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Physiologic Response to Increased Oxygen Partial Pressure I. Clinical Observations

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ABSTRACT

Eight healthy, young airmen were experimental subjects in 2 space cabin simulator experiments. Two other healthy volunteers served as outside controls for each experiment. Experiment 63-3 had an average total pressure of 700 mm. Hg with a P_{O_2} of 233 mm. Hg and a P_{N_2} of 436 mm. Hg. Experiments 63-4 had an average P_T of 258 mm. Hg with a P_{O_2} of 254 mm. Hg. Experiment 63-4 had an average P_T of 258 mm. Hg with a P_{O_2} of 254 mm. Hg and an average P_{N_2} of 0.5 mm. Hg. The atmosphere was well-tolerated by the young subjects who demonstrated very few of the previously described symptoms of oxygen toxicity.[5, 6, 11] The aural atelectasis and nasal congestion were bothersome but did not interfere with mission completion. This was the only area where the presence or absence of nitrogen made a noticeable difference.

Dark adaptation studies and renal function measurements failed to outline any decrease in function, either at 700 mm. Hg or 258 mm. Hg. The use of a single gas, 258 mm. Hg P_T atmosphere seems to be feasible for periods up to 30 days without any impairment of man's ability to carry out his duties or without creating any physiologic decrement.

THE NEED FOR definitive physiologic information in the selection of spacecraft atmospheres has been and remains a critical area. This is particularly true in considering atmospheres that are very different from that on earth. One such atmosphere is the 258 mm. Hg, 100 per cent oxygen atmosphere.

The amount of data accumulated from both animal[9, 10] and human experiments[2, 3, 5] in the 258 mm. Hg "pure" oxygen atmosphere is still very limited. Data[1] obtained with rats exposed to a 258 mm. Hg "pure" oxygen atmosphere for 1 week[10] shows an increased number and size of liver mitochondria, possibly as a result of hyperoxia.

The conclusions drawn from the human experiments are not entirely consistent and their ultimate meaning remains to be elucidated. For example, Helvey, *et al.*[2] reported a slight anemia in conjunction with abnormalities in the size, shape, and staining characteristics of red blood cells. In addition, abnormal renal function was suggested by the presence of casts and protein in the urine. Morgan, *et al.*[6] and Mammen, *et al.*[3] reported a small drop in hematocrit without the morphological abnormalities. No positive renal findings were reported. The true significance of these findings and their importance is not clear. Additional experiments conducted at 380 mm. Hg in a "pure" oxygen atmosphere[2] suggested the presence of an oxidative anemia. Also, the relative difference in nitrogen partial pressures (0.5 mm. Hg in the work of Helvey, *et al.*[2]; 3 to 5 mm. Hg in the work reported by Morgan, *et al.*,[6] and Mammen, *et al.*[3] may or may not be of importance.[9]

Since the manifestations of oxygen effects may be related to both time of exposure and concentration,[11] the experiments reported here were conducted to determine the following:

a. The clinical, pulmonary and hematologic effects of a 30-day exposure to an atmosphere which provides an alveolar oxygen partial pressure (PA_{O_2}) of approximately 170 mm. Hg, and

b. The effects of nitrogen in this atmosphere by conducting one experiment with a nitrogen partial

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pressure of approximately 0.5 mm. Hg, the other with a nitrogen partial pressure of approximately 436 mm. Hg. Results of the clinical observation are reported here. Results of the pulmonary and hematologic studies are presented in following papers.[8, 12]

METHODS AND MATERIALS

Two experiments were performed using 4 experimental and 2 control subjects in each. The subjects were assigned to the department for a period of 9 weeks. The first and last weeks were spent undergoing a physical evaluation in the Clinical Sciences Laboratory at the USAF School of Aerospace Medicine. The experiments were 42 days in duration. Seven days for control values, 30 days in the experimental environment, and 5 follow-up days was the profile used for both experiments. The environmental conditions maintained during the experiments are listed in Table I.

TABLE I. SUMMARY OF ENVIRONMENTAL CONDITIONS

	EXPERIMENT	
	63-3	63-4
Total pressure (mm. Hg)	700	258
Oxygen partial pressure (mm. Hg)	233.1	254.1
Carbon dioxide partial pressure (mm. Hg)	4.1	1.3
Nitrogen partial pressure (mm. Hg)	436.1	0.5
Relative humidity (%)	71.9	36.9
Water vapor pressure partial pressure (mm. Hg)	16.8	9.0
Temperature (°C.)	24.7	25.6

* Inert gas = approx. 7 mm. Hg in Exp. 63-3.

Experiment 63-4 was a 30-day exposure to essentially pure oxygen at a total pressure (P_T) of 258 mm. Hg. The alveolar oxygen tension ($P_{A_{O_2}}$) in this particular atmosphere was approximately 170 mm. Hg. This same alveolar oxygen tension ($P_{A_{O_2}}$) of approximately 170 mm. Hg was then selected for use in the experiment with the high atmospheric nitrogen content. By using the alveolar gas exchange equations of Rahn,[7] one was able to calculate the percentage of oxygen needed to produce the desired $P_{A_{O_2}}$ in the nitrogen-rich, 700 mm. Hg P_T experiment. By taking this approach, it was possible to determine the effects of an increased amount of oxygen on the pulmonary, hematopoietic and renal systems.

The environment for experiment 63-3 was established by flushing the chamber with pure oxygen for 1 hour while evacuating it to a total pressure (P_T) of 700 mm. Hg. The atmosphere was then maintained by flushing into the chamber an oxygen-air mixture. The rate of flush was used to regulate the carbon dioxide concentration. A small baralyme bed was also used with a recirculating fan when the carbon dioxide levels went above 5 mm. Hg P_{CO_2}.

The environment for experiment 63-4 was established by flushing the chamber with oxygen at ground level while the subjects were denitrogenating. A 3-hour denitrogenation period was accomplished by breathing from aviator's oxygen masks connected to pressure demand regulators. The regulators were set to deliver 100 per cent oxygen. Following the pre-breathing, a gradual ascent to a total pressure of 258 mm. Hg was accomplished over a 2-hour period. By the time the ascent was completed, the oxygen in the chamber had reached 245 mm. Hg P_{O_2}. At this time, the subjects were allowed to remove the masks and begin the daily routine.

The converted altitude chamber used for these experiments had a rectangular main test cell 2.43m × 2.43m × 6.09m, and a lock 2.43m × 2.43m × 3.04m with a total volume of 54m^3. The temperature was noted from a mercury bulb thermometer calibrated in degrees Centigrade. The oxygen was sensed by a Beckman F-3 paramagnetic oxygen analyzer. The carbon dioxide sensor was a Beckman infrared analyzer, model 15A, and nitrogen was measured with a Nitralyzer, model 300AR nitrogen analyzer made by Med Sciences Electronics. The relative humidity was recorded with an El-Tronics relative humidity sensor. Total pressure readings were recorded every 15 minutes from a direct reading aneroid pressure gauge which was monitored constantly by an altitude chamber technician. The other ground crew members read the gas analyzers every 15 minutes and recalibrated the instruments at least every 12 hours. All analyzers were calibrated on a dry gas basis. Periodically, a Beckman E-2 oxygen analyzer was used as a cross-check. Nitrogen was also checked on a Waters nitrogen analyzer. Oxygen was supplied from a 1900 liter liquid oxygen converter which required servicing approximately every 3 days with 1600-1800 liters of aviation grade liquid oxygen. The oxygen flush rate necessary to maintain the P_{N_2} below 0.75 mm. Hg was between 8,000 and 12,000 liters of gaseous oxygen per hour.

The test subjects were volunteer airmen from Lackland Air Force Base selected upon the basis of motivation, past medical history, and educational back-

TABLE II. PHYSICAL CHARACTERISTICS OF TEST SUBJECTS

SUBJECT NUMBER	AGE (yrs.)	HEIGHT (cm.)	WEIGHT (kg.)	
			Pre-exp.	Post-exp.
		EXPERIMENT 63-3 (P_T 700 mm. Hg)		
38	19	182.9	80.81	85.00
39	19	190.5	86.60	89.45
40	21	172.7	61.94	61.91
41	24	173.9	71.22	76.14
* 42	19	187.9	72.27	72.27
* 43	19	187.9	90.00	90.00
		EXPERIMENT 63-4 (P_T 258 mm. Hg)		
44	18	172.7	59.31	61.97
45	18	175.3	65.75	69.00
46	19	182.9	69.74	73.55
47	19	167.6	65.65	69.65
* 48	18	185.4	71.81	72.27
* 49	21	170.2	66.81	66.81

* Outside control subjects.

TABLE III. EXPERIMENTAL PROTOCOL—EXPERIMENTS 63-3 AND 63-4

Sunday					Monday					Tuesday					Wednesday					Thursday					Friday					Saturday				
P	R	V	C	H	P	R	V	C	H	P	R	V	C	H	P	R	V	C	H	P	R	V	C	H	P	R	V	C	H	P	R	V	C	H
					1 2	1 2	1	1 2 3	1 3 4	1 2 3	1	1			1 2 5	1 2	1	1 2 3	1 3 4	1 2 3	1	1			1 2 5	1 2	1	1 2 3	1 3 4	1 2	1	1		
1 2	1	1			1 2 3	1	1		* 1	1 2 3	1 2	1	1 2 3	1 3 4	1 2	1	1		1 3	1 2	1 2	1	1 2 3	1 3 4	1 2	1	1			1 2 3	1 2	1	1 2	1 3 4
1 2	1	1			1 2	1 2	1	1 2 3	1 2	1 2	1	1			1 2	1	1			1 2 3 5	1 2	1	1 2 3	1 3 4	1 2	1	1			1 2	1	1		
1 2	1 2	1	1 2 3	1 3 4	1 2	1	1			1 2 3	1	1			1 2	1 2	1	1 2 3	1 3 4	1 2	1	1			1 2	1 2	1		2 3 4	1 2	1	1		
1 2 3	1	1			1 2 5	1 2	1	1 2 3	2 3 4	1 2	1	1			1 2	1	1		2	1 2	1	1			1 2 3	1 2	1	1 2 3	2	1 2	1	1		
1 2	1	1		2	1 2	1	1			1 2	1	1			1 2 3 4 5	1 2	1	1 2 3	** 2 3 4	1 2	1	1			1 2 3	1 2	1	1 2	3 4 3	1 2	1	1		
1 2	1	1			1 2 5	1 2	1	1 2 3	3 4																									

* First day of experimental atmosphere.
** Last day of experimental atmosphere.

TABLE III. KEY TO SYMBOLS

P=Pulmonary Studies
- P_1=Basal metabolic rate and Rahn sample.
- P_2=Forced Vital Capacity.
- P_3=Maximum breathing capacity.
- P_4=Diffusion capacity and residual volume.
- P_5=Arterial and alveolar gas analysis.

H=Hematology
- H_1=Cr^{51} TAG and samples.
- H_2=Fe^{59} TAG and samples.
- H_3=CBC, reticulocyte count, osmotic fragility, Heinz body prep, methemoglobin.
- H_4=Glucose 6-phosphate dehydrogenase and glutathione and glutathione stability.

R=Renal Function
- R_1=Urinalysis with microscopic and osmolarity.
- R_2=Urine creatinine for creatinine clearance.

V=Vision Studies
- V_1=Dark adaptation studies.

C=Chemistry Determinations.
- C_1=Urine urobilinogen.
- C_2=Bilirubin—direct, indirect and creatinine.
- C_3=Serum proteins and electrophoresis and fecal urobilinogen—carried out on 3-day sample.

ground. The pertinent characteristics of these subjects are listed in Table II.

The general experimental design for both experiments is outlined in Table III. The morning routine of BMRs, blood pressures, temperatures (rectal), electrocardiograms, body weights (nude, after voiding, to ±5 gm.), pulmonary function studies, and venepunctures required about 120 minutes. Following this, they ate breakfast which was recorded on a tally sheet with all food and liquid intakes as well as a complete output record. The noon meal was served at 1330 hours. At 1500 hours, 2 subjects performed dark adaptation studies on each other. The evening meal was served at 1900 hours. The remainder of the time was free for them to watch television, read, listen to music, or sleep. The subjects were required to have at least 7 hours of sleep before the basal metabolic rates were determined. Two subjects were awake at all times while the altitude phases of the experiments were conducted.

The materials amd methods for the pulmonary and hematologic portions of these experiments are noted in two following papers.[8, 12]

Creatinine clearances using 24-hour urine samples and serum creatinine concentrations at 0800 hours the morning following the urine collection were used as an approximation of renal function. Daily urinalyses on freshly voided morning samples were performed. Specific gravity, pH, protein, glucose, occult blood, osmolar concentration by freezing point depression, and a complete microscopic examination were carried out on each sample. Combistix* were used for the protein and glucose determinations.

A Goldman-Weekers dark adaptometer was used to determine a series of dark adaptation curves for each subject. Three pre-experiment, 15 experiment, and 3 post-experiment curves were determined for each subject. The subjects had a 2-minute period of dark adaptation and 5 minutes of light adaptation. Following this, a maximum contrast target illuminated at a level of 1.1 lux was exposed to the subjects and the measurements were carried out for 40 minutes.

The meals were prepared from frozen foods stored near the chamber and passed in through the pass-

* Trade name for Ames Company, Inc. brand of urinary test sticks.

lock. A typical breakfast consisted of fruit or fruit juice, toast with butter and jelly, cereal with milk and sugar, and milk and coffee. Lunch consisted of meat and cheese sandwiches or "pot" pies with milk, cookies, coffee and fruit juice. Dinner featured a "TV" dinner package, supplemented with fruit, bread, milk, cookies or cake, and coffee. Rock candy and cookies served as evening snacks. The subjects were allowed an ad libitum diet, the one requirement being to record all food consumed.

RESULTS

Clinical Observations:—The 700 mm. Hg P_T experiment was very remarkable in that the subjects had no complaints whatsoever. The number of symptoms expressed during the 258 mm. Hg experiment also were surprisingly small in view of previous experience in the space cabin simulator.[5, 6] The notable findings from that experiment are tabulated in Table IV. The only consistent findings were aural atelectasis and nasal congestion. The aural atelectasis normally was noticed immediately upon awakening in the morning and usually could be cleared by a Valsalva maneuver. One individual had persistent difficulty which required the use of Pseudoephedrine—30 mgm. every 6 hours for 4 days with ¼% neosynepherine nasal spray used as needed. The nasal congestion was most troublesome in the first 10 days of the experiment. During the first week, this was related to the low relative humidity maintained in the chamber. This low relative humidity was due mostly to the high flush rate of approximately 8-12,000 liters of gaseous oxygen per hour. When the atmosphere was well-established and the humidity was increased, the mucous membrane problem disappeared.

TABLE IV. POSITIVE RESPONSES TO MEDICAL APPRAISAL—EXPERIMENT 63-4

	INCIDENCE	OCCURRENCE
Nasal congestion	4 of 4	multiple
Aural atelectasis	4 of 4	multiple
Cracked lips	4 of 4	4 times
Trapped intestinal gas	2 of 4	3 times
Burning of eyes	1 of 4	3 times
Parasthesiae	1 of 4	1 time
Nasal hemorrhage	1 of 4	1 time
Dermatitis	1 of 4	1 time

The conjunctival injection and burning previously reported by Morgan *et al.*[6] was much less prevalent. One subject reported a "burning" of the eyes during the first 2 days of the experiment.

Intestinal gas complaints occurred 3 times, twice on the same subject. By massaging the abdomen and changing position, he was able to expel the trapped gas.

Parasthesiae occurred in only 1 subject. This occurred on the first day at altitude within several hours after mask removal and was most likely due to hyperventilation.

Thorough weekly examinations of the head, neck and chest were performed as well as any other checks deemed necessary. The only positive findings were erythema and edema of the nasal mucous membranes and decreased mobility of the tympanic membranes while doing a Valsalva maneuver. Crepitant rales were heard posteriorly at the bases bilaterally in 2 subjects on one occasion. One subject developed a papular rash on the seventh day of the altitude phase of experiment 63-4. The rash began on the anterior thorax and neck as small papules about 3 mm. in diameter. The rash progressed down the flexar surfaces of the forearms with areas of erythema 2-3 cm. in diameter surrounding the papules. In 10 days, the erythema receded but some of the papules were still present on the arms at the termination of the experiment. The rash greatly resembled parasitic bites but only 1 of 4 men had the rash and it remained well localized.

Comparison of Pre- and Post-Experiment Evaluations:—The 8 airmen, who were the actual inside experimental subjects were examined by an ophthalmologist within 2 hours after the termination of the experimental phase of the study. The ophthalmological examinations did not reveal any changes post-experimentally when compared to the pre-experimental examinations.

Work capacity as determined by the angle-increment treadmill method of Balke[1] was measured before the pre-experiment control period and after the post-experiment control period. The results of these tests are shown in Table V. The post-experiment decrease in treadmill time has been a uniform finding in all of the space cabin simulator subjects, and is probably related to confinement and lack of activity. This decrement of 35 per cent agrees with the previously noted

TABLE V. TREADMILL TOLERANCE AFTER 30-DAY CONFINEMENT

SUBJ. NO.	AGE (yrs.)	TREADMILL TIME (min.) Pre-exp.	Post-exp.	CHANGE (min.)	PERCENT DECREASE
		EXPERIMENT 63-3			
38	19	21	15	-6	28.6
39	19	19	11	-8	42.1
40	21	16	9	-7	43.7
41	24	13	9	-4	30.8
MEAN		17.25	11	6.25	36.3
		EXPERIMENT 63-4			
44	18	17	10	-7	41.2
45	18	16	10	-6	37.5
46	19	18	15	-3	16.7
47	19	18	11	-7	38.9
MEAN		17.25	11.5	5.75	33.6
MEAN FOR 8 SUBJECTS		17.25	11.25	6	34.9

decrement[5] of 29 per cent observed in an experiment in the two-man space cabin simulator.

The dark adaptation curves were subjected to statistical analysis at the 5- and 30-minutes points of the curves. There was no decrement in the ability to dark-adapt either while in the increased oxygen atmosphere or following the return to ambient air. Composite curves were made for each man and these did not show any change when compared pre-experimentally, experimentally, and post-experimentally.

The daily urinalyses did not reveal any change during the entire 42-day period. No trends or indications of renal embarrassment were found. The creatinine clearances and osmolarity determinations did not reveal any urinary function decrement. Thirty and sixty-day followup studies were normal in 7 of the 8 experimental subjects. The eighth had pyuria on the 60-day study but 3 morning samples a week later were normal.

DISCUSSION

These experiments were designed to add additional quantitative data to the pool of physiologic information being gathered to make space cabin atmosphere selection a process based on solid, well-documented experimentation rather than hypothetical considerations.

The nitrogen content of the atmosphere in experiment 63-3 was maintained at a P_{N_2} of 436 mm. Hg, whereas, the nitrogen content of the atmosphere in experiment 63-4 was kept below 1 mm. Hg P_{N_2}. These gas concentrations were checked on the auxiliary analyzers which supported the findings of the monitoring equipment. There were three exceptions to the above conditions. The first incident occurred 74 hours after establishing the 258 mm. Hg environment. An adjacent chamber using the same vacuum source was evacuated at a rate exceeding the vacuum pump capacity, thereby allowing ambient air to bleed into the experimental chamber. This resulted in a rise of 15 mm. Hg in total pressure and a nitrogen increase to 9.03 mm. Hg P_{N_2}. The pressure was corrected immediately but it required 3 hours to bring the nitrogen level back to 0.50 mm. Hg P_{N_2}.

On the twelfth day of the experiment, two bolts on the pass-lock were stripped and it became necessary to bring the examining medical officer to ground level in the large chamber lock. This lock was then flushed for 1 hour with 100 per cent oxygen but the nitrogen content remained sufficiently high that the entire test cell equilibrated at a P_{N_2} of 11.7 mm. Hg. The oxygen flush rate was increased and the P_{N_2} of 0.5 mm. Hg was reached within two and one-half hours. The third incident occurred 48 hours prior to the termination of the experiment when the sump for waste water drainage was left open to ambient air and the nitrogen rose to 3.09 mm. Hg P_{N_2}. This, however, was corrected rapidly and atmospheric conditions were re-established within 1 hour.

During the course of experiment 63-4, three clinical rectal thermometers were broken on the inside of the chamber. These thermometers were broken on the fifth and tenth and twenty-ninth days of the hyperoxic phase of this experiment. The subjects scrupulously cleaned the floor in the lock where the thermometers were broken and passed all cleaning utensils to the outside in a paper bag.

The most interesting points of these experiments were the lack of complaints or symptoms usually attributed to signs of oxygen toxicity.[5, 6, 11] The subjects in the 700 mm. Hg P_T experiment had no complaints at all. The 5 psi or 258 mm. Hg P_T subjects had very few symptoms. These people were given an Air Force passenger-type altitude indoctrination course which explained basic altitude physiology. However, caution was taken to prevent the suggesting of symptoms by refraining from asking leading or provocative questions.

Difficulties due to decompression sickness were not encountered in these studies. The 3 hours of denitrogenation accomplished at an ambient pressure of 750 mm. Hg ± 5 mm. Hg followed by 2 more hours of 100 per cent oxygen administered by aviator's masks, while a gradual ascent to 258 mm. Hg was made, was adequate to prevent the occurrence of any evolved gas-type of decompression sickness.

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