AD 664 899

CARBON DIOXIDE TOLERANCE STUDIES

H. A. GLATTE, JR., Captain, USAF, MC
G. J. MOTSAY, Captain, USAF, MC
B. E. WELCH, Ph.D.

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.

GEORGE E. SCHAFER
Colonel, USAF, MC
Commander

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.

CARBON DIOXIDE TOLERANCE STUDIES

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 b. "Arterialized" P_{CO_2}, pH on capillary blood	Daily
Urine a. Na, K, Cl, Ca, Mg, P, creatinine b. NH_4^+, HCO_3^-, titratable acidity, pH c. 24-hour hydrogen ion excretion $NH_4^+ + T.A. - HCO_3^- = 24\ H^+$ excretion	24-hr. 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)	699.2	699.6	699.2	699.3	699.9	699.7
Po_2 (mm. Hg)	157.4	136.1	156.7	157.0	136.2	156.3
Pco_2 (mm. Hg)	4.4	21.4	1.6	2.1	21.4	1.3
PN_2 (mm. Hg)	540.5	535.6	541.2	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	X	X	X	X	
55					
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)			P_{CO_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
P_{CO_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[illegible].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 Pa_{CO_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

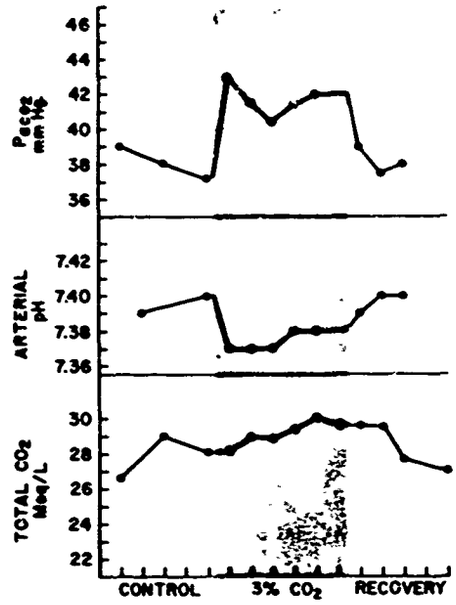

FIGURE 2

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	0.6	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	5.830	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.

REFERENCES

1. Alexander, J. K., J. R. West, J. A. Wood, and D. W. Richards. Analysis of respiratory response to carbon dioxide inhalation in varying clinical states of hypercapnia, anoxia and acid-base derangement. J. Clin. Invest. 34:533 (1955).

2. Brackett, N. C., J. J. Cohen, and W. B. Schwartz. Carbon dioxide titration curve of normal man. New Eng. J. Med. 272:6 (1965).

3. Consolazio, W. B., M. B. Fisher, N. Pace, L. J. Pecora, and A. R. Behnke. Effects of man of high concentrations of carbon dioxide in relation to various oxygen pressures during exposures as long as 72 hours. Amer. J. Physiol. 151:479 (1947).

4. Cunningham, D. J., B. B. Lloyd, and C. C. Michel. Acid-base changes in blood during hypercapnia and hypocapnia in normal man. J. Physiol. (London) 161:26P (1962).

5. Cutler, R. G., W. G. Robertson, J. E. Herlocher, R. E. McKenzie, F. Ulvedal, J. J. Harl eaves, and B. E. Welch. Human response to carbon dioxide in the low-pressure, oxygen rich atmosphere. Aerospace Med. 35:317 (1964).

6. Dripps, R. D., and J. H. Comroe, Jr. The respiratory and circulatory response of normal man to inhalation of 7.6 and 10.4 per cent CO_2 with a comparison of the maximal ventilation produced by severe muscular exercise, inhalation of CO_2 and maximal voluntary hyperventilation. Amer. J. Physiol 149:43 (1947).

7. Dull, T., and P. H. Henneman. Urinary hydroxyproline as an index of collagen turnover in bone. New Eng. J. Med. 268:132 (1963).

8. Fawcett, R., and P. P. Newman. Operation Hideout (preliminary report). NMRL Report 228 (1953).

9. Fenn, W. O., H. Eahn, and A. B. Otis. A theoretical study of the composition of the alveolar air at altitude. Amer. J. Physiol. 146:637 (1946).

10. Froeb, H. F. Ventilatory response of SCUBA divers to carbon dioxide inhalation. J. Appl. Physiol. 16:8 (1961).

11. Fiske, C. H., and Y. Subbarow. The colorimetric determination of phosphorus. J. Biol. Chem. 66:375 (1925).

12. Gambino, S. R., P. Astrup, R. G. Bates E. J. M. Campbell, F. P. Chinard, G. G. Nahas, O. Sigaard-Anderson, and R. Winters. Report of the AD HOC Committee on Methodology. Ann. N.Y. Acad. Sci. 133:259 (1966).

13. Gambino, S. R. Comparisons of pH in human arterial, venous and capillary blood. Amer. J. Clin. Path. 32:298 (1959).

14. Glatte, H., and S. J. Menn. The study of man in 4% CO_2. (In preparation)

15. Hastings, B. K., K. E. Schaefer, G. Nichols, Jr., and C. R. Carey. Effects of prolonged exposure to elevated levels of carbon dioxide on respiration, alveolar carbon dioxide tension and lung volume. NMRL Report 250 (1954).

16. Hawk, P. B., B. L. Oser, and W. H. Summerson. Practical physiological chemistry, 12th ed. New York: McGraw-Hill Book Company, Inc., 1947.

17. Henneman, P. H., T. Dull, and T. Lynch. Immobilization and aspirin in Paget's disease. Clin. Res. 11:45 (1963).

18. Hoffman, W. S. A rapid photoelectric method for the determination of glucose in blood and urine. J. Biol. Chem. 120:51 (1937).

19. Jorgensen, K., and P. Astrup. Standard bicarbonate, its clinical significance and a new method for its determination. Scand. J. Clin. Lab. Invest. 9:122 (1957).

20. Kety, S. S., and C. F. Schmidt. The effects of altered arterial tensions of carbon dioxide and oxygen on cerebral blood flow and cerebral oxygen consumption of normal young men. J. Clin. Invest. 27:484 (1948).

21. Keiser, H. R., J. R. Gill, A. Sjoerdsma, and F. C. Bartter. The effect of parathyroid extract on hydroxyproline metabolism. Clin. Res. 11:41 (1963).

22. King, E. J., and A. R. Armstrong. A convenient method for determining serum and bile phosphatase activity. Canad. Med. Ass. J. 31:376 (1934).

23. Klein, L., F. W. Lafferty, O. H. Pearson, and P. H. Curtiss. Correlation of urinary hydroxyproline, serum alkaline phosphatase and skeletal calcium turnover. Metabolism 13:272 (1964).

24. Lamb, L. E., R. L. Johnson, P. M. Stevens, and B. E. Welch. Cardiovascular deconditioning from space cabin simulator confinement. Aerospace Med. 35:420 (1964).

25. Lambertson, C. J. Carbon dioxide and respiration in acid-base homeostasis. Anesthesiology 21: 642 (1960).

26. Logsdon, E. E. Method for the determination of ammonia in biological fluids on the Auto-Analyzer. Ann. N. Y. Acad. Sci. 87:801 (1960).

27. Maas, A. H. J., and A. N. P. van Heijst. The accuracy of the micro-determination of the Pco_2 of blood from the ear-lobe. Clin. Chim. Acta 6:34 (1961).

28. Malloy, H T., and K. A. Evelyn. The determination of bilirubin with the photoelectric colorimeter. J. Biol. Chem. 119:481 (1937).

29. Miller, P. B., R. L. Johnson, and L. E. Lamb. The effects of four weeks of absolute bed rest on circulatory functions in man. Aerospace Med. 35:1194 (1964).

30. Ney, R. L., J. R. Gill, H. R. Keiser, and F. C. Bartter. Regulation of hydroxyproline excretion in hyperparathyroidism. J. Clin. Endocr. 26:815 (1966).

31. Patterson, J. L., A. Heyman, L. L. Battey, and R. W. Ferguson. Threshold response of cerebral vessels of man to increase in blood carbon dioxide. J. Clin. Invest. 34:1257 (1955).

32. Pitts, R. F. Physiology of the kidney and body fluids. Chicago: Year Book Medical Publishers, Inc., 1963.

33. Pitts, R. F. The renal excretion of acid. Fed. Proc. 7:418 (1948).

34. Prockop, D. J., and A. Sjoerdsma. Significance of urinary hydroxyproline in man. J. Clin. Invest. 40:843 (1961).

35. Rector, F. C., Jr., D. W. Seldin, A. D. Roberts, Jr., and J. S. Smith. The role of plasma CO_2 tension and carbonic anhydrase activity in the renal reabsorption of bicarbonate. J. Clin. Invest. 39:1706 (1960).

36. Relman, A. S. Renal acidosis and renal excretion of acid in health and disease. Advances in internal medicine, vol. XII. Chicago: Year Book Medical Publishers, Inc., 1964.

37. Rodgin, D. W., and B. O. Hartman. The study of man during a 56-day exposure to an oxygen-helium atmosphere at 258 mm. Hg total pressure. XIII. Behavior factors. Aerospace Med. 37:605 (1966).

38. Schaefer, K. E. Respiration and acid-base balance during prolonged exposure to 3% carbon dioxide. Pflueger Arch. Ges. Physiol. 251:689 (1949).

39. Schaefer, K. E. Adaptation of men and animals during prolonged exposure to increased carbon dioxide concentration. Amer. J. Physiol. 163: 747 (1950).

40. Schaefer, K. E. Studies of carbon dioxide toxicity in submarine medicine. NMRL Report 181 (1951).

41. Schaefer, K. E. The effect of prolonged exposure to low carbon dioxide concentrations on flicker fusion frequency and alpha blocking. NMRL Report 258 (1954).

42. Schaefer, K. E. Respiratory pattern and respiratory response to CO_2. J. Appl. Physiol. 13:1 (1958).

43. Schaefer, K. E. Experiences with submarine atmospheres. J. Aviation Med. 30:350 (1959).

44. Schaefer, K. E. Respiratory adaptation to chronic hypercapnia. Ann. N. Y. Acad. Sci. 109:772 (1963).

45. Schaefer, K. E., B. J. Hastings, C. R. Carey, and G. Nichols. Respiratory acclimatization to carbon dioxide. J. Appl. Physiol. 18:107 (1963).

46. Schaefer, K. E., G. Nichols, Jr., and C. R. Carey. Calcium and phosphorus metabolism in man during acclimatization to carbon dioxide. J. Appl. Physiol. 18:1079 (1963).

47. Schaefer, K. E., G. Nichols, and C. R. Carey. Acid-base balance and blood and urine electrolytes of man during acclimatization to CO_2. J. Appl. Physiol. 19:48 (1964).

48. Schneider, E. C., and D. Truesdale. Effects on the circulation and respiration of an increase in the carbon dioxide content of blood in man. Amer. J. Physiol. 63:155 (1922).

49. Schwartz, W. B., N. C. Brackett, and J. J. Cohen. The response of extracellular hydrogen ion concentration of graded degrees of chronic hypercapnia: The physiologic limits of the defense of the pH. J. Clin. Invest. 44:291 (1965).

50. Sigma-Frankel procedure. Sigma Technical Bulletin No. 505, pp. 1-10, Jan. 1961.

51. Skeggs, L. T. An automated method for colorimetric analysis. Amer. J. Clin. Path. 28:311 (1957)

52. Skeggs, L. T. An automatic method for the determination of carbon dioxide in blood plasma. Amer. J. Clin. Path. 33:181 (1960).

53. Stanmeyer, W. R., C. T. G. King, H. Scofield, and R. Colby. The effect of prolonged exposure to carbon dioxide on calcification. *In* Schaefer, K. E. (ed.). Man's dependence on the earthly atmosphere. New York: Macmillan Company, 1962.

54. Steel, R. G. D., and J. H. Torrie. Principles and procedures of statistics. New York: McGraw-Hill Book Company, Inc., 1961.

55. Sullivan, W. J., and P. J. Dorman. Renal response to chronic respiratory acidosis. J. Clin. Invest. 34:268 (1955).

56. Technicon Laboratory, New York. AutoAnalyzer method N-20A.

57. White, C. S., J. H. Humm, E. D. Armstrong, and N. P. V. Lundgren. Human tolerance to acute exposure to carbon dioxide. J. Aviation Med. 23:439 (1952).

58. Woessner, J. F., Jr. The determination of hydroxyproline in tissue and protein samples containing small proportions of this imino acid. Arch. Biochem. 93:440 (1961).

59. Zharov, S. G., Ye. A. Il'in, Ye. A. Kovalenko, I. R. Kalinichenko, L. I. Karpova, N. S. Mikerova, M. M. Osipova, and Ye. Simonov. Effect on man of prolonged exposure to atmospheres with high carbon dioxide content. Aviation and space medicine (Moscow), pp. 182-185, 1963.

Unclassified

Security Classification

DOCUMENT CONTROL DATA - R&D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1 ORIGINATING ACTIVITY (Corporate author) USAF School of Aerospace Medicine Aerospace Medical Division (AFSC) Brooks Air Force Base, Texas	2a REPORT SECURITY CLASSIFICATION Unclassified 2b GROUP

3 REPORT TITLE

CARBON DIOXIDE TOLERANCE STUDIES

4 DESCRIPTIVE NOTES (Type of report and inclusive dates)

1966

5. AUTHOR(S) (Last name, first name, initial)

Glatte, H. A., Jr., Captain, USAF, MC
Motsay, G. J., Captain, USAF, MC
Welch, B. E.

6 REPORT DATE	7a TOTAL NO OF PAGES	7b NO OF REFS
August 1967	22	59

8a CONTRACT OR GRANT NO. NAS contract No. T-41829-G b PROJECT NO. 7930 c Task No. 793002 d.	9a ORIGINATOR'S REPORT NUMBER(S) SAM-TR-67-77 9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)

10 AVAILABILITY/LIMITATION NOTICES

This document has been approved for public release and sale; its distribution is unlimited.

11. SUPPLEMENTARY NOTES	12. SPONSORING MILITARY ACTIVITY USAF School of Aerospace Medicine Aerospace Medical Division (AFSC) Brooks Air Force Base, Texas

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 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.

DD FORM 1 JAN 64 1473

Unclassified

Security Classification

Unclassified
Security Classification

14 KEY WORDS	LINK A ROLE	LINK A WT	LINK B ROLE	LINK B WT	LINK C ROLE	LINK C WT
Physiology, respiratory and exercise						
Carbon dioxide studies						
Acid-base studies						
Calcium studies						
Electrolyte metabolism						
Psychomotor studies						

INSTRUCTIONS

1. ORIGINATING ACTIVITY: Enter the name and address of the contractor, subcontractor, grantee, Department of Defense activity or other organization *(corporate author)* issuing the report.

2a. REPORT SECURITY CLASSIFICATION: Enter the overall security classification of the report. Indicate whether "Restricted Data" is included. Marking is to be in accordance with appropriate security regulations.

2b. GROUP: Automatic downgrading is specified in DoD Directive 5200.10 and Armed Forces Industrial Manual. Enter the group number. Also, when applicable, show that optional markings have been used for Group 3 and Group 4 as authorized.

3. REPORT TITLE: Enter the complete report title in all capital letters. Titles in all cases should be unclassified. If a meaningful title cannot be selected without classification, show title classification in all capitals in parenthesis immediately following the title.

4. DESCRIPTIVE NOTES: If appropriate, enter the type of report, e.g., interim, progress, summary, annual, or final. Give the inclusive dates when a specific reporting period is covered.

5. AUTHOR(S): Enter the name(s) of author(s) as shown on or in the report. Enter last name, first name, middle initial. If military, show rank and branch of service. The name of the principal author is an absolute minimum requirement.

6. REPORT DATE: Enter the date of the report as day, month, year; or month, year. If more than one date appears on the report, use date of publication.

7a. TOTAL NUMBER OF PAGES: The total page count should follow normal pagination procedures, i.e., enter the number of pages containing information.

7b. NUMBER OF REFERENCES: Enter the total number of references cited in the report.

8a. CONTRACT OR GRANT NUMBER: If appropriate, enter the applicable number of the contract or grant under which the report was written.

8b, 8c, & 8d. PROJECT NUMBER: Enter the appropriate military department identification, such as project number, subproject number, system numbers, task number, etc.

9a. ORIGINATOR'S REPORT NUMBER(S): Enter the official report number by which the document will be identified and controlled by the originating activity. This number must be unique to this report.

9b. OTHER REPORT NUMBER(S): If the report has been assigned any other report numbers *(either by the originator or by the sponsor)*, also enter this number(s).

10. AVAILABILITY/LIMITATION NOTICES: Enter any limitations on further dissemination of the report, other than those imposed by security classification, using standard statements such as:

(1) "Qualified requesters may obtain copies of this report from DDC."

(2) "Foreign announcement and dissemination of this report by DDC is not authorized."

(3) "U. S. Government agencies may obtain copies of this report directly from DDC. Other qualified DDC users shall request through _____."

(4) "U. S. military agencies may obtain copies of this report directly from DDC. Other qualified users shall request through _____."

(5) "All distribution of this report is controlled. Qualified DDC users shall request through _____."

If the report has been furnished to the Office of Technical Services, Department of Commerce, for sale to the public, indicate this fact and enter the price, if known.

11. SUPPLEMENTARY NOTES: Use for additional explanatory notes.

12. SPONSORING MILITARY ACTIVITY: Enter the name of the departmental project office or laboratory sponsoring *(paying for)* the research and development. Include address.

13. ABSTRACT: Enter an abstract giving a brief and factual summary of the document indicative of the report, even though it may also appear elsewhere in the body of the technical report. If additional space is required, a continuation sheet shall be attached.

It is highly desirable that the abstract of classified reports be unclassified. Each paragraph of the abstract shall end with an indication of the military security classification of the information in the paragraph, represented as *(TS)*, *(S)*, *(C)*, or *(U)*.

There is no limitation on the length of the abstract. However, the suggested length is from 150 to 225 words.

14. KEY WORDS: Key words are technically meaningful terms or short phrases that characterize a report and may be used as index entries for cataloging the report. Key words must be selected so that no security classification is required. Identifiers, such as equipment model designation, trade name, military project code name, geographic location, may be used as key words but will be followed by an indication of technical context. The assignment of links, rules, and weights is optional.

GPO 886-551

Unclassified
Security Classification