 | 1.259 | 1.323 | 1.231 |
| | 35-40 min. | 1.367 | 1.398 | 1.290 | 1.260 | 1.263 | 1.180 |
| | 50-55 min. | 1.283 | 1.393 | 1.365 | 1 178 | 1 293 | 1.215 |

TABLE XVIII

*1-Hour exercise-pulse response (beats/min.) (period means of 6 subjects)*

| | Cont. 1 | | Exp. | | Cont. 2 | |
|---|---|---|---|---|---|---|
| | A | B | A | B | A | B |
| Resting | 68 | 65 | 76 | 73 | 68 | 69 |
| 4-5 min. | 114 | 119 | 125 | 132 | 133 | 127 |
| 14-15 min. | 128 | 130 | 135 | 144 | 144 | 139 |
| 24-25 min. | 135 | 129 | 145 | 152 | 149 | 145 |
| 34-35 min. | 132 | 126 | 142 | 151 | 144 | 138 |
| 44-45 min. | 137 | 128 | 144 | 148 | 147 | 143 |
| 49-50 min. | 142 | 135 | 142 | 147 | 148 | 143 |
| 59-60 min. | 143 | 137 | 141 | 148 | 147 | 142 |

Correlation of urinary hydroxyproline data on 4 subjects failed to show any changes which could be attributed to the atmosphere. Some increases seen in peptides were felt to be secondary to a "deconditioning" phenomenon closely akin to bed rest studies (24, 29), as the subjects were quite confined and exercised only during the six sessions. In addition to relatively normal hydroxyproline studies, no metabolic changes with relation to calcium and phosphorus were seen in urine and serum. Unpublished data from this laboratory have failed to denote any calcium, phosphorus, or hydroxyproline changes at 4% $CO_2$ for a 5-day exposure. The whole problem of calcium-phosphorus metabolism, however, has yet to be answered when considering man and chronic hypercapnia. It will remain for this question to be answered in the future with continuing studies at higher carbon dioxide levels. A definitive answer could be obtained with a study long enough to incorporate calcium balance experiments.

Basal respiratory studies failed to show any decrease or increase in oxygen consumption ($\dot{V}O_2$) during exposure to the carbon dioxide atmosphere. A mean of two determinations on each subject during the control phase of the experiment revealed the RQ was 0.85 (table XI). This dropped significantly during the experimental phase of the study. Follow-up control RQ's returned to 0.85. The reason for this change is still unclear and is possibly secondary to the fact that the subjects were not adequately trained in the use of respiratory equipment. One study carried out by Schaefer and co-workers (since reported in many places from 1949 until 1965) does allude to changes in the RQ in high carbon dioxide (40-45). Currently, more sophisticated studies are being planned to answer this question. The mild increases in resting minute ventilation are to be expected and agree with other studies done at similar levels (1, 10, 15, 48). Since only two resting minute ventilations were determined during the experimental phase, no trends were noted. The tidal volume studies were calculated indirectly from minute ventilation and mean respiratory rates and are only approximations. Large deviations are felt to be secondary to a lack of pulmonary training because the deviations occur both in experimental and control phases.

The significance of the exercise studies in this environment is obvious as 6 men were able to carry out moderate workloads for 1 hour without stopping. As noted earlier, none of them felt it was particularly difficult other than the increased ventilation they experienced. Although a low resistance valve was used for gas sampling, it was apparent that it made breathing more difficult, and leaks around the mouthpiece cannot be ruled out. As shown in table XIV, a small increase in minute ventilation ($\dot{V}E$) was noted during the resting state in the experimental phase with no significant change in oxygen consumption. This increase in ventilation was quite marked with the onset of exercise (20 to 25 liters/min.) and probably explains the mild but definite increase in oxygen consumption secondary to the increased work of breathing. Carbon dioxide production remained within control values. This rather marked increase in ventilation with moderate exercise was also seen in Froeb's exercise studies (10) at ambient levels of 1.5% and 3.4% $CO_2$. A similar increase in $O_2$ consumption was also noted and thought to be secondary to the increased work of breathing. Although a minimal decrease in ventilation and oxygen consumption was seen during exercise on the fifth day of carbon dioxide exposure, no subjective changes were noted by the men.

They did not feel that the exercise was more or less difficult when compared with the acute study.

Table XV shows definite increases in pulse response during the experimental phase, and these persisted during the followup control period. The explanation for this is twofold. First, exercise in the carbon dioxide environment would tend to increase pulse response with the increased ventilation and work of breathing. Second, the factor of deconditioning was also present as these previously vigorous, active young men who had just completed basic training were suddenly confined to a small area with little exercise except for the programmed 6 hours. This obviously was not enough to keep good muscle tone, and they developed a hypodynamic state. This condition is well described in simulator studies in several communications by Lamb et al. (24, 29) from the USAF School of Aerospace Medicine.

The psychomotor phases of the experiment were carried out a large number of times and in great detail. Repetitive psychologic testing parameters (tracing of geometric figures, letter canceling tests, etc.) were programmed into the study to compare with similar measurements made by other groups. It was felt that this was necessary as there is conflicting evidence in the literature with respect to psychomotor performance and carbon dioxide atmospheres, especially at the 3% $CO_2$ level. Several researchers have failed to note significant performance changes at ambient $P_{CO_2}$'s ranging from 20 to 38 mm. Hg (3, 5, 57). Schaefer (38, 40), however, reported definite changes in performance in submarine crew members during World War II. Although definite changes were seen, it is difficult to attribute them to carbon dioxide alone as no information was provided concerning contaminants (carbon monoxide, methane, etc.) known to build up in closed systems.

A statistical analysis of psychomotor tests performed during the exercise studies failed to show any changes from control to experimental conditions. It should be remembered that the data from subject 4 (maximum effort on bike) were also included in the analysis.

Finally, a brief discussion concerning the mild frontal headaches is in order. Carbon dioxide is a known cerebrovascular dilator (20). Studies by Patterson et al. (31) have noted increases of 10% or more in cerebral blood flow, with ambient carbon dioxide levels between 3% and 4%. These increases, together with secondary changes in spinal fluid pressure, probably contribute to headaches and make them of a vascular nature. Further studies concerning cerebrovascular blood flow in chronic hypercapnia would be of interest, but were not indicated here.

During the 5-day period in carbon dioxide, the subjects did not feel the environment was hostile or particularly uncomfortable. They were able to carry out all duties with a maximum of efficiency and were able to sleep without difficulty. Outbursts of euphoria, depression, or anxiety were not noted. Complaints from the subjects related mainly to the frequent venipunctures and monotonous liquid diet.

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13 ABSTRACT

Seven normal volunteers were exposed to an environment of 21 mm. Hg $CO_2$ (3%) for a 5-day experimental period bracketed by two 5-day control periods. Measurements included daily serum and urine electrolytes, blood gas studies, and net acid excretion studies. Also included were detailed investigations of respiratory physiology, exercise resporse, and psychomotor performance. All subjects tolerated the experimental atmosphere with no undue problems. Arterial and alveolar $P_{CO_2}$'s increased 3 to 4 mm. Hg with a mild reduction in arterial pH from 7.40 to 7.37. Arterial pH values returned to near control values by the fourth day. No increases were noted in net acid excretion. Exercise was tolerated remarkably well.

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