HEI HEALTH EFFECTS INSTITUTE

Maximal Aerobic Capacity at Several Ambient Concentrations of Carbon Monoxide at Several Altitudes

Steven M. Horvath, James W. Agnew, Jeames A. Wagner, and John F. Bedi

Institute of Environmental Stress, University of California, Santa Barbara, CA

Includes the Report of the Institute's Health Review Committee

Research Report Number 21

HEALTH EFFECTS INSTITUTE

HEI

The Health Effects Institute (HEI) is a nonprofit corporation founded in 1980 to assure that objective, credible, high-quality scientific studies are conducted on the potential human health effects of motor vehicle emissions. Funded equally by the U.S. Environmental Protection Agency (EPA) and 27 automotive manufacturers or marketers in the United States, HEI is independently governed. Its research projects are selected, conducted, and evaluated according to a careful public process, including a rigorous peer review process, to assure both credibility and high scientific standards. HEI makes no recommendations on regulatory and social policy. Its goal, as stated by former EPA Administrator William D. Ruckelshaus, is "simply to gain acceptance by all parties of the data that may be necessary for future regulations."

Research Agreement No. 84-6

Printed at Capital City Press, Montpelier, VT

TABLE OF CONTENTS

Research Report No. 21

Maximal Aerobic Capacity at Several Ambient Concentrations of Carbon Monoxide at Several Altitudes

INVESTIGATORS' REPORT Steven M. Horvath, James W. Agnew, Jeames A. Wagner, and John F. Bedi

HEALTH REVIEW COMMITTEE'S REPORT Health Effects Institute

ABBREVIATIONS

ANOVA	analysis of variance
$C_{a_{O_2}}$	content of oxygen in arterial blood
CO	carbon monoxide
CO_2	carbon dioxide
COHb	carboxyhemoglobin
fc max	maximal heart rate
fR	respiratory rate
Hb	hemoglobin
maximum $\dot{V}_{O_2}$	highest $\dot{V}_{O_2}$ achieved in exercise test
metHb	methemoglobin
O_2Hb	oxyhemoglobin
$P_{a_{O_2}}$	partial pressure of oxygen in arterial blood
P_{O_2}	partial pressure of oxygen
R	respiratory exchange ratio
STPD	standard temperature and pressure (0°C, 760 mm Hg), dry
$\dot{V}_E$ BTPS	volume of expired gas; body temperature and pressure, saturated with water vapor
$\dot{V}_{O_2}$	oxygen uptake per minute
$\dot{V}_{O_2}$max	maximal aerobic capacity
WI	work increment

Maximal Aerobic Capacity at Several Ambient Concentrations of Carbon Monoxide at Several Altitudes

Steven M. Horvath, James W. Agnew, Jeames A. Wagner, and John F. Bedi

ABSTRACT

In order to assess the combined effects of altitude and acute carbon monoxide exposure, 11 male and 12 female subjects, nonsmokers in good health, were given incremental (two minutes at each workload) maximal aerobic capacity tests at four levels of ambient carbon monoxide (0, 50, 100, and 150 parts per million) at four altitudes (55, 1,524, 2,134, and 3,048 m). Five male and four female subjects completed all 16 experiments. The remaining subjects completed either eight or 12 experiments; at least eight male and eight female subjects were tested at each combination of carbon monoxide and altitude. Test conditions were double-blind.

Subjects initially were screened with a medical history questionnaire, a 12-lead electrocardiogram, pulmonary function tests, anthropometric and body fat measurements, blood volume determinations, and a maximal aerobic capacity test. Each subject, after attaining the required altitude and ambient carbon monoxide level, performed the maximal aerobic capacity test (maximum $\dot{V}_{O_2}$) meeting required conditions to assure that a maximal level was attained. Blood samples were drawn prior to the aerobic capacity test; at workloads of 50 watts, 100 watts, 150 watts, and maximum; at the fifth minute of recovery; and prior to repressurization to sea level. Blood was analyzed for hemoglobin, hematocrit, plasma proteins, lactates, and carboxyhemoglobin. Carbon-monoxide-carboxyhemoglobin uptake rates were derived from the submaximal workloads.

Maximum $\dot{V}_{O_2}$ was similar at 55 m and 1,524 m, and decreased from the 55-m value by 4 percent at 2,134 m and by 8 percent at 3,048 m. Despite increases in carboxyhemoglobin, no additional significant decreases in maximal aerobic capacity were observed. With increasing carbon monoxide, a decrease in maximum $\dot{V}_{O_2}$ independent of altitude was observed. Carboxyhemoglobin concentrations at maximum $\dot{V}_{O_2}$ were highest at 55 m and lowest at 3,048 m. Carboxyhemoglobin concentrations were lower in female subjects than in male subjects. Immediately prior to and at maximal workloads, carbon monoxide shifted into extravascular spaces and returned to the vascular space within five minutes after exercise stopped.

We demonstrated that altitude hypoxia and carbon monoxide hypoxia act independently on the parameters of the maximal aerobic capacity test. We also demonstrated a decrease in the carbon monoxide concentration to carboxyhemoglobin as altitude increased, which can be attributed to the decrease in driving pressure of carbon monoxide at altitude.

INTRODUCTION

It has been suggested that the ambient CO standards set for sea level are probably too low for altitudes of 1,500 m (4,920 feet) and above (Mitchell et al. 1979). This opinion is based upon studies conducted prior to 1950 (U.S. Environmental Protection Agency 1979) that were concerned with psychophysiological effects of hypoxia induced by exposure to combinations of altitude and carbon monoxide. These evaluations provided the basis for a concept that there are physiologically equivalent altitudes dependent upon the ambient concentrations of carbon monoxide.

In 1976, the states of California and Nevada adopted ambient standards for the Lake Tahoe air basin (1,900 m; 6,231 feet) that were more stringent than federal standards, that is, 6 parts per million (ppm) rather than 9 ppm averaged over eight hours (Collier and Goldsmith 1983). Mitchell and associates (1979) justified this concept by stating that COHb levels at sea level would occur during exposure to lower ambient CO concentrations at 1,500 m. The state standards were calculated from the model developed by Coburn, Foster, and Kane (CFK) (1965). The CFK model was originally developed for quasi-steady-state responses to low ambient CO concentrations and was primarily concerned with an attempt to describe the endogenous formation of COHb. Collier and Goldsmith (1983) acknowledged an error in their original calculations for the California-Nevada standard and used the CFK model to recalculate, expanding the computations to include factors relating to the ambient CO concentration and altitude. They concluded that the expected altitude effect would be small. These conflicting opinions required experimental evidence to resolve the question(s) whether altitude and CO exposure induced additive effects. Studies involving exposure to combinations of several CO

Dr. Steven Horvath, Professor of Physiology and Biomedical Engineering, Institute of Environmental Stress, University of California, Santa Barbara, CA 93106.

concentrations and several altitudes of 1,500 m or more where more than two million people lived and engaged in strenuous activity would provide definitive confirmation of the additive hypothesis.

Some experimental evidence has indicated that physiological functions are altered by elevated COHb concentrations. Horvath and colleagues (1975) reported that maximal oxygen uptake was reduced in the presence of 4 to 5 percent COHb induced by a bolus technique. Similar observations were made by Klein and colleagues (1980) and Klausen and associates (1983). Raven and coworkers (1974) noted a diminished exercise time with smaller COHb levels, which were obtained by the continuous breathing of 50 ppm CO. Gliner and associates (1975) found higher heart rates occurred during submaximal work with elevated COHb levels. As blood COHb levels increase to approximately 30 percent, further and greater decreases in maximal oxygen uptake are observed, the relationship being essentially linear, that is, percent decrease in oxygen uptake = 0.91 (Δ percent COHb) + 2.2 (Horvath et al. 1975).

Linear decreases in maximal aerobic capacity are also observed in individuals acutely exposed to increasingly higher altitudes (Dill et al. 1966; Elliot and Atterbom 1978; Wagner et al. 1979; Horvath 1981; Squires and Buskirk 1982).

There are few studies dealing with the effects of air pollutants at high altitudes on human health and physiological responses. The psychophysiological effects provided the basis for a concept that there are physiological equivalents. For example, for an individual who reaches COHb equilibrium at an altitude of 3,048 m with an ambient CO concentration of 100 ppm, the altitude equivalent is 5,468 m when an ambient CO concentration is 0 ppm. There is, however, no concensus in the literature on whether the effects of the combination of hypoxic states are additive or synergistic. Increased COHb levels could aggravate the oxygen deficiency present at altitude. However, decreased partial pressure of oxygen (P_{O_2}) in inspired air and increased COHb induce different physiological responses. They have different effects on the P_{O_2} in blood, on the affinity of oxygen for hemoglobin, on ventilatory drive, and on the position of the oxygen dissociation curve (the presence of COHb shifts the curve to the left while a decrease in the partial pressure of oxygen in arterial blood [$P_{a_{O_2}}$] shifts it to the right). Consequently, CO (as COHb) lowers the oxygen content of the blood, but, more important, its presence impairs oxygen unloading at the tissue level.

In resting humans, these hypoxic stressors could cause serious impairment to hypoxic intolerant organs such as heart, brain, and eye. A more critical situation may occur during physical work when increased oxygen delivery is needed. During maximal exercise, where capacity for effort is dependent mainly on aerobic metabolism, Horvath and coworkers (1975) found that a linear decline in maximal aerobic capacity ($\dot{V}_{O_2}$max) occurred when COHb levels induced by a bolus inhalation of CO ranged from 4 to 33 percent; that is $\dot{V}_{O_2}$max (percent decrease) = 0.91 (percent COHb) $\pm$ 2.2. Subjects breathing 50 ppm CO while undergoing a progressively increasing work level test requiring 15 to 24 minutes to reach $\dot{V}_{O_2}$max showed no reduction in $\dot{V}_{O_2}$max. Carboxyhemoglobin concentrations were 2.8 percent at the end of this exposure (Raven et al. 1974). Horvath and associates (1975), in a double-blind study in which a small number of subjects breathed either filtered air or air with CO (75 ppm and 100 ppm), showed that the threshold level of COHb was 4.3 percent for statistically significant physiological alterations in $\dot{V}_{O_2}$max to be demonstrated. All of these studies were conducted at sea level conditions and utilized men as experimental subjects.

The physiological responses of humans exposed to CO at high altitudes are not known. Louomanmaki and Coburn (1969) presented evidence that CO may pose a threat at altitude in excess of the altitude hypoxic effect. When arterial P_{O_2} in dogs was lowered, CO shifted out of the blood and into the tissue space. CO may also move into the extravascular compartment during maximal excerise when venous P_{O_2} may be drastically lowered. In the present study, maximum $\dot{V}_{O_2}$ was evaluated while individuals exercised while breathing different concentrations of ambient carbon monoxide at several altitudes up to 3,048 meters.

AIMS

Previous research has shown that carboxyhemoglobin (COHb) concentrations of approximately 4 to 5 percent and above significantly reduced human ability to perform at maximal levels (Horvath et al. 1975). The decreases in maximal aerobic capacity were linearly related to the concentration of COHb. However, in these studies COHb levels were induced by inhalation of high concentrations of carbon monoxide (CO). In only one study did individuals breathe a fixed ambient concentration of CO while performing a maximal aerobic test (Raven 1974). While maximal oxygen uptake was not affected, the duration of performance was reduced. There was a need to replicate this study and to have individuals perform maximal aerobic tests while breathing several different concentrations of carbon monoxide. The studies reported here were performed at sea level, where oxygen availability was reduced by increasing carboxyhemoglobin concentrations.

It had been projected that individuals in a hypoxic state

due to breathing lower partial pressures of oxygen (as at altitude) who were also exposed to CO would result in additive effects due to further reductions in the oxygen-carrying capacity of the blood. These projections suggest that reduced maximal aerobic capacity at high altitudes would be further reduced when ambient carbon monoxide was also present in the atmosphere. We therefore conducted experiments at altitudes of 55, 1,524, 2,134, and 3,048 meters with ambient CO concentrations of 0, 50, 100, and 150 ppm to evaluate this additive hypothesis. The studies were conducted at altitudes equal to those in areas where significant U.S. populations reside and ambient carbon monoxide concentrations exceed the U.S. Environmental Protection Agency (EPA) standard.

METHODS

SUBJECTS

Eleven male and 12 female subjects, nonsmokers between the ages of 18 and 36 years and in good health, served as experimental subjects. The nature and purpose of the study and the risks involved were explained verbally and on a written form given to each subject prior to his or her voluntary consent to participate. The protocol and procedures for this study were approved by the Committee on Activities Involving Human Subjects, University of California, Santa Barbara. Five of the male and four of the female subjects (Group I) completed all of 16 experimental conditions. The remaining subjects completed either eight or 12 experiments, which were organized so that a total of eight male and eight female subjects participated in each experimental CO condition at sea level, 2,134-m, and 3,048-m altitudes, and nine male and nine female subjects participated in each CO condition at 1,524-m altitude. Subjects were initially screened with a medical history questionnaire, a 12-lead electrocardiogram (ECG), pulmonary function tests, anthropometric and percent body fat measurements, blood volume determination (Dahms et al. 1975), and the maximal exercise test used during the actual experiments. All pertinent subject data are included in Table 1.

The subjects reported to the laboratory at the same time of day, between 12:00 and 2:00 p.m. Each subject was weighed and a catheter with a heparin lock was then inserted into an antecubital vein for serial blood sampling during the experiment. Upon entering the hypobaric chamber, three ECG spot leads were positioned on the thorax.

EXPOSURE CONDITIONS

Four ambient CO levels (0, 50, 100, and 150 ppm) were used at each of the four altitudes employed: sea level (55 m) and simulated altitudes of 1,524 m (5,000 feet, 632 torr), 2,134 m (7,000 feet, 586 torr), and 3,048 m (10,000 feet, 523 torr). The simulated altitudes were obtained by depressurization of the hypobaric chamber at a rate of 1,000 feet per minute. In preparation for the sea level conditions the chamber was depressurized to 3,000 feet and then repressurized, at the same rate, to simulate depressurization procedures during altitude conditions. Table 2 illustrates the steps of the exposure protocol.

Generally two subjects were studied on each occasion, and consecutive experiments were separated by at least one to three weeks. The order of subject rotation through the experiments was randomized. When it became clear that some subjects would not continue with all 16 exposures, two of these subjects were assigned to an altitude group and exposed to different CO levels within the altitude group, counterbalanced for ambient CO level. That is, each subject was assigned to an altitude group. Within that group, two subjects received each CO concentration, cycling through the four concentrations. The experiments were conducted in a double-blind fashion.

Ambient temperature for all experiments was 21°C to 23°C and 30 to 40 percent relative humidity. After calibration of all equipment and before CO was admitted to the altitude chamber, the subjects breathed filtered room air with no CO through standard oxygen masks until they began to exercise.

Carbon monoxide was delivered into the air conditioning system of the hypobaric chamber from high-pressure cylinders outside the chamber. The concentration of CO was continuously monitored and recorded by operators outside the chamber who observed the analog meters of three Energetics Science ecolyzers (Series 2000) within the chamber through a glass panel in the chamber. The ecolyzers were positioned so that neither the observers inside the chamber nor subjects could view the analog meters.

EXERCISE PROTOCOL

Each male and female subject performed a maximal exercise test with the same increments on a Monark (model 1409) stationary bicycle. This test consisted of pedaling at 50 rpm for two minutes at progressively increasing workloads. Beginning at no resistance, the resistance was increased to 50 watts (300 kgm/min), and then by 25 watts (150 kgm/min) for each subsequent workload until the subject could no longer maintain the required pedaling frequency or volitional termination. A recovery period of five minutes followed in which the subjects continued pedaling at the same frequency with no resistance.

Table 1. Anthropometric Data of the Subjects

Subject	Age (yr)	Height (in)	Weight (kg)	BSA[a] (m^2)	% Fat	Maximal Aerobic Capacity (l/min^{-1})	Maximal Aerobic Capacity ($ml/kg^{-1}/min^{-1}$)
Men							
1	26	72.8	72.0	1.95	10.5	3.52	46.41
3	20	73.5	97.5	2.24	20.0	4.64	47.80
4	20	75.8	77.8	2.05	8.0	4.26	54.18
5	20	72.0	75.0	1.97	12.0	4.30	55.90
9	22	66.7	60.7	1.72	16.5	3.22	53.82
10	22	66.0	59.6	1.67	13.0	2.80	47.60
13	24	69.0	66.6	1.78	9.0	3.04	47.42
14	31	71.0	87.0	2.10	13.0	4.67	55.80
20	33	76.8	89.6	2.22	9.0	4.84	52.53
21	19	67.5	66.0	1.79	13.0	4.00	60.43
23	18	74.8	78.8	2.04	9.0	3.55	43.96
Mean	23.2	71.5	75.6	1.96	12.1	3.89	51.44
SD	4.9	3.7	12.2	0.20	3.6	0.71	5.09
Women							
2	31	67.2	53.4	1.61	16.0	2.10	39.96
6	36	54.5	58.0	1.63	22.0	2.16	37.18
7	18	61.7	45.8	1.43	14.0	1.72	37.10
8	23	68.0	54.3	1.64	15.0	2.72	49.98
11	27	65.3	58.8	1.64	25.0	1.88	31.44
12	28	64.0	56.5	1.61	23.0	2.29	39.75
15	25	70.3	65.8	1.83	23.0	2.68	40.96
16	18	62.0	48.4	1.46	23.0	2.80	47.60
17	27	61.0	50.3	1.47	24.0	1.80	35.83
19	28	68.4	58.0	1.70	17.6	2.08	35.87
25	18	67.9	62.0	1.73	17.0	—[b]	—
26	18	69.0	64.2	1.78	25.0	2.77	42.87
Mean	24.8	64.9	56.3	1.63	20.4	2.27	39.86
SD	5.9	4.5	6.2	0.13	4.1	0.41	5.39

[a] BSA = body surface area in square meters.

[b] — = missing data.

METABOLIC DATA COLLECTION

The ECG was continuously monitored on an oscilloscope and recorded on a Sanborn 320 strip recorder. During work and recovery, the subject breathed chamber air through a three-way Hans Rudolph respiration valve. Minute ventilation and respiratory frequency were measured using Fleish pneumotachographs. Expired oxygen and carbon dioxide (CO_2) concentrations were measured using appropriate analyzers. Oxygen uptake and CO_2 production were calculated via standard open-circuit techniques. The output from the measuring devices were input to a Digital PDP-11/60 laboratory computer that sampled the data at a frequency of 50 Hz. Basic metabolic data (volume of expired gas [$\dot{V}_E$] at body temperature and pressure, saturated with water vapor [BTPS], respiratory rate [fR], exhaled gas composition, oxygen uptake, CO_2 production, heart rate, percent $\dot{V}_{O_2}$max, and ventilatory equivalents for oxygen and CO_2) were averaged and displayed on a terminal every 30 seconds, stored on a disk, and later transferred to tape for additional analysis.

BLOOD SAMPLING TECHNIQUES

Blood was sampled with a 20-gauge 1¼-inch Angiocath (Desenet Medical Corp.) intravenous catheter placement unit with a Parmaseal K55 (Desenet) extension tube. The catheter was inserted into an antecubital vein and the extension tube flushed with sterilized heparin saline. This assembly was then secured in place with surgical tape and further stabilized by taping the arm to a padded board in order to minimize flexion at the elbow.

After at least 20 minutes, during which the subject re-

Table 2. Experimental Protocol

1. Subjects enter chamber.
2. Desired altitude is obtained.
3. Subjects put on a free-flow mask breathing external chamber air.
4. Ambient CO conditions are established.
5. Subject 1 removes mask and starts exercise protocol.
6. Subject 1 terminates protocol and puts on breathing mask.
7. Subject 2 removes mask and starts exercise protocol.
8. Subject 2 terminates protocol.
9. Analyzers are calibrated after the protocol, and the chamber depressurized.

mained seated inside the hypobaric chamber at sea level, an initial blood sample was obtained. The blood sampling during the exercise took place during the last 30 seconds of the 50-, 100-, 150-, and 200-watt workloads. Additional samples were then taken immediately before or after subjects had completed their maximal level of work, during the last 30 seconds of the fifth minute of recovery, and prior to repressurization of the chamber. Immediately upon collection, blood samples were covered with aluminum foil, iced, and passed through a chamber port for analysis. All samples were assayed within one to three minutes for hematocrit by micromethod, hemoglobin by IL 282 CO-Oximeter (Instrumentation Laboratories, Lexington, MA), and COHb both by CO-Oximeter and periodically by a chromatographic techique (Dahms and Horvath 1974) to verify the results of IL 282 with an independent technique. The regression equation obtained for spot samples was as follows:

$$\textit{CO-Oximeter (\% COHb)} = 1.0069\ (\text{COHb chromatograph}) - 0.0100$$
$$r = 0.99$$

The CO-Oximeter was calibrated prior to and immediately after all the blood samples were analyzed using a reference solution with viscosity adjusted to approximately that of whole blood (Cal Dye: Instrumentation Laboratory). Accuracy and precision were validated with a solution of stabilized bovine erythrocytes containing known values for total hemoglobin (Hb), oxyhemoglobin (O_2Hb), COHb, and methemoglobin (metHb). The temperature of the bath was repeatedly checked. All COHb values reported are from the CO-Oximeter. Further checks on total Hb were made by comparing CO-Oximeter values against those obtained by the cyanmethemoglobin method. Plasma proteins were determined by refractometer. Plasma lactates were determined using a Yellow Springs model 23L lactate analyzer (Yellow Springs, OH).

STATISTICAL ANALYSIS

The original design was to have each subject participate in 16 exposures presented in random order. A two-way analysis of variance (ANOVA) with repeated measures of altitude and CO concentration would, with a significant interaction term, allow us to conclude whether there was an effect when altitude and CO were present. The data for male and female subjects were analyzed separately because of differences in erythrocyte mass and ventilatory requirements for exercise work loads exceeding the anaerobic threshold. In the case of the five male and four female subjects who completed all 16 experiments, this analysis was performed. The result from this analysis was designated as Group I. The difference in maximum $\dot{V}_{O_2}$ from filtered air at 55 meters was also analyzed for Group I, increasing the number to nine in the subsequent analysis. Data for all subjects (Group II) were analyzed with a two-way analysis of variance with one grouping factor (altitude) and one repeated-measures factor (CO). The treatment sum of squares was subdivided into linear and deviation terms. The results from this analysis procedure were designated as Group II.

The data from the blood samples were analyzed by first performing least squares linear regression techniques on the parameters of interest with time or workload as the independent variable. This allowed us to compensate for minor differences in sampling times during the exposure and for the problem of an occasional missing blood sample. We examined the uptake of CO during submaximal work periods where the metabolic activity at the tissue level is insufficient to lower P_{O_2} to 40 torr or less. Analysis of the uptake curves was limited to the first portions of the incremental work and exposures, since a stabilization, reduction, or both in the COHb percentage occurred at maximal and during the two preceeding work loads. Consequently linear analysis of uptake against either time of exposure or work load was limited to 150 watts for female subjects and 200 watts for male subjects. A two-way ANOVA with one grouping factor (altitude) and one repeated measure (CO) was used to assess changes in the slope or predicted parameters or both at a fixed time.

The rate of change of metabolic parameters with workload, and hence time since the protocol was fixed, were assessed during submaximal work by linear regression. The slopes of the regression lines were tested for differences between exposures.

When a significant F score was observed for any of the comparisons or interactions (ANOVA), the Tukey post-hoc test (Winer 1971) was used to determine which conditions were responsible for the difference at a minimal acceptance level of $p < 0.05$.

RESULTS

The physical characteristics and $\dot{V}_{O_2}$max for all subjects are listed in Table 1. Male subjects numbers 5, 9, 10, 13, and 14 and female subjects numbers 6, 11, 12, and 16 completed all 16 experimental exposures. The maximal time required to complete all runs was approximately eight months. Male subject number 20 and female subject number 19 completed all CO exposures at 55-, 1,524-, and 2,134-m altitudes. The remaining subjects completed all CO exposures of at least two altitudes. Blood characteristics and oxygen-carrying capacity of all subjects during rest at sea level (55 m) are given in Table 3, and the results of their preliminary pulmonary function tests are given in Table 4. Table 5 shows the mean ambient CO conditions during each of the 16 experimental conditions. For any given ambient CO target concentration the measured level was consistent for each altitude. Figures 1 and 2 illustrate the results of the analysis for $\dot{V}_{O_2}$max for male subjects in Group I and Group II respectively.

GROUP I RESULTS

No significant interaction term was observed in the analysis of the male subjects' data. Significant main effects of altitude were observed for maximum $\dot{V}_{O_2}$, cardiac frequency, kilocals, and ventilatory equivalences for oxygen and CO_2 production. There was no significant CO effect. The analysis of the female subjects' results revealed a significant interaction term for maximum $\dot{V}_{O_2}$ and significant main effects for altitude for maximal ventilation, kilocals, CO_2 output, respiratory quotient, and the ventilory equivalents for oxygen and CO_2. The analysis of the difference measures of $\dot{V}_{O_2}$max resulted in main effects for altitude and CO with

Table 3. Blood Volumes, Hemoglobin, and Oxygen-Carrying Capacity

Subject	Hemoglobin (g/dl)	Blood Volume (l)	Red Cell Volume (l)	Plasma Volume (l)	Total Hemoglobin (g)	Total Hemoglobin (g/kg)	Oxygen-Carrying Capacity (ml)
Men (n = 11)							
3	13.8	8.10	3.25	4.86	1,118	11.6	1,507
4	14.0	7.52	3.00	4.53	1,053	13.6	1,419
5	13.0	6.94	2.46	4.47	867	14.2	1,168
9	14.0	6.65	2.63	4.02	932	15.3	1,255
10	12.3	5.66	2.09	3.58	696	11.7	938
1	14.7	6.95	2.80	4.15	1,021	11.6	1,376
13	13.6	5.83	2.22	3.61	792	11.9	1,067
14	14.2	8.57	3.24	5.33	1,217	13.7	1,639
20	14.2	8.34	3.26	5.08	1,189	13.3	1,602
21	13.8	7.53	2.93	4.59	1,042	15.8	1,404
23	11.6	7.07	2.64	4.44	941	11.6	1,268
Mean	13.6	7.20	2.77	4.42	988	13.1	1,331
SD	0.91	0.94	0.42	0.56	161.8	1.55	217.9
Women (n = 12)							
6	11.1	4.57	1.42	3.15	508	8.8	684
7	11.6	4.97	1.86	3.12	577	12.6	777
8	12.2	5.04	2.05	2.99	615	11.3	829
2	10.6	4.90	1.96	2.94	520	9.7	700
11	12.4	4.59	1.61	2.99	570	9.9	793
16	12.5	3.86	1.40	2.45	482	10.0	649
15	10.7	6.09	2.23	3.87	649	9.9	875
12	10.9	5.09	1.57	3.53	555	9.8	748
17	10.9	4.03	1.25	2.77	439	8.6	592
26	12.0	5.93	2.08	3.85	712	11.1	959
25	11.3	6.04	1.98	4.06	682	11.0	919
19	10.8	4.65	1.46	3.20	503	8.8	678
Mean	11.4	4.98	1.74	3.24	568	10.1	766
SD	0.70	0.73	0.32	0.49	83.6	1.19	113.5

Table 4. Spirographic Values of Subjects

Subject	FVC[a] (ml)	FEV_1[b] (ml)	FEV_3[b] (ml)	ERV[c] (ml)	FRC[d] (ml)	MVV[e] (l/min)	MMEF[f] (l/sec)	$MEF_{50\%}$[f] (l/sec)	$MEF_{25\%}$[f] (l/sec)	$\%FEV_1$[g]
Men										
1	6,490	5,220	6,470	3,188	4,934	227	4.73	5.14	2.40	80.4
3	6,010	5,130	5,910	2,428	3,550	222	5.10	5.13	3.59	85.4
4	6,300	5,200	6,140	2,880	4,686	187	5.21	5.83	2.94	82.5
5	6,060	4,370	5,890	2,208	3,244	168	3.58	3.57	2.17	72.1
9	4,490	3,290	4,240	1,586	2,560	170	2.50	2.96	1.23	73.3
10	5,170	4,400	5,020	1,904	2,957	200	4.74	6.10	2.35	85.1
13	5,420	4,760	5,310	2,140	3,627	215	5.90	7.09	2.72	87.8
14	6,530	5,710	6,390	2,520	4,132	240	6.62	7.39	3.42	87.4
20	7,640	5,190	7,280	2,554	5,420	230	3.93	5.26	1.96	67.9
21	5,660	4,710	5,470	1,671	2,878	188	4.89	5.85	2.32	83.2
23	5,730	4,010	5,240	2,334	3,851	146	2.59	3.76	1.03	70.0
Mean	5,954.6	4,726.4	5,760	2,310.4	3,803.5	199.4	4.53	5.28	2.38	79.6
SD	823.1	680.1	825.2	484.9	911.5	30.1	1.28	1.40	0.80	7.4
Women										
2	4,110	3,680	4,080	1,768	3,194	150	4.13	4.46	2.28	89.5
6	3,770	3,320	3,760	1,874	3,217	157	3.66	3.62	2.56	88.1
7	3,311	3,060	3,260	1,138	2,404	136	3.72	4.29	1.88	92.4
8	4,240	3,700	4,230	1,733	2,900	139	3.79	4.22	2.52	87.3
11	4,220	3,600	4,160	1,942	3,081	157	4.25	5.41	2.16	85.3
12	4,280	3,490	4,270	1,966	3,128	157	3.37	3.37	1.73	81.5
15	4,620	4,110	4,590	2,089	3,551	190	4.14	3.13	2.23	89.0
16	3,680	3,230	3,660	1,580	2,604	116	3.76	3.86	1.94	87.8
17	3,710	3,440	3,690	1,578	2,867	116	5.01	6.03	2.64	92.7
19	4,460	3,360	4,390	1,885	3,357	152	2.76	4.92	1.00	75.3
25	4,080	3,560	4,000	1,562	2,510	158	4.57	5.85	2.28	87.3
26	3,950	3,350	3,850	1,343	2,428	133	3.56	4.25	1.85	84.8
Mean	4,035.9	3,491.7	3,995.0	1,795.3	2,846.3	146.8	3.89	4.45	2.09	86.8
SD	369.3	270.0	368.9	321.4	586.3	20.5	0.58	0.94	0.45	4.7

[a] FVC = forced vital capacity.

[b] FEV_1 = forced expiratory volume in one second (3 indicates three seconds).

[c] ERV = expiratory reserve volume.

[d] FRC = functional residual capacity.

[e] MVV = maximum ventilatory volume.

[f] MMEF = mean maximum expiratory flow; $MEF_{50\%}$ = maximum expiratory flow at 50 percent (or at 25 percent) of FVC.

[g] $\%FEV_1 = FVC/FEV_{10} \times 100$.

Table 5. Ambient Carbon Monoxide Concentrations in the Exposure Chamber

Target Concentration (ppm)	Altitude (m)			
	50	1,524	2,134	3,048
0	0.4	0.1	0.2	0.2
50	50.2	51.7	51.4	50.8
100	99.1	102.0	102.3	100.8
150	151.3	150.6	151.3	151.9

no significant interaction term. The following describes the results for some of the above variables.

Maximum $\dot{V}_{O_2}$ (l/min) for male subjects was significantly higher at sea level (55 m) than at 3,048 m, regardless of ambient CO levels (Table 6), and $\dot{V}_{O_2}$max during the 1,524-m exposure was less than at sea level. Total work output achieved by the male subjects during these exposures is shown in Table 7. The total work achieved during the 3,048-m exposure was significantly less than that achieved at lower altitudes. In female subjects, $\dot{V}_{O_2}$max (l/min) dur-

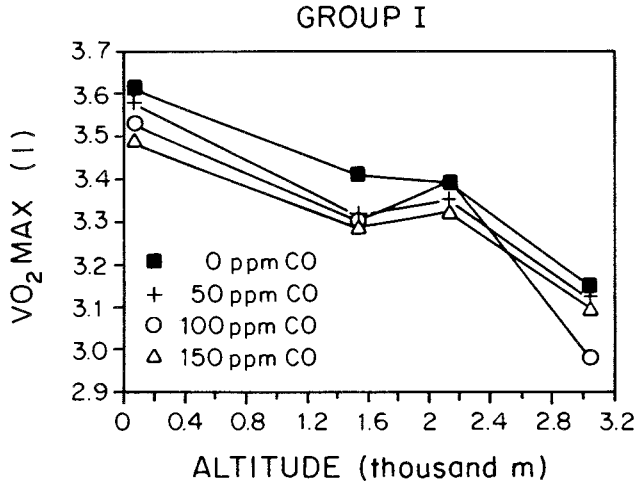

Figure 1. $\dot{V}_{O_2}$max for Group I men as a function of altitude and CO.

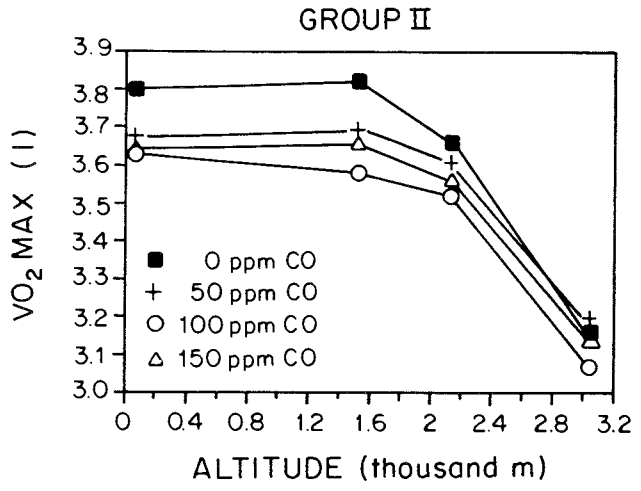

Figure 2. $\dot{V}_{O_2}$max for Group II men as a function of altitude and CO.

Table 6. Maximal Oxygen Uptake in Young Men During Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048	All[a]
Group I[b]						
0	5	3.61[c]	3.41	3.39	3.15	
		0.82	0.67	0.69	0.57	
50	5	3.58	3.31	3.35	3.12	
		0.82	0.50	0.50	0.53	
100	5	3.53	3.30	3.39	2.98	
		0.74	0.54	0.56	0.43	
150	5	3.49	3.29	3.32	3.10	
		0.73	0.63	0.56	0.39	
All[a]	20	3.55[d]	3.33	3.36	3.09	
		0.70	0.53	0.53	0.45	
Group II[e]						
0	8	3.80	3.82	3.66	3.16	3.62[f,g]
		0.77	0.73	0.67	0.44	0.69
50	9	3.67	3.69	3.61	3.19	3.55[c]
		0.70	0.66	0.56	0.42	0.61
100	8	3.63	3.58	3.52	3.07	3.45
		0.66	0.66	0.52	0.36	0.57
150	8	3.63	3.66	3.56	3.14	3.50
		0.69	0.66	0.57	0.31	0.59

[a] "All" indicates mean ± SD values for all four altitude or CO conditions where statistical main effects occurred.

[b] Group I includes five men who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[c] Values are mean ± SD in l/min STPD.

[d] $p < 0.05$ compared to 3,048-m altitude.

[e] Group II includes Group I with others who completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

[f] $p < 0.05$ compared to 150 ppm CO.

[g] $p < 0.05$ compared to 100 ppm CO.

Table 7. Total Work Performed by Young Men During Maximal Bicycle Work Tests at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048	All[a]
Group I[b]						
0	5	3,058[c]	3,025	3,007	2,660	2,938[d]
		739	910	775	695	
50	5	3,085	2,907	2,882	2,715	2,897
		724	603	617	716	
100	5	2,910	2,715	2,903	2,393	2,730
		587	711	757	487	
150	5	3,100	2,745	2,960	2,437	2,811
		861	943	837	706	
All[a]	20	3,038[e]	2,848[e]	2,938[e]	2,551	
Group II[f]						
0	8	3,122	3,274	3,136	2,613	3,036[d]
		672	738	623	535	
50	9	3,139	3,140	3,070	2,666	3,004[d]
		660	526	559	576	
100	8	3,013	3,086	2,983	2,445	2,882
		604	710	603	400	
150	8	3,103	3,062	3,088	2,473	2,932
		820	790	675	542	

[a] "All" indicates mean values for all four altitudes or CO conditions where statistical main effects occurred.

[b] Group I includes five men who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[c] Values are means ± SD in watts.

[d] $p < 0.05$ compared to 100 ppm CO.

[e] $p < 0.05$ compared to 3,048-m altitude.

[f] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

Table 8. Maximal Oxygen Uptake in Young Women During Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048
Group I[a]					
0	4	2.09[b]	2.12[c]	2.08	1.96
		0.17	0.21	0.19	0.14
50	4	2.14[c]	2.15[c]	2.05	1.93
		0.17	0.23	0.19	0.14
100	4	2.09	2.08	2.00	1.99
		0.17	0.20	0.19	0.11
150	4	2.16[c]	2.11[c]	2.03	1.92
		0.19	0.21	0.18	0.08
Group II[d]					
0	8	2.20	2.19[e,f]	2.29[e]	1.88
		0.36	0.37	0.30	0.37
50	9	2.21	2.02	2.24	1.93
		0.29	0.32	0.32	0.36
100	8	2.15	2.10	2.18	1.95
		0.33	0.37	0.30	0.33
150	8	2.20	2.14	2.19	1.91
		0.35	0.41	0.26	0.32

[a] Group I includes four women who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[b] Values are means ± SD in l/min STPD.

[c] $p < 0.05$ compared to 3,048-m altitude.

[d] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

[e] $p < 0.01$ compared to 100 ppm CO.

[f] $p < 0.05$ compared to 50 ppm CO.

Table 9. Maximal Oxygen Uptake in Young Women During Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048
Group I[a]					
0	4	37.7[b]	38.3[c]	37.4	35.6
		4.7	5.7	4.8	3.0
50	4	38.6[c]	38.8[c]	37.3	35.0
		5.0	5.7	4.4	4.5
100	4	37.8	37.3	36.2	35.7
		5.7	5.7	5.5	3.8
150	4	39.2[c]	39.5[c,d]	36.7	35.2
		5.9	6.4	5.3	3.5
Group II[e]					
0	8	39.3	38.6[d]	38.7	35.3
		5.5	4.8	4.0	5.8
50	9	39.7	37.0	38.3	36.2
		4.8	4.9	4.2	6.2
100	8	38.8	36.7	37.0	36.4
		5.3	5.0	4.3	5.7
150	8	39.6	38.4	37.3	36.1
		5.9	5.9	3.8	5.3

[a] Group I includes four women who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[b] Values are means ± SD in ml/kg/min STPD.

[c] $p < 0.05$ compared to 3,048-m altitude.

[d] $p < 0.05$ compared to 100 ppm CO.

[e] Group II includes Croup I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

ing exposures at 3,048 m was less than during 0-ppm exposure at 1,524 m (Table 8). During 50- and 150-ppm CO exposures, female subjects had lower $\dot{V}_{O_2}$max (l/min) at 3,048-m altitude than at either 55-m or 1,524-m altitudes. There were no statistically significant altitude effects on $\dot{V}_{O_2}$max in female subjects during 100-ppm CO exposures. In female subjects, $\dot{V}_{O_2}$max (ml/kg/min) at 1,524 m and 150-ppm exposure was higher than at 1,524 m and 100-ppm exposure (Table 9).

Total work achieved by female subjects was higher at sea level than at 3,048 m, regardless of CO exposure (Table 10). Maximal ventilation in female subjects was lower at sea level than at higher altitudes, regardless of CO exposure. Maximal heart rates (fc max) in male subjects were lower at 3,048 m than at sea level, regardless of CO exposure (Table 11). In female subjects, respiratory exchange ratio (R) was lower at sea level than at any altitude, regardless of CO exposure (Table 12). In male subjects, mean submax fc = 11.8 work increment (WI) + 66.8 during 0-ppm exposures, fc = 12.4 WI + 63.7 during 50-ppm exposures, and fc = 12.7 WI + 63.6 during 100-ppm exposures. The slopes during 50-, 100-, and 150-ppm exposures were significantly greater than during 0-ppm exposure ($p < 0.05$). As in female subjects, the slope of mean submax fc versus WI in male subjects was not affected by altitude.

The change in $\dot{V}_{O_2}$max from the filtered air sea-level exposure was analyzed for both male and female subjects raising the number to nine. Significant CO and altitude effects were noted in the repeated measures analysis, but no interaction.

Table 10. Total Work Performed by Young Women During Maximal Bicycle Work Tests at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048
Group I[a]					
0	4	1,400[b]	1,319	1,363	1,156
		174	298	217	175
50	4	1,359	1,247	1,294	1,179
		199	228	252	183
100	4	1,309	1,251	1,250	1,213
		118	280	252	169
150	4	1,381	1,269	1,244	1,197
		203	236	198	181
All[c]	16	1,362[d]	1,271	1,288	1,186
Group II[e]					
0	8	1,466	1,435	1,503	1,094
		340	427	220	301
50	9	1,479	1,378	1,463	1,122
		349	386	298	286
100	8	1,410	1,336	1,427	1,166
		351	403	287	348
150	8	1,439[d]	1,396	1,394	1,033
		334	448	226	481

[a] Group I includes four women who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[b] Values are means ± SD in watts.

[c] "All" indicates mean values for all four CO conditions at each altitude illustrating a main effect of altitude.

[d] $p < 0.05$ compared to 3048-m altitude.

[e] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

Table 11. Maximal Heart Rates in Young Men During Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048
Group I[a]					
0	5	184.2[b]	186.4	183.8	180.4
		16.5	18.9	16.6	16.2
50	5	189.4	182.4	183.0	183.8
		15.3	19.0	17.4	17.6
100	5	186.8	185.4	183.0	180.8
		22.5	12.6	15.5	16.7
150	5	185.6	183.8	182.2	178.7
		18.3	19.7	18.4	17.5
All[c]	20	186.5[d]	184.5	183.2	180.9
		16.5	16.0	15.2	15.4
Group II[e]					
0	8	184.8	182.7	183.0	182.0
		14.9	15.3	15.0	15.2
50	9	188.4	179.7	181.9	185.6
		14.8	16.0	14.3	14.4
100	8	185.8	182.7	183.5	173.6
		18.4	11.6	13.3	22.5
150	8	184.4	180.7	182.5	181.4
		15.8	16.8	14.3	15.7

[a] Group I includes five men who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[b] Values are means ± SD in beats/min.

[c] "All" indicates mean ± SD values for all four altitude conditions where statistical main effects occurred.

[d] $p < 0.05$ compared to 3,048-m altitude.

[e] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

GROUP II RESULTS

No significant altitude effect on $\dot{V}_{O_2}$max in male subjects was observed in this analysis. There was however a significant linear trend ($p < 0.018$) for decrease in $\dot{V}_{O_2}$max with altitude. The deviation from linearity was nonsignificant ($p > 0.1$). Male subjects had higher $\dot{V}_{O_2}$max during 0-ppm than during 150-ppm CO experiments, regardless of altitude, and higher $\dot{V}_{O_2}$max during 0-ppm and 50-ppm than during 100-ppm CO experiments. When expressing $\dot{V}_{O_2}$max in the male subjects on the basis of body weight (ml/kg/min; Table 13), the effect of CO exposures remained the same, and altitude effects were more evident. In male subjects, $\dot{V}_{O_2}$max at 3,048-m altitude was less than that at either sea level or 1,524-m altitude. The total work achieved during 0-ppm and 50-ppm exposures was greater than during 100-ppm exposures, regardless of altitude.

There was a significant interaction of altitude and ambient CO levels on $\dot{V}_{O_2}$max in female subjects. Identical altitude-CO interaction effects occurred in $\dot{V}_{O_2}$max in female subjects when expressed on the basis of body weight (Table 9). At 1,524 m and 2,134 m, $\dot{V}_{O_2}$max (l/min) in female subjects was higher during 0-ppm than 100-ppm exposures, and at 1,524 m, $\dot{V}_{O_2}$max (l/min) was higher during 0-ppm than 50-ppm exposures (Table 8). Expressed as ml/kg/min, $\dot{V}_{O_2}$max in female subjects was higher only at 1,524 m and 0-ppm exposure than at 1,524 m and 100-ppm

Table 12. Repiratory Exchange Ratios[a] in Young Women During Maximal Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048
Group I[b]					
0	4	1.14[c]	1.19	1.17	1.22
		0.03	0.03	0.03	0.02
50	4	1.15	1.21	1.20	1.19
		0.08	0.01	0.06	0.03
100	4	1.15	1.18	1.21	1.17
		0.06	0.07	0.05	0.04
150	4	1.10	1.22	1.20	1.20
		0.12	0.04	0.05	0.03
All[d]	16	1.13	1.20[e]	1.20[e]	1.20[e]
		0.04	0.04	0.04	0.04
Group II[f]					
0	8	1.17	1.18	1.15	1.20
		0.04	0.05	0.05	0.04
50	9	1.15	1.19	1.18	1.21
		0.07	0.06	0.06	0.06
100	8	1.15	1.18	1.18	1.19
		0.05	0.07	0.08	0.06
150	8	1.13	1.16	1.18	1.21
		0.10	0.08	0.06	0.04

[a] V_{CO_2}/V_{O_2} = respiratory exchange ratio.

[b] Group I includes four women who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[c] Values are means ± SD.

[d] "All" indicates mean ± SD values for all four CO conditions at each altitude illustrating a main effect of altitude.

[e] $p < 0.05$ compared to 55-m altitude.

[f] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

Table 13. Maximal Oxygen Uptake in Young Men During Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048	All[a]
Group I[b]						
0	5	52.1[c]	48.8	48.4	44.8	
		4.3	2.6	2.8	1.0	
50	5	51.2	47.9	48.1	44.5	
		3.8	2.0	2.2	1.6	
100	5	50.5	46.6	48.5	43.1	
		2.9	1.3	1.4	2.2	
150	5	50.5	47.4	47.7	44.7	
		3.6	2.9	1.6	3.4	
All[a]	20	51.1[d,e]	47.7[d]	48.2[d]	44.3	
		3.3	2.2	2.0	2.2	
Group II[f]						
0	8	52.2	50.0	47.7	44.6	48.7[g,h]
		5.5	2.8	2.8	2.7	4.3
50	9	50.1	48.4	47.1	44.9	47.7[h]
		4.1	2.2	2.5	2.4	3.3
100	8	49.5	46.5	46.0	43.4	46.4
		3.2	2.1	3.6	2.8	3.5
150	8	49.6	48.2	46.7	44.7	47.3
		3.4	3.2	1.9	3.3	3.3
All	33	50.3[d]	48.3[d]	46.9	44.4	
		3.9	2.8	2.8	2.8	

[a] "All" indicates mean ± SD values for all four altitude or CO conditions where statistical main effects occurred.

[b] Group I includes five men who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[c] Values are means ± SD in ml/kg/min STPD.

[d] $p < 0.05$ compared to 3,048-m altitude.

[e] $p < 0.05$ compared to 1,524-m altitude.

[f] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

[g] $p < 0.05$ compared to 150 ppm CO.

[h] $p < 0.05$ compared to 100 ppm CO.

exposure (Table 9). Total work achieved was not affected by either altitude or CO.

Maximal ventilation was not affected in either gender by altitude or CO (Tables 14 and 15). Maximal respiratory rates in male subjects (Table 16) or female subjects (Table 17) were also unaffected by experimental condition. Experimental conditions had no effect on fc max in male subjects (Table 11) or female subjects (Table 18). In male subjects, the mean respiratory exchange ratio (R) at maximal effort was significantly lower at sea level than at 2,134 m and 3,048 m regardless of CO exposure (Table 19). Respiratory exchange ratio was higher during 100-ppm exposures than during 0- or 150-ppm exposures regardless of altitude (Table 19).

During incremental submaximal work loads, neither altitude nor CO exposure affected the slope of $\dot{V}_{O_2}$ versus work increment (therefore workload or time) in male or female subjects. In male subjects, submaximal $\dot{V}_{O_2}$ = 0.285 WI + 0.490 for all conditions; in female subjects, submaximal $\dot{V}_{O_2}$ = 0.254 WI + 0.389, where $\dot{V}_{O_2}$ is in l/min and WI = one increment for every 25 watts. Likewise, neither altitude nor CO exposure affected the slope of the mean submaximal fc (beats/min) versus work increment in female

Table 14. Maximal Ventilatory Volumes in Young Men During Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048
Group I[a]					
0	5	136.2[b]	150.0	150.3	153.6
		36.7	34.0	39.3	31.7
50	5	141.4	145.4	150.2	154.3
		36.4	35.1	31.4	36.4
100	5	141.6	145.1	150.4	145.6
		29.4	36.7	30.3	40.7
150	5	143.8	141.6	149.7	142.5
		33.7	29.5	35.0	36.0
Group II[c]					
0	8	143.0	158.8	155.6	153.3
		30.6	31.4	34.8	24.0
50	9	147.5	151.5	156.0	159.7
		33.6	30.1	32.0	28.8
100	8	143.5	154.7	152.4	152.8
		26.3	32.4	31.5	33.0
150	8	144.5	148.3	156.0	145.5
		28.6	25.0	31.7	29.4

[a] Group I includes five men who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[b] Values are means ± SD in l/min BTPS.

[c] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

Table 15. Maximal Ventilatory Volumes in Young Women During Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048
Group I[a]					
0	4	93.4[b]	104.4	101.6	101.7
		17.2	12.3	15.9	11.6
50	4	94.3	105.6	104.2	102.2
		4.6	11.7	12.4	15.4
100	4	83.5	103.8	104.2	101.5
		15.5	10.0	13.1	10.6
150	4	92.7	103.7	105.3	102.8
		9.4	13.6	12.9	9.5
All[c]	16	91.0[d]	104.4	103.8	102.0
		11.8	10.4	11.8	10.4
Group II[e]					
0	8	93.8	99.7	101.5	89.9
		15.1	12.4	11.6	18.8
50	9	92.8	95.3	105.3	94.6
		9.3	14.9	12.2	16.6
100	8	85.8	96.8	100.5	93.7
		14.5	11.1	11.8	14.5
150	8	91.0	95.9	103.7	95.6
		11.2	17.6	10.0	13.1

[a] Group I includes four women who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[b] Values are means ± SD in l/min BTPS.

[c] "All" indicates mean ± SD values for all four CO conditions at each altitude illustrating a main effect of altitude.

[d] $p < 0.05$ compared to 1,524-, 2,134-, and 3,048-m altitudes.

[e] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

subjects (fc = 15.4 WI + 87.6), but CO exposures increased the slopes of these relationships in male subjects. In male subjects, fc = 11.3 WI + 68.1 during 0-ppm exposures, fc = 11.8 WI + 66.3 during 50-ppm exposures, fc = 12.0 WI + 66.0 during 100-ppm exposures, and fc = 11.7 WI + 66.5 during 150-ppm exposures. The slopes during 50- and 100-ppm exposures were significantly greater than during 0-ppm exposure ($p < 0.05$).

Plasma lactates at exhaustion and at the fifth minute of recovery were similar at all altitudes and concentrations of ambient CO (means of 15.4 and 16.0 mM/l for male subjects and 11.8 and 12.6 mM/l for female subjects). Since plasma lactates were available during the submaximal work periods, an analysis was made to determine if the anaerobic threshold was modified as a result of altitude and ambient CO exposure. The anaerobic threshold was assumed to occur at a plasma lactate of 2 mM/l. It is evident in Figure 3 that there was a gender-related difference in anaerobic threshold with female subjects' thresholds occurring at a lower workload and a lower oxygen uptake than the male subjects'. The presence of increased levels of COHb at any altitude had no impact on anaerobic threshold. The only significant shift occurred at an altitude of 3,054 m in both genders.

Predictive equations for CO uptake while exercising at submaximal work loads are presented in Table 20.[1] Figure 4 and Table 21 summarize the significant differences in slopes (T-test comparisons between slopes) for all combinations of ambient CO and altitude observed in either male or

[1] Data on individual subjects are given in Appendix A, which is available upon request from the Health Effects Institute.

Table 16. Maximal Respiratory Rates in Young Men During Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048
Group I[a]					
0	5	52.4[b]	56.2	61.8	62.6
		7.7	5.0	20.0	11.1
50	5	53.0	54.2	62.2	61.8
		6.6	6.4	15.4	17.1
100	5	53.0	53.0	61.4	60.2
		6.2	6.1	13.1	17.0
150	5	55.6	53.2	60.6	58.4
		9.2	6.3	13.0	18.4
Group II[c]					
0	8	51.9	59.1	60.3	59.6
		5.9	14.6	17.5	10.4
50	9	54.4	54.1	60.5	60.5
		7.6	9.2	15.3	13.2
100	8	52.4	51.3	56.3	58.5
		4.9	4.6	12.5	13.2
150	8	54.3	51.1	60.0	57.5
		7.3	5.5	13.0	14.2

[a] Group I includes five men who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[b] Values are means ± SD in breaths/min.

[c] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

Table 17. Maximal Respiratory Rates in Young Women During Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048
Group I[a]					
0	4	50.5[b]	52.8	54.5	54.8
		3.4	2.1	5.7	5.1
50	4	50.5	52.5	55.0	51.0
		3.7	2.1	3.6	3.6
100	4	49.0	52.5	53.3	52.8
		3.6	3.0	5.1	3.0
150	4	49.5	52.8	53.8	51.3
		3.8	5.0	2.5	3.3
Group II[c]					
0	8	50.0	52.3	51.9	51.4
		4.5	11.2	6.1	6.4
50	9	51.3	50.0	53.4	51.1
		5.6	5.0	4.5	6.7
100	8	48.9	50.0	51.5	52.6
		3.1	5.1	5.0	5.9
150	8	49.8	51.0	52.1	52.4
		4.0	4.6	3.4	6.4

[a] Group I includes four women who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[b] Values are means ± SD in breaths/min.

[c] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

female subjects. Figures 5 (male subjects) and 6 (female subjects) show these slopes adjusted to generalized slopes for the male and female subjects. When the slope of the CO uptake (rate of increase of COHb with time) was analyzed with the ANOVA design, a significant main effect of altitude and CO was noted but no interaction was evident. As the altitude increased there was a significant decrease in the uptake of CO at each concentration of CO. At every altitude the rate of increase of COHb increased with CO concentration. These results are illustrated in Figure 7.

Mean ± SD blood COHb levels measured immediately prior to the maximal work tests, within one minute or more of exhaustion, and during the fifth recovery minute of each exposure are given in Table 22. Figure 8 presents changes in COHb data as percents of control values at maximal effort and five minutes after maximal effort (recovery period 5) for a male subject, and Figure 9 illustrates this response in a female subject. Carboxyhemoglobin levels were similar in male and female subjects at corresponding sampling times. During 50-, 100-, and 150-ppm exposures, COHb levels at exhaustion were significantly lower than during the fifth recovery minute. During similar ambient CO exposures, the COHb levels measured at exhaustion and the fifth recovery minute tended to be lower as altitude increased. It appears (Figure 6), however, that this liberation of CO from the extravascular space where it probably was held in combination with myoglobin was related to the concentration of COHb achieved, as noted by the regression equation $y = 0.0017 + 0.3047\,x$, where x is the COHb concentration at exhaustion.

The predictive equations for all CO uptake curves are presented in Table 20.[2] Computations of significant differences in the slopes are summarized in Figure 4 and Table

[2] Individual curves for all subjects are given in Appendix A, which is available upon request from the Health Effects Institute.

Table 18. Maximal Heart Rates in Young Women During Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048
Group I[a]					
0	4	185.8[b]	185.8	182.5	185.3
		6.4	11.3	7.6	9.6
50	4	184.5	183.5	183.8	181.3
		8.2	9.6	8.9	12.6
100	4	183.3	183.5	182.3	183.3
		11.6	8.6	8.4	12.6
150	4	185.5	185.5	158.8	183.8
		10.3	12.7	8.5	11.0
Group II[c]					
0	8	184.4	184.4	180.1	179.0
		6.4	13.0	6.9	15.1
50	9	185.5	182.0	183.4	179.6
		5.9	10.9	7.0	11.6
100	8	182.8	181.9	178.8	182.1
		9.9	8.2	7.9	9.7
150	8	185.8	183.0	182.0	183.1
		8.1	12.1	8.3	9.7

[a] Group I includes four women who completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[b] Values are means ± SD in beats/min.

[c] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

Table 19. Respiratory Exchange Ratios[a] in Young Men During Maximal Bicycle Work at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)	n	Altitude (m) 55	1,524	2,134	3,048	All[b]
Group I[c]						
0	5	1.15[d]	1.20	1.17	1.23	
		0.06	0.03	0.04	0.02	
50	5	1.14	1.20	1.21	1.24	
		0.06	0.06	0.04	0.06	
100	5	1.19	1.20	1.21	1.24	
		0.03	0.08	0.03	0.11	
150	5	1.15	1.21	1.21	1.19	
		0.05	0.07	0.05	0.08	
Group II[e]						
0	8	1.14	1.17	1.19	1.21	1.18[f]
		0.06	0.04	0.05	0.05	0.06
50	9	1.15	1.18	1.23	1.23	1.20
		0.05	0.06	0.06	0.05	0.06
100	8	1.19	1.19	1.22	1.24	1.21
		0.02	0.06	0.03	0.09	0.06
150	8	1.15	1.18	1.20	1.18	1.18[f]
		0.04	0.07	0.05	0.07	0.06
All[b]	33	1.16[g,h]	1.18	1.21	1.21	
		0.06	0.06	0.06	0.06	

[a] V_{CO_2}/V_{O_2} = respiratory exchange ratio.

[b] "All" indicates mean ± SD values for all four altitudes or CO conditions where statistical main effects occurred.

[c] Group I includes five men that completed tests in all 16 conditions. Analysis was repeated measures across altitude and CO.

[d] Values are means ± SD.

[e] Group II includes Group I with others that completed tests in four CO conditions at two or three altitudes. Analysis was repeated measures across CO only.

[f] $p < 0.05$ compared to 100 ppm CO.

[g] $p < 0.05$ compared to 3,048-m altitude.

[h] $p < 0.05$ compared to 2,134-m altitude.

21. There was a highly significant ($p < 0.001$) decrease in the slope as found at ambient CO levels of 100 and 150 ppm with increasing altitude. These data are essentially in agreement with the observed changes in the COHb values observed at maximal effort. They represent the first available information as to the uptake of CO during submaximal work.

DISCUSSION

The lack of a significant interaction term in the analysis confirms the independence of the CO and altitude effects on the measured parameters, making an additive effect a possible result. However, the decrease in COHb with altitude at identical ambient CO concentrations confounds that possible conclusion.

In our male subjects, the reductions in $\dot{V}_{O_2}$max either in terms of l/min or ml/kg/min were essentially as predicted (5, 8, and 13 percent respectively for 1,524, 2,134, and 3,048 m) (Horvath 1981). However, our female subjects were apparently more resistent to the hypoxic effects of increasing altitudes; statistically significant decrements (15 percent) in $\dot{V}_{O_2}$max were observed only at 3,048 m. Wagner and colleagues (1979) reported linear decreases in their female subjects similar to those observed in male subjects. No ready explanation is available for this discrepancy, although it may be related to relative differences in fitness. It has been reported (Squires and Buskirk 1982) that, at least up to

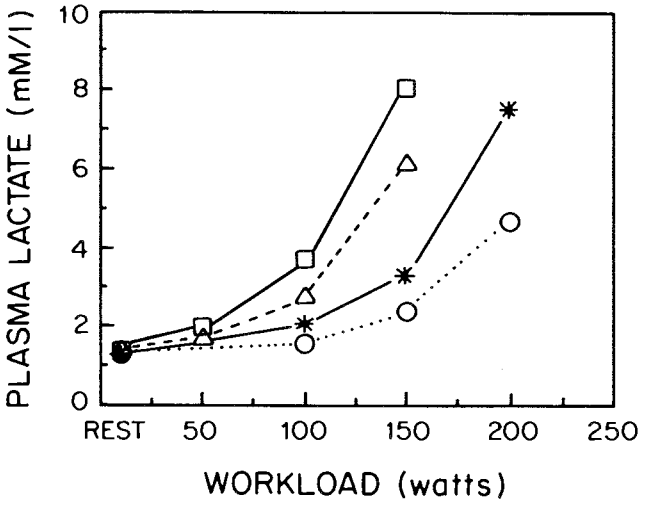

Figure 3. Anaerobic threshold (plasma lactate levels) as influenced by gender, altitude, and COHb concentrations.

2,286 m, subjects with higher aerobic capacities per unit of body weight exhibited smaller decrements in $\dot{V}_{O_2}$max than subjects with lower aerobic capacities.

Maximal aerobic capacity values, which diminished in male subjects during exposure to the combination of altitudes and increasing ambient CO concentrations were not diminished further due to the presence of CO. It should be noted that in all individuals, maximal aerobic capacity was attained in all experimental conditions. The criteria for maximal effort were a leveling or a decrease in the final oxygen uptake, a respiratory exchange ratio greater than 1.15, and a blood lactate in excess of 8 mM/l.

Several factors may be involved in these responses. First, COHb concentrations were significantly different at each altitude (see later discussion of this point), and second, COHb increased gradually as work levels increased, in contrast to situations in which the level of COHb was high prior to the onset of a maximal performance, possibly having a different impact on oxygen delivery to the active muscle tissue than was observed in the bolus exposure conditions. However, total work performed (Table 7), which remained constant at sea level with increasing ambient CO, generally tended to decrease both at increasing altitudes and at increased CO at the higher altitudes. Our female subjects' maximal aerobic capacities were uninfluenced by altitudes up to 3,048 m in the presence of increasing ambient concentrations of CO. This may reflect the different level of physical fitness between the male and female subjects. Total work performed by the female subjects, as well as $\dot{V}_{O_2}$max, lowered only at 3,048 m, but no further changes were observed as ambient CO concentrations were increased at this altitude. Reductions in $\dot{V}_{O_2}$max and maximum work output

Table 20. Predictive Equations for Carbon Monoxide Uptake[a]

Men		
	Ambient CO 0 ppm	
55 m	%COHb = −0.016x + 0.650	R = −0.467
1,524 m	%COHb = −0.016x + 0.505	R = −0.445
2,134 m	%COHb = −0.016x + 0.589	R = −0.439
3,047 m	%COHb = −0.020x + 0.757	R = −0.455
	Ambient CO 50 ppm	
55 m	%COHb = 0.040x + 0.764	R = 0.632
1,524 m	%COHb = 0.030x + 0.674	R = 0.695
2,134 m	%COHb = 0.030x + 0.510	R = 0.555
3,047 m	%COHb = 0.032x + 0.665	R = 0.663
	Ambient CO 100 ppm	
55 m	%COHb = 0.101x + 0.825	R = 0.889
1,524 m	%COHb = 0.083x + 0.565	R = 0.905
2,134 m	%COHb = 0.082x + 0.523	R = 0.852
3,047 m	%COHb = 0.071x + 0.679	R = 0.883
	Ambient CO 150 ppm	
55 m	%COHb = 0.160x + 0.765	R = 0.901
1,524 m	%COHb = 0.138x + 0.537	R = 0.954
2,134 m	%COHb = 0.121x + 0.696	R = 0.936
3,047 m	%COHb = 0.099x + 0.531	R = 0.820
Women		
	Ambient CO 0 ppm	
55 m	%COHb = −0.024x + 0.543	R = −0.648
1,524 m	%COHb = −0.025x + 0.708	R = −0.632
2,134 m	%COHb = −0.494x + 0.610	R = −0.494
3,047 m	%COHb = −0.028x + 0.787	R = −0.438
	Ambient CO 50 ppm	
55 m	%COHb = 0.038x + 0.652	R = 0.572
1,524 m	%COHb = 0.035x + 0.779	R = 0.600
2,134 m	%COHb = 0.027x + 0.813	R = 0.764
3,047 m	%COHb = 0.036x + 0.749	R = 0.665
	Ambient CO 100 ppm	
55 m	%COHb = 0.137x + 0.592	R = 0.903
1,524 m	%COHb = 0.100x + 0.886	R = 0.925
2,134 m	%COHb = 0.097x + 0.948	R = 0.849
3,047 m	%COHb = 0.084x + 0.947	R = 0.852
	Ambient CO 150 ppm	
55 m	%COHb = 0.206x + 0.865	R = 0.927
1,524 m	%COHb = 0.179x + 0.895	R = 0.926
2,134 m	%COHb = 0.148x + 1.183	R = 0.778
3,047 m	%COHb = 0.129x + 0.950	R = 0.905

[a] Minutes of exposure during an incremental exercise test to mean maximal capacity (that is, three to five minutes before maximum). Maximal values for COHb at maximum were always less than at these times. R = correlation coefficient.

may be related to the decrease in arterial oxygen content ($C_{a_{O_2}}$) and its effect in lowering arterial and mixed venous oxygen values. Horvath and associates (1975) found that a decrease of greater than 4 percent in $C_{a_{O_2}}$ was necessary to

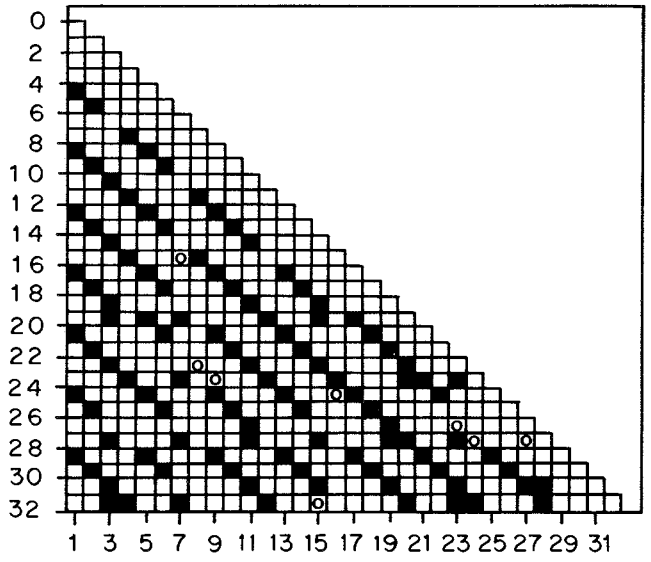

Figure 4. Significant differences in slopes of CO uptake (as COHb) at different concentrations of ambient CO (0, 50, 100, 150 ppm) and at altitudes of 55, 1,524, 2,134, and 3,048 m. These uptakes are determined up to one level of work (25 watts) below maximum. (Refer to Table 21 for details.) The filled-in blocks represent no statistically significant differences; blocks with circles represent $p > 0.05$, and blank blocks represent statistically significant differences ($p > 0.02$ to 0.002).

induce a significant reduction in maximum $\dot{V}_{O_2}$ due to the presence of COHb. A similar decrease (4.8 percent) in $C_{a_{O_2}}$ was required to induce a reduction in maximum $\dot{V}_{O_2}$ in individuals exposed to a simulated altitude of 1,219 m (Squires and Buskirk 1982). However, other factors may be involved in this reduction, such as oxygen delivery, alterations in cardiac output, and the partial pressure of oxygen at the tissue level. Evaluation of these additional factors is needed.

Both the male and female subjects had control levels of COHb within the concentrations found in the normal United States population. According to Wallace and Ziegenfus (1985), who reported on data obtained in the NHANES II survey, the mode level of COHb for nonsmokers was 0.7 percent, with 1 percent of the 1,658 subjects having levels greater than 4 percent and 10 percent of the subjects having COHb values below 0.4 percent (0.0 to 0.39 percent). In general, our female subjects had slightly higher initial COHb concentrations. This may be partially a reflection of the long intervals between tests and the number of months required to complete all of the exposures. We could not effectively control for menstrual periods and their influence on endogenous CO production.

We were able to maintain constant ambient CO concentration at all levels and altitudes (Table 5). When subjects performed their maximal aerobic capacity tests, a consistent decrease in their COHb levels occurred at all altitudes at 0 ppm CO. This elimination of CO was due to the increased minute ventilations due to the increased oxygen requirements for work. As ambient CO concentration increased, COHb at maximal work load also increased. The highest COHb levels at maximal work load were 4.42 and 3.98 percent respectively for male and female subjects exposed to 150 ppm at 55 m. The maximal levels of COHb at 150 ppm CO decreased as altitude increased to 2.56 and 2.77 percent at 3,048 m for male and female subjects, respectively. Similar patterns were observed at 50 ppm CO and 100 ppm CO. The increments in percent COHb were linearly related to the ambient concentrations of CO and increased altitude. These observations provide additional information for the data base (Stewart et al. 1970; Stewart 1975) on exposure of humans to varying concentrations of ambient CO, ambient pressures of oxygen, and the effect of excercise.

We did not observe any effects from the combined exposure to altitude and CO. Thus no synergistic effect was

Table 21. Exposure Conditions for Each Subject[a]

Subject	Gender	Altitude	CO (ppm)
1	Man	55	00
2	Man	55	50
3	Man	55	100
4	Man	55	150
5	Woman	55	00
6	Woman	55	50
7	Woman	55	100
8	Woman	55	150
9	Man	1,524	00
10	Man	1,524	50
11	Man	1,524	100
12	Man	1,524	150
13	Woman	1,524	00
14	Woman	1,524	50
15	Woman	1,524	100
16	Woman	1,524	150
17	Man	2,134	00
18	Man	2,134	50
19	Man	2,134	100
20	Man	2,134	150
21	Woman	2,134	00
22	Woman	2,134	50
23	Woman	2,134	100
24	Woman	2,134	150
25	Man	3,047	00
26	Man	3,047	50
27	Man	3,047	100
28	Man	3,047	150
29	Woman	3,047	00
30	Woman	3,047	50
31	Woman	3,047	100
32	Woman	3,047	150

[a] Refer to Figure 4.

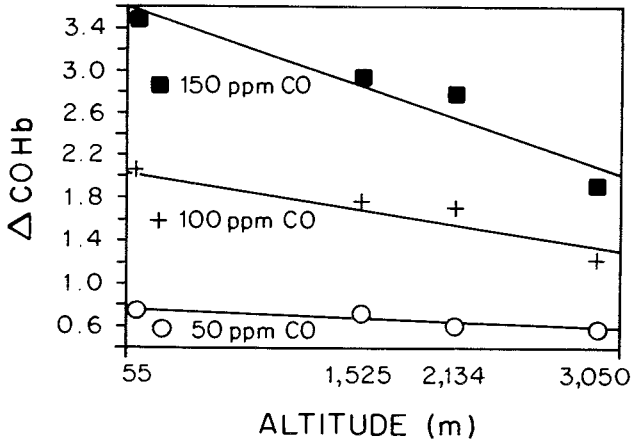

Figure 5. Maximal increment in percent COHb (Δ % COHb) over basal (control) levels for male subjects during tests conducted at various altitudes and ambient CO concentrations. At 150 ppm Δ % COHb = 3.618 − 4.926 × 10^{-4} m. At 100 ppm Δ % COHb = 2.122 − 2.538 × 10^{-4} m. At 50 ppm Δ % COHb = 0.753 − 5.657 × 10^{-5} m.

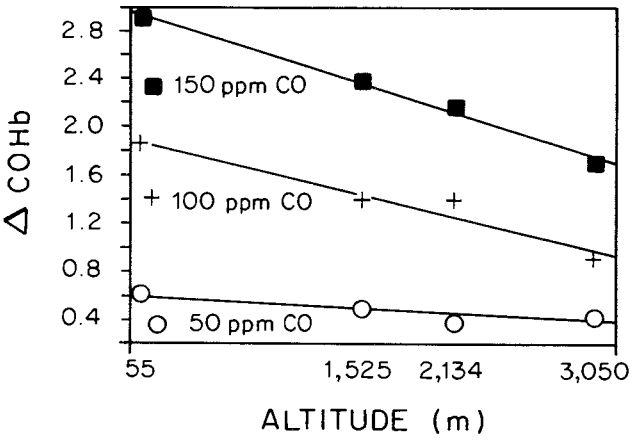

Figure 6. Maximal increment in percent COHb (Δ % COHb) over basal (control) levels for female subjects during tests conducted at various altitudes and ambient CO concentrations. At 150 ppm Δ % COHb = 2.963 − 3.983 × 10^{-4} m. At 100 ppm Δ % COHb = 1.897 − 2.999 × 10^{-4} m. At 50 ppm Δ % COHb = 0.597 − 6.920 × 10^{-5} m.

documented. We were, however, able to show independence of the altitude and CO hypoxia effects in some parameters. In some variables there was no main effect of CO, due to the decreased relationship of CO concentration to COHb uptake at increased altitudes (Table 22 and Figure 10). Exposure to identical concentration of a pollutant (in ppm) at different altitudes does not expose the recipient to identical moles of pollutant per unit volume of air. The main influence of altitude is that of pressure, which alters the number of molecules of a gas per unit volume. The reduced partial pressure of CO decreases absorption of the pollutant gas. The striking differences in COHb levels at increasing altitudes provides a ready explanation for the lack of additive or synergistic hypoxic effects between CO and exercising at altitudes. In order to answer adequately the question of additive influences of altitude and COHb hypoxias, it would be necessary to induce the same elevation in COHb at all altitudes, but the ambient concentrations of CO would have to be excessive in order to accomplish this.

Coburn (1977) reviewed available evidence that indicates that when the P_{O_2} at the tissue level was approximately 40 torr, CO shifted out of the blood into the vascular space and returned to the blood when P_{O_2} rose above 40 torr. A theoretical evaluation by Agostoni and colleagues (1980) strengthened this concept with a report that when venous P_{O_2} was below 20 torr, the quantity of CO bound to myoglobin increased dramatically. When arterial oxygen pressure is lowered (as at altitude) CO would shift out of the blood. Luomanmaki and Coburn (1969) presented data from dog studies that suggested that CO exposure might pose a special threat at altitude. Outward shifts may also occur during maximal exercise when venous P_{O_2} may be lowered to levels approaching tissue P_{O_2}. Clark and Coburn (1975) raised COHb concentrations to appproximately 2 percent, levels that do not influence maximal aerobic capacity, and had their subjects perform short-term (1.5 to 2.0 minutes or six to seven minutes) maximal exercise tests both at sea level and while breathing 13 to 14 percent oxygen. Myoglobin P_{O_2} fell during maximal exercise in both conditions, but the decrease was greater when breathing the low-oxygen mixture. Consequently, CO left the vascular area and entered the extravascular area. No direct evidence for this shift is available, but it probably occurs because myoglobin is the only potentially adequate source for CO uptake and the tissues that become hypoxic at maximal exercise are

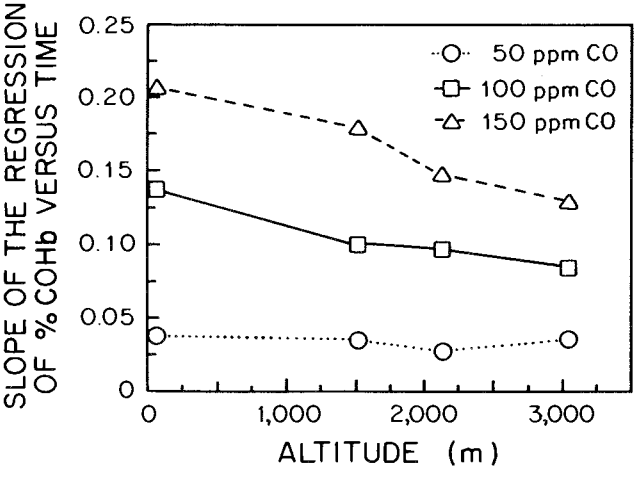

Figure 7. The mean slope of the increase in percent COHb with exposure time for the women as a function of altitude.

Table 22. Percent Carboxyhemoglobin Concentrations at Various Altitudes and Ambient Carbon Monoxide Levels

CO (ppm)		Men			Women		
		Before Exercise	Maximum Work Load	5 Minutes After Exercise	Before Exercise	Maximum Work Load	5 Minutes After Exercise
55 Meters[a]							
0	Mean	0.54	0.20	0.21	0.55	0.13	0.13
	SD	0.24	0.24	0.24	0.23	0.13	0.17
50	Mean	0.81	1.55	2.10	0.57	1.18	1.57
	SD	0.39	0.35	0.80	0.22	0.45	0.48
100	Mean	0.92	2.98	3.87	0.59	2.45	3.48
	SD	0.35	0.23	0.39	0.18	0.34	0.29
150	Mean	0.94	4.42	5.59	1.06	3.98	5.06
	SD	0.50	0.40	0.42	0.51	0.49	0.60
1,524 Meters[a]							
0	Mean	0.44	0.07	0.04	0.71	0.28	0.28
	SD	0.33	0.09	0.11	0.19	0.18	0.18
50	Mean	0.67	1.37	1.65	0.84	1.34	1.73
	SD	0.26	0.20	0.35	0.28	0.36	0.52
100	Mean	0.62	2.37	3.24	0.98	2.38	3.09
	SD	0.29	0.37	0.76	0.16	0.31	0.51
150	Mean	0.62	3.57	4.58	1.08	3.45	4.56
	SD	0.32	0.48	0.53	0.39	0.68	0.95
2,134 Meters[a]							
0	Mean	0.56	0.18	0.21	0.62	0.36	0.39
	SD	0.42	0.16	0.26	0.12	0.16	0.24
50	Mean	0.53	1.14	1.26	0.79	1.17	1.54
	SD	0.42	0.29	0.51	0.19	0.21	0.25
100	Mean	0.57	2.28	2.90	1.03	2.42	3.28
	SD	0.32	0.56	1.05	0.31	0.46	0.83
150	Mean	0.86	3.45	4.42	1.23	3.39	4.45
	SD	0.42	0.27	0.38	0.52	0.77	0.82
3,048 Meters[a]							
0	Mean	0.82	0.44	0.24	0.75	0.38	0.46
	SD	0.42	0.64	0.22	0.34	0.21	0.32
50	Mean	0.72	1.30	1.53	0.76	1.19	1.49
	SD	0.45	0.22	0.30	0.17	0.27	0.28
100	Mean	0.79	2.04	2.59	1.04	1.95	2.62
	SD	0.31	0.39	0.60	0.30	0.27	0.37
150	Mean	0.64	2.56	3.65	1.06	2.77	3.63
	SD	0.41	0.75	0.63	0.24	0.43	0.68

[a] n = 9 for 1,524-m altitude; n = 8 for all others.

muscles. Furthermore, the quanitity of CO that can be dissolved in tissue water must be small based on the Bunsen solubility coefficient of CO in blood.

We provide further evidence for the transfer of CO out of the blood in Figure 10 and Table 22. The amount of CO shifted into extravascular spaces, probably in temporary combination with myoglobin, appears to depend upon the concentration of COHb at the time when a critical tissue P_{O_2} is reached. The data suggest that such a transfer begins at levels below the maximal work load. As noted ear-

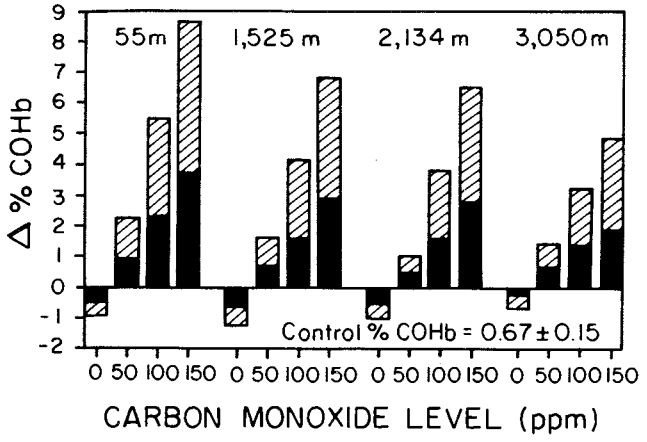

Figure 8. Increment in percent COHB (Δ % COHb) over basal (control) levels at the end of the maximal aerobic capacity test and at the fifth minute of recovery in a male subject. Altitudes are 55, 1,524, 2,134, and 3,048 m, and exercise was conducted with ambient CO concentrations of 0, 50, 100, and 150 ppm.

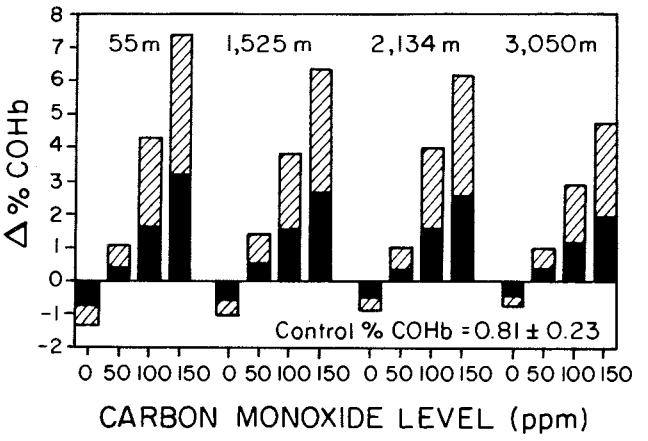

Figure 9. Increment in percent COHb (Δ % COHb) over basal (control) levels at the end of the maximal aerobic capacity test and at the fifth minute of recovery in a female subject. Altitudes are 55, 1,524, 2,134, and 3,048 m, and exercise was conducted with ambient CO concentrations of 0, 50, 100, and 150 ppm.

lier, the linear uptake curves for CO were limited to work loads of 150 watts for the female subjects and 200 watts for the male subjects, which were one or more work loads below their maximal efforts. Although we have no direct evidence that arterial P_{O_2} was at or below 40 torr, apparently this level was approached (Clark and Coburn 1975). Further evaluation of the CO shift suggests that approximately 30 percent of the blood COHb was moved out at all maximal COHb concentrations. After maximal exercise, carbon monoxide was released from extravascular "storage" during the recovery period when presumably the tissue P_{O_2} increased to a level higher than the critical P_{O_2} of 40 torr. CO is returned to the blood, perfusing the muscle resulting in the increased COHb observed during this recovery period. The fraction of CO transferred to the extracellular space when COHb concentrations are between 5 percent and 30 percent remains to be determined. Based on the greater reductions in maximal aerobic capacity at these higher COHb levels (Horvath et al. 1975), it appears that a greater fraction is transferred. This reduces the driving force for oxygen transfer and binds more of the heme pigments in muscle, and so explains the greater reduction in aerobic capacity and provides a physiological explanation for the inability of humans to exercise when COHb concentrations exceed 50 percent.

The present study provides information to determine whether or not altitude and ambient CO concentrations (two hypoxic stresses) induce greater or lesser effects on physiological function of humans than each stressor alone. There was no further reduction in metabolic parameters when exposed to the combination of altitude and CO. For those variables exhibiting the effects of altitude and CO, we have demonstrated the independence of the effects, implying an additive nature of the combined hypoxia. For many of the variables, no CO effect was observed. We cannot demonstrate numerically the additive nature of the main effects of CO and altitude. We have shown that the reduction in CO concentration to COHb uptake at altitude is more than likely the cause of these results. We have been able to partially abate the concerns expressed in the U.S. Environmental Protection Agency (1978) document by showing that the concentration of ambient CO in ppm does not reflect the effect of ambient CO in the COHb levels attained during submaximal exercise in and at maximal effort at elevated altitudes. Carbon monoxide was temporarily transferred out of the blood into the tissue spaces, probably in combination

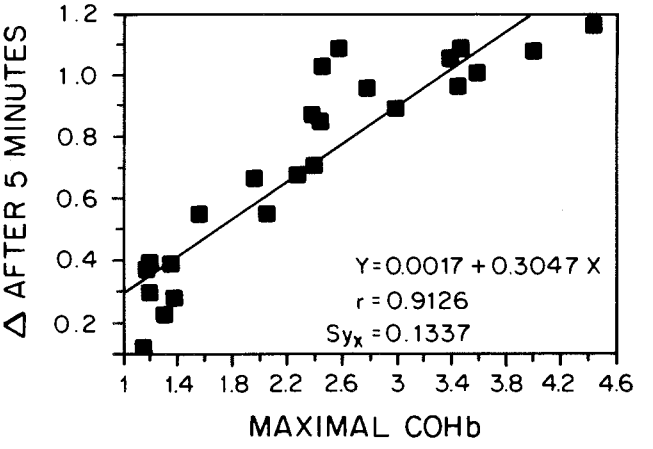

Figure 10. The higher concentrations of COHb at the end of the five-minute recovery period indicate that the liberation of CO from the tissue stores is linearly related to the COHb concentration present at exhaustion.

with myoglobin. This shift occurred when exercise levels were in excess of 80 percent $\dot{V}_{O_2}$max.

RECOMENDATIONS FOR FUTURE RESEARCH

A number of problems relating to CO exposure could be addressed. One, on which we have data at this time, is to determine the relation between actual intake of CO from the ambient air and the equivalent blood COHb concentration. We developed techniques for doing this for our pilot studies (one one-hour exposure at rest and with a fixed exercise load). This knowledge of CO concentration and minute ventilation could lead to a more precise predictive model than the CFK model, which is currently over-used.

Another major problem that needs to be addressed is the potential action of COHb levels in patients with angina who live at altitudes up to 2,134 m. A third interest is the effect of anemia in residents of high altitudes who are exposed to CO. Fourth, it is also of some importance to evaluate patients with chronic obstructive pulmonary disease at altitude and CO exposure. Finally, some individuals are exposed to higher CO levels than the one-hour standard allows, especially in high altitudes for much longer than one hour. Little is known about individual response to altitude and COHb buildups that occur gradually over several hours.

ACKNOWLEDGMENTS

We could not have conducted this research without the extraordinary commitment of our subjects and the efforts of our staff, Ms. D. Batterton, Ms. V. Smith, Ms. L. Weir, and Ms. R. Luera. Graduate students, Mr. T. Nadle, Mr. R. Williams, Ms. M. Wills, and Ms. H.-M. Chen, also contributed to the successful completion of this program. Our gratitude to Dr. Virginia Clark for statistical guidance, and to Mrs. D. Bedi for her excellent typing.

REFERENCES

Agostoni A, Stabilini R, Viggiano G, Luzzana M, Samada M. 1980. Influence of capillary and tissue P_{O_2} on carbon monoxide binding to myoglobin: A theoretical evaluation. Microvasc Res 20:81–87.

Clark BJ, Coburn RF. 1975. Mean myoglobin oxygen tension during exercise at maximal oxygen uptake. J Appl Physiol 39:135–144.

Coburn RF, Foster RE, Kane PB. 1965. Considerations of the physiological variables that determine the blood carboxyhemoglobin concentrations in man. J Clin Invest 44: 1899–1910.

Coburn RF (ed.). 1977. The biologic effects of carbon monoxide on the human organism. Report of a committee of the National Research Council, National Academy of Science. U.S. Government Printing Office, Washington, DC.

Collier CR, Goldsmith JR. 1983. Interactions of carbon monoxide at high altitude. Atmos Environ 17:723–728.

Dahms TE, Horvath SM, Gray DJ. 1975. Technique for accurately producing desired carboxyhemoglobin levels during rest and exercise. J Appl Physiol 38:366–368.

Dahms TE, Horvath SM. 1974. Rapid, accurate technique for determination of carbon monoxide in blood. Clin Chem 20:533–37.

Dill DB, Myhre LG, Phillips EA Jr., Browen DK. 1966. Work capacity in acute exposure to altitude. J Appl Physiol 21:1168–1176.

Elliot PR, Atterbom HA. 1978. Comparison of exercise responses of males and females during acute exposure to hypobaria. Aviat Space Environ Med 9:415–418.

Gliner JA, Raven PB, Horvath SM, Drinkwater BL, Sutton JC. 1975. Man's physiologic response to long-term work during thermal and pollutant stress. J Appl Physiol 39: 628–632.

Horvath SM. 1981. Aging and adaptation to stressors. In: Environmental Physiology: Aging, Heat and Altitude (Horvath SM, Yousef MK, eds.) pp. 437–451. Elsevier Science Publishing Co., New York, NY.

Horvath SM, Raven PB, Dahms TE, Gray DJ. 1975. Maximal aerobic capacity at different levels of carboxyhemoglobin. J Appl Physiol 38:300–303.

Klausen K, Anderson C, Nandrup S. 1983. Acute effects of cigarette smoking and inhalation of carbon monoxide during maximal exercise. Eur J Appl Physiol 51:371–379.

Klein JP, Forester HV, Stewart RD, Wu A. 1980. Hemoglobin affinity for oxygen during short-term exposure to carbon monoxide. J Appl Physiol 48:236–242.

Louomanmaki K, Coburn RF. 1969. Effects of metabolism and distribution of carbon monoxide on blood and body stores. Am J Physiol 217:354–362.

Mitchell RS, Judson FM, Moulding TS, Wiser P, Broch LL,

Kebble DL, Pollard J. 1979. Health effects of urban air pollution: Special considerations of areas at 1,500 m and above. JAMA 242:1163–1167.

Raven PB, Drinkwater BL, Ruhling RO, Bolduan NW. 1974. Effect of carbon monoxide and peroxyacetyl nitrate on man's maximal aerobic capacity. J Appl Physiol 36:288–293.

Squires RW, Buskirk ER. 1982. Aerobic capacity during acute exposure to simulated altitude, 914 to 2,286 meters. Med Sci Sports Exercise 14:36–40.

Stewart RD, Peterson JE, Baretta ED, Bachand RT, Hosko MJ, Herrmann AA. 1970. Experimental human exposure to carbon monoxide. Arch Environ Health 21:154–164.

Stewart RD. 1975. The effect of carbon monoxide on humans. Annu Rev Pharmacol 15:409–423.

U.S. Environmental Protection Agency. 1979. EPA Air Quality Criteria for Carbon Monoxide. EPA-600/8–79–022. Research Triangle Park, NC.

U.S. Environmental Protection Agency. 1978. Altitude as a Factor in Air Pollution. EPA-600/9–78–015. Research Triangle Park, NC.

Wagner JA, Miles DS, Horvath SM, Reyburn JA. 1979. Maximal work capacity of women during acute hypoxia. J Appl Physiol 47:1223–1227.

Wallace LA, Ziegenfus RC. 1985. Comparison of carboxyhemoglobin concentrations in adult nonsmokers with ambient carbon monoxide levels. J Air Pollut Control Assoc 35:944–949.

Winer BJ. 1971. Statistical Principles of Experimental Design. McGraw-Hill, New York, NY.

ABOUT THE AUTHORS

Steven Michael Horvath received his doctorate degree from Harvard in 1942 in physiology while working at the Harvard Fatique Laboratory. He was the director of physiological research at Metropolitan State Hospital for the Insane, Waltham, MA; Armored Medical Research Laboratory, Fort Knox, KY; and Institute of Gerontology, State University of Iowa, College of Medicine, Iowa City, IA. He was head of the Physiology Department at Lankenau Hospital, Philadelphia, PA; and the Institute of Environmental Stress, University of California, Santa Barbara, CA; and is chairperson of the Department of Ergonomics & Occupational Health Sciences where he has been principal investigator on numerous research awards and is an author of over 500 publications.

James W. Agnew received his doctorate degree in physiology from the University of Oregon, Eugene, OR, in 1983. He was a postgraduate research physiologist at the Institute of Environmental Stress, University of California, Santa Barbara, CA, during the time of the study reported here. He is currently an assistant professor at Springfield College, Springfield, MA.

Jeames A. Wagner received his doctorate degree in physiology in 1970 from the University of Western Ontario. He was a visiting assistant professor of physiology with Dr. Sid Robinson at Indiana University, Bloomington, IN, from 1969 through 1971, and came to the Institute of Environmental Stress, University of California, Santa Barbara, CA, as a research physiologist in 1971. He has been a principal investigator in research projects primarily concerning the physiological changes associated with cold exposure. He has also investigated CO exposure and altitude effects. He is an author on over 25 articles.

John F. Bedi received his doctorate degree in physics and biomechanics from Indiana University, Bloomington, IN, in 1974. He was awarded an NIH fellowship in health studies in 1974 at the Institute of Environmental Stress, University of California, Santa Barbara, CA, and has been a research physiologist there since 1975. He has been a principal investigator in major research projects concerning the health effects of air pollution exposure. He is an author of 37 publications.

INTRODUCTION

In the summer of 1983, the HEI issued a Request for Applications (RFA 83–1) soliciting proposals on "Cardiovascular and Other Health Effects of Carbon Monoxide." The intent of this RFA was to obtain a better, more quantitative, understanding of the health effects of carbon monoxide at levels to which people are ambiently exposed. In the fall of 1983, Dr. Steven M. Horvath, of the Institute of Environmental Stress at the University of California, Santa Barbara, CA, proposed a study entitled "Cardiorespiratory Responses to Maximum Work During Carbon Monoxide Exposure at High Altitude." The HEI approved the two-year project (later granting a four-month extension) and, in the spring of 1984, authorized total expenditures of $496,734. The project began in March, 1984, and the final report was accepted by the Health Review Committee in January, 1988. The Health Review Committee's Report is intended to place the Investigators' Report in perspective as an aid to the sponsors of the HEI and to the public.

THE CLEAN AIR ACT

Under Sections 202(a) and 202(b)(1) of the Clean Air Act, the U.S. Environmental Protection Agency (EPA) imposes specific requirements for reductions in motor vehicle emissions of carbon monoxide (and other pollutants). The Act also provides EPA with limited discretion to modify those requirements. The determination of the appropriate standards for emissions from mobile sources depends in part on an assessment of the risks to health they present. Research on the health effects of carbon monoxide at altitudes above sea level can contribute to such risk assessment and, therefore, to informed regulatory decision-making.

In addition, Section 109 of the Clean Air Act provides for the establishment and periodic review of national ambient air quality standards to protect the public health and welfare. A set of primary (that is, health-related) standards currently applies to carbon monoxide. Under Section 109, such standards must allow "an adequate margin of safety." Potential additive effects of carbon monoxide and altitude on human health are relevant to the risk assessments that underlie current and future standards for carbon monoxide. Thus, research on such effects can contribute to a more informed assessment of risks from carbon monoxide and of the margin of safety that is adequate with respect to those risks.

Finally, the legislative history of the Clean Air Act makes it clear that, in setting ambient air quality standards, the EPA is required to consider the health of particularly sensitive subgroups of the population. The Senate report on the legislation states: "An ambient air quality standard . . . should be the maximal permissible air level of air pollution agent or class of such agents (related to a period of time) which will protect the health of any group of the population" (U.S. Senate 1970). The identification of such groups is not clear, but the report does specify that "included among those persons whose health should be protected by the ambient air standard are particularly sensitive citizens (such as bronchial asthmatics and emphysematics) who in the normal course of daily activity are exposed to the ambient environment." The report further states that "in establishing an ambient standard necessary to protect the health of these persons, reference should be made to a representative sample of persons in such a group." In identifying groups potentially particularly sensitive to the health effects of carbon monoxide, the U.S. Environmental Protection Agency (1985) observed: "Visitors to high altitude locations are also expected to be more vulnerable to carbon monoxide health effects due to reduced levels of oxygen in the air they breathe." Thus, research on the potential additive effects of carbon monoxide and altitude can contribute to an assessment of the combined risk to an identifiable group that may be especially vulnerable to the effects of carbon monoxide.

BACKGROUND

Carbon monoxide is a product of incomplete combustion. Motor vehicles are the major source of carbon monoxide, although stationary combustion of coal, fuel oil, natural gas, and wood, solid-waste combustion, industrial processes, and miscellaneous types of fires also contribute to the atmospheric burden of carbon monoxide.

The EPA has set National Ambient Air Quality Standards (NAAQS) for carbon monoxide. These standards include an eight-hour average of 9 ppm carbon monoxide and a one-hour average of 35 ppm, and are based on health effects data generated at sea level. Many citizens (2.2 million) of this country, most notably those of the Rocky Mountain states, reside at higher altitudes (National Research Council 1977). It is uncertain whether or not the noted health effects of air pollutants would continue to be the same as one ascends to higher altitudes.

Inhaled oxygen diffuses rapidly through the lung tissues and binds to hemoglobin inside the red blood cells. The oxyhemoglobin complex is transported in the blood, until the oxygen is eventually released into the tissues.

If carbon monoxide is present in the air, the carbon monoxide and oxygen compete for uptake by the oxygen-binding sites on the hemoglobin molecule in the red blood cell. When carbon monoxide occupies some of these sites, the oxygen-carrying capacity of hemoglobin is reduced. In addition, the delivery of oxygen to the tissues is further impaired because, in the presence of carbon monoxide, hemoglobin releases oxygen into the tissues more slowly. This impaired delivery interferes with cellular respiration of oxygen and results in tissue hypoxia. Tissue hypoxia may cause transient or permanent damage to tissues, especially in those organs that demand high oxygen delivery such as the brain, heart, and fetal tissues.

The physiological effect of high altitude, on the other hand, is due to the lower partial pressure of oxygen in the air. Because there are fewer molecules of oxygen available in the air, the hemoglobin does not saturate with oxygen. Reduced partial pressure of oxygen, or oxygen-saturation, also decreases oxygen delivery and leads to tissue hypoxia. Although carbon monoxide and altitude produce different initial physiological responses, their end health effects would be expected to be additive because they both reduce the quantity of oxygen carried by hemoglobin.

Tissue hypoxia in the heart muscle initiates a variety of responses that attempt to compensate for a decrease in oxygen availability. The mechanisms vary somewhat, depending on whether they are initiated by carbon monoxide hypoxia or by altitude hypoxia. These compensatory responses include functional changes, such as increased cardiac output and vasodilation, which increase the rate of oxygen delivery to the tissues by increasing the volume of accessible blood. Upon either carbon monoxide or altitude exposure, functional changes occur immediately. Other compensatory responses are hematological and morphological in nature, and occur only after prolonged exposures. These changes include cardiac hypertrophy (enlargement) and increased production of red blood cells (polycythemia).

Exposure to altitude imposes stress on the body, the severity of which is determined by the absolute altitude and the duration of time spent at the altitude. Increased hemoglobin concentration and right ventricular hypertrophy are known to occur. Cardiac output is believed to increase on ascent to high altitude, but then to decrease after a few days because of pulmonary vasoconstriction (Lenfant and Sullivan 1971). Acute exposure to carbon monoxide increases coronary blood flow and heart rate (Ayres et al. 1970). Although the chronic effects on cardiac output are uncertain, most studies indicate that prolonged carbon monoxide exposure leads to polycythemia and hypertrophy involving the whole heart (see review by Penney 1988).

The high metabolic rate during exercise increases the oxygen demand in the muscles. Increased carbon dioxide, produced by the muscles, must be removed simultaneously to avoid severe tissue acidosis. To satisfy the increased gas exchange needs of the muscle cells, the lungs, pulmonary circulation, the heart, and peripheral circulation must work together smoothly. However, the heart extracts oxygen extremely efficiently, even at rest. With exercise, the heart muscle must increase its oxygen supply through increased blood flow and vasodilation (Wasserman et al. 1986). Exposure to either carbon monoxide or altitude exacerbates the body's physiological responses to exercise by decreasing the oxygen availability to muscle tissue.

An individual's state of health can be evaluated by monitoring physiological parameters during well-controlled exercise routines. Some of the parameters commonly evaluated to determine the capacity of the cardiovascular and respiratory systems to perform gas exchange are (1) maximal oxygen uptake during exercise; (2) maximal aerobic capacity ($\dot{V}_{O_2}$max, the ability to increase utilization of oxygen during exercise); (3) anaerobic threshold (the level of exercise above which aerobic energy production is supplemented with anaerobic mechanisms, evaluated by levels of lactate in the blood); and (4) heart rate measures with submaximal exercise.

To measure the effects of exposure to carbon monoxide or altitude on human health, the exercise performance of normal, healthy subjects is monitored while exposure conditions are controlled. In the past, the effects of carbon monoxide and of altitude have been studied separately. The acute effects of carbon monoxide and altitude in combination have been examined in humans only sparsely, and there are virtually no studies of the long-term effects of these stresses in combination.

Horvath and coworkers (1975) measured the $\dot{V}_{O_2}$max in four male subjects with carboxyhemoglobin levels ranging from 3.18 percent to 4.30 percent. These studies complemented previous studies that encompassed carboxyhemoglobin levels above 7 percent and below 2.7 percent (Ekblom and Huot 1972; Vogel et al. 1972; Raven et al. 1974). Taken as a whole, these studies indicate that, above a critical level of carboxyhemoglobin, a linear decline in maximal aerobic power occurs with progressive increase in carboxyhemoglobin. An 8.1 percent decrease in exercise performance capacity was found with 4.3 percent carboxyhemoglobin, below which no effect was noted (Horvath et al. 1975).

It is well known that work capacity is diminished upon arrival at altitudes of 1,600 meters or higher (Weiser et al. 1978; Myhre 1980). This is most often attributed to a decrease in oxygen consumption (aerobic capacity) that

results from the reduction in partial pressure of inspired oxygen. A review by Buskirk (1978) that studied the physiological effects of altitude on permanent Highlander residents concluded that the decrease in work ability is always directly related to the decrease in oxygen consumption. Anaerobic capacity is also found to be reduced upon exercise at altitude. Many investigators in the field have observed lowered values for blood lactate after maximal exercise at high altitudes (Klausen et al. 1970; Dill and Adams 1971; Myhre and Robinson 1971), although the effect is not as noticeable in highly trained athletes (Pugh 1967).

Weiser and coworkers (1978) have conducted the only clinical study in which aerobic capacity measurements were made in subjects breathing carbon monoxide at high altitude (1,610 meters). Generating low-level carbon monoxide exposures that led to 5.1 percent carboxyhemoglobin, the group found that work performance was not impaired beyond that reported for sea-level studies with identical carboxyhemoglobin levels. However, they did note elevated heart rates and lowered anaerobic threshold, which leads to hyperventilation, because of carbon monoxide exposure.

Dr. Horvath and his associates have now examined the combined effects of carbon monoxide exposure and altitude. In the study reported here, 23 healthy subjects were used, more than in the Weiser study (four men), and the physiological responses in both men and women were evaluated. In addition, 16 combinations of four carbon monoxide levels and four altitudes comprised the exposure conditions. While subjects performed a standardized exercise protocol on a stationary bicycle, a host of respiratory variables were measured, as well as cardiac output and systolic time intervals. The results were then compared to determine the effects attributable to exposure to carbon monoxide alone, to altitude alone, or to the exposure conditions combined.

GOALS AND OBJECTIVES

The study was designed to examine the interactive effects induced by exposure to altitude and carbon monoxide. It proposed to extend existing observations in humans to include higher altitudes and additional levels of carboxyhemoglobin to test the hypothesis that these effects are additive.

The authors' specific aims were the following:

1. To examine the responses to exercise of men and women with increased carboxyhemoglobin levels, or at higher altitudes, or both.
2. To confirm whether or not $\dot{V}_{O_2}$max at sea level is reduced when exercise is performed while carboxyhemoglobin levels are high.
3. To test the hypothesis that men and women differ in their physiological responses to these two hypoxic stressors.
4. To determine if the hypoxic states induced by carbon monoxide or by lowered ambient oxygen are additive.

STUDY DESIGN

To achieve these aims, the authors used the unique facilities of the Institute of Environmental Stress in Santa Barbara, CA, including its hyperbaric chamber. They studied, in a blinded manner, the exercise response on a bicycle ergometer in healthy young nonsmokers living at sea level, breathing air containing 0, 50, 100, or 150 ppm carbon monoxide (intended to produce 0, 4, 6, or 8 percent carboxyhemoglobin, respectively) in a decompression chamber adjusted to simulate altitudes of 0, 1,524, 2,134, or 3,048 meters, a total of 16 different exposures in all. Each subject was monitored for ventilatory rates, oxygen consumption, carbon monoxide and carbon dioxide exchange rates, heart rate, and blood levels of carboxyhemoglobin, hemoglobin, and lactate.

SUMMARY OF INVESTIGATORS' CONCLUSIONS

Although the study included 23 healthy nonsmoking subjects, only nine subjects (five men and four women) completed all experimental conditions (16 exposures). The authors' major focus was on $\dot{V}_{O_2}$max. They report that $\dot{V}_{O_2}$max in men decreased with altitude, as predicted, by 5 percent at 1,524 meters, 8 percent at 2,134 meters, and 13 percent at 3,048 meters.

Upon simultaneous exposure to carbon monoxide, no additional significant decreases in $\dot{V}_{O_2}$max were observed despite increases in carboxyhemoglobin, regardless of the altitude at which $\dot{V}_{O_2}$max was measured. Total work performed exhibited a general tendency to decrease, both at increasing altitudes and at increased carbon monoxide at each of the altitudes above sea level. However, the lack of significant carbon monoxide alterations at sea level prevented the confirmation of additivity or the determination of equivalent responses of the two hypoxic agents. For a given level of carbon monoxide, carboxyhemoglobin concentrations attained at $\dot{V}_{O_2}$max were highest at sea level and lowest at 3,048 meters. This decrease in percent carboxyhemoglobin, due to the decrease in the partial pressure of

carbon monoxide at increasing altitude, further confounded the conclusion of additivity.

The authors report that women subjects' $\dot{V}_{O_2}$max and total work decreased only at 3,048 meters, and were not influenced by carbon monoxide exposure at any altitude. No physiological effects were noted that could be attributed to the combined exposure to altitude and carbon monoxide. Prior to maximal work loads, carbon monoxide was reported to shift into extravascular spaces (outside of the blood vessels), and to return to the vascular space within five minutes after exercise.

TECHNICAL EVALUATION

ASSESSMENT OF METHODS AND STUDY DESIGN

Dr. Horvath has long-standing experience in this field, and the Institute of Environmental Stress is very well equipped to conduct such studies. The methods of physiological measurement used in the study seem to be adequate and standardized. However, certain problems can be identified in the study design.

The duration of total exposure to carbon monoxide or to simulated altitude, or both, is not explicitly stated in the report; this information is critical in the interpretation of the results. It is well known that the duration of exposure to altitude is very important in assessing the effect of altitude. By using information about the exercise protocol and the values for total work, a rough figure for the exposure time can be calculated: The values appear to be about 14 minutes for women and 22 minutes for men, both very short exposure times. Marked circulatory adjustments occur during the first five to 10 days at altitude, with a decrease in stroke volume and an increase in arteriovenous oxygen difference (Myhre 1980). The long-term exposure to high altitude, together with potential carbon monoxide exposure, is probably a more relevant environmental health concern than the artificial, short-term exposure. Of course, long-term laboratory studies would present numerous and very difficult practical problems. However, the authors have not presented any justification for the assumption that short-term effects are related to long-term effects.

A computation of statistical power, based on known effects of carbon monoxide, or altitude, or both, would have strengthened or undermined the authors' choice of number of subjects. The number of subjects who actually completed the experiment appears to be too small for each exposure combination for statistical analysis, and the inclusion of men and women exacerbates this. With the deletion of one carbon monoxide level and one altitude level from the protocol, the investigators could have had a larger number of complete statistical cells (in nine exposure conditions). The authors have provided rationale for the inclusion of subthreshold-effects levels of both altitude and carbon monoxide that would, if different from sea level or 0 ppm carbon monoxide, or both, raise important health concerns. Perhaps the use of nine combinations would have sufficed; and, if only males were used, the sample size could have been two to three times larger. The authors indicate that they had hoped to test 20 subjects in all 16 conditions, but the number of exposures and the heavy work load was too imposing to maintain subject interest. Seven subjects dropped out after several exposures.

The chamber arrangement for maintaining both carbon monoxide and altitude levels is a major strength of this study. Carbon monoxide was administered into the chamber at equivalent concentration levels, in ppm, at each altitude. The levels were maintained with the aid of ecolyzers that were calibrated before and after each experimental run at the selected altitude level. Table 4 of the Investigators' Report demonstrates that the chamber concentrations were monitored and, at each altitude level, equivalent concentrations of carbon monoxide, in ppm, were achieved. The subjects' carboxyhemoglobin levels were found to decrease linearly with increasing altitude.

DATA ANALYSIS

The major tools used for data analysis were tests for linearity and significance among means. Many complex data have been generated in this study. However, data analysis has not been directed to the main goal of the study, that is, the exploration of the additivity of the responses to altitude and carbon monoxide. It might have been possible to analyze the data so as to examine the equivalence relationship of altitude and carbon monoxide on subjects' responses. In addition, some of the analyses are performed using linear regression; yet the relationship in the data appears to be curvilinear. (See, for example, Figure 6, depicting the analysis of maximal carboxyhemoglobin achieved versus increment of percent carboxyhemoglobin [over control levels] five minutes after exercise.)

A more efficient approach to analysis of the data can be envisioned. The authors reported data for the subjects completing all exposures, analyzed by two-way analysis of variance with repeated measures, and for all subjects who completed four carbon monoxide exposures at any altitude condition, analyzed with one grouping factor for altitude and one repeated measure for carbon monoxide. Analysis by both factors individually would have allowed more powerful inferences about the health effects of either exposure separately, or both together.

From the data presented, the subjects do not appear to have been randomly assigned to exposure conditions. Appropriate analysis of variance assumes the random order (by use of a table of random numbers) of experimental conditions for each subject. Instead, when it became clear to the investigators that they could not fulfill their subject number requirement, they assigned each subject to an altitude, and tested at the four carbon monoxide levels within this altitude level. This confounded altitude effects with interperson effects.

INTERPRETATION OF RESULTS

Although the authors were technically able to achieve the exercise, altitude, and carbon monoxide exposure goals they initially sought in individual subjects, their perhaps overly ambitious design greatly interferes with the interpretation of their final results. The individual studies were demanding and time consuming. It is not surprising that only nine of 23 subjects completed all 16 experimental visits. Statistical inference from the data was further compromised because the carboxyhemoglobin levels achieved were variable, and because both genders were included in the study sample. Individuals of both genders were studied, although their numbers were too small to differentiate any gender-based difference in responsiveness. The authors appropriately defend their separate analyses for men and women as based on inherent differences in physiology (red cell mass, hemoglobin, and so forth) and in $\dot{V}_{O_2}$max.

In addition, as the authors state in retrospect, the finding of reduced carboxyhemoglobin levels at altitude could be expected from the known effects of altitude on gas partial pressures, oxygen saturation of hemoglobin, and the hemoglobin dissociation curve. As the air pressure decreases with increasing altitude, the partial pressure of each gas decreases. The dissociation characteristics of hemoglobin for oxygen protects the body by making oxygen available without increasing ventilation. This means that the identical concentration (in ppm) of carbon monoxide in ambient air will result in a lower dose to individuals at high altitudes than at sea level because ventilation does not increase to compensate for the reduced pressure. The reduced dose of carbon monoxide explains the lower carboxyhemoglobin levels and the failure to observe an additive or interactive effect of carbon monoxide hypoxia on the hypoxic effects of exercising at high altitude.

This report encompasses two issues that should be differentiated: (1) are altitude hypoxia and carbon monoxide effects additive? and (2) does the carbon monoxide standard need to be lower at high altitude, because the low partial pressure of oxygen possibly makes humans more susceptible to low concentrations of carbon monoxide? The first issue is incompletely addressed by this study, mainly because the dose of carbon monoxide administered at higher altitude, given in constant ppm, would be lower than at sea level. Because both altitude hypoxia and carbon monoxide exert their effects by decreasing intracellular partial pressure of oxygen at sites of oxygen utilization, it would seem logical that the effects would be additive. However, this study does not support that presumption. Regarding the second issue, it is clear that if carbon monoxide concentrations (in ppm) are kept constant, carbon monoxide and oxygen partial pressures decrease in parallel with progressive increases in altitude. This study found the expected, that carbon monoxide uptake was decreased at high altitude due to several different effects, the major effect being the progressive decrease in partial pressure of carbon monoxide with the progressive increase in altitude without compensating increases in ventilation. Thus, the carboxyhemoglobin levels at high altitude were lower than the carboxyhemoglobin levels achieved at sea level. Because the Clean Air Act standards are based on ambient carbon monoxide levels, and not blood carboxyhemoglobin levels, the results of this study suggest that no special consideration need be given to ambient carbon monoxide standards at the altitudes tested.

CONCLUSIONS

Given the small number of subjects, and the small magnitude of the potential effects, the results of this study should be interpreted cautiously. These results are the same as those of the earlier study by Weiser and coworkers (1978); namely, that carbon monoxide exposure aimed at increasing carboxyhemoglobin 2 to 4 percent had no effect on decreases in $\dot{V}_{O_2}$max and other parameters seen at altitude.

The results reported here do not provide the information necessary to determine whether or not carbon-monoxide- and altitude-induced hypoxic effects are additive. The problems with study design (such as inadequate number of subjects, nonrandom exposure assignments, and failure to achieve comparable carboxyhemoglobin levels) preclude the detection of physiologically significant effects of carbon monoxide versus altitude hypoxia.

The data do show, however, that carbon monoxide shifts out of the blood and into extravascular spaces at maximal work loads, and returns to the blood within five minutes. This confirms the earlier work by Clark and Coburn (1975). It also suggests that ambient carbon monoxide concentrations (in ppm) at elevated altitudes do not induce the carboxyhemoglobin levels that are expected to result from ambient carbon monoxide concentrations at sea level because

of the absence of compensating increases in ventilation. This finding appears to diminish special concern for the effects of acute carbon monoxide exposure in healthy individuals at high altitude.

IMPLICATIONS FOR FUTURE RESEARCH

Designs of future studies need to simulate more realistic human situations, which include more prolonged exposure to high altitude and to carbon monoxide. Appropriate carboxyhemoglobin levels must be achieved in order to assess the relationship between ambient exposure and health effects. Adequate documentation of both carbon monoxide uptake rates in normal individuals, and the consequence of altitude on partial pressure, now exists to support such goals. When planning further research in this area, the issues of projected study power, sample size, statistical analysis appropriate for the study design, and subject participation also need to be considered.

REFERENCES

Ayres SM, Giannelli S, Mueller H. 1970. Effects of low concentrations of carbon monoxide: Myocardial and systemic responses to carboxyhemoglobin. Ann NY Acad Sci 174:268–293.

Buskirk ER. 1978. Work capacity of high altitude natives. In: Biology of High Altitude Peoples (Baker PT, ed.) pp. 173–187. Cambridge University Press, Cambridge, England.

Clark BJ, Coburn RF. 1975. Mean myoglobin oxygen during exercise at maximal oxygen uptake. J Appl Physiol 39:135–144.

Dill DB, Adams WC. 1971. Maximal oxygen uptake at sea level and at 3,090-m altitude in high school champion runners. J Appl Physiol 30:854–859.

Ekblom B, Huot R. 1972. Response to submaximal and maximal exercise at different levels of carboxyhemoglobin. Acta Physiol Scand 86:474–482.

Horvath SM, Raven PB, Dahms TE, Gray DJ. 1975. Maximal aerobic capacity at different levels of carboxyhemoglobin. J Appl Physiol 38:300–303.

Klausen K, Dill DB, Horvath SM. 1970. Exercise at ambient and high oxygen pressure at high altitude and at sea level. J Appl Physiol 29:456–463.

Lenfant C, Sullivan K. 1971. Adaptation to high altitude. N Engl J Med 284:1298–1309.

Myhre LG. 1980. Biochemical adaptations to exercise and altitude. In: Environmental Physiology: Aging, Heat and Altitude (Horvath SM, Yousef MK, eds.). Elsevier Science Publishing Co., New York, NY.

Myhre LG, Robinson S. 1971. The influence of altitude on the anaerobic capacities of men. Proc Int Union Physiol Sci 9:411.

National Research Council. 1977. Carbon Monoxide. Committee on Medical and Biological Effects of Environmental Pollutants. National Academy of Sciences, Washington, DC.

Penney DG. 1988. A Review: Hemodynamic response to carbon monoxide. Environ Health Perspect 77:121–130.

Pugh LG. 1967. Athletes at altitude. J Physiol (London) 192:619–646.

Raven PB, Drinkwater BL, Ruhling RO, Bolduan NW, Taguchi S, Gliner JA, Horvath SM. 1974. Effect of carbon monoxide and peroxyacetylnitrate on man's maximal aerobic capacity. J Appl Physiol 36:288–293.

U.S. Environmental Protection Agency. 1985. Review of the National Ambient Air Quality Standards for Carbon Monoxide: Final Rule. Fed. Reg. 50:37484–37491.

U.S. Senate. 1970. Rep. No. 1196, 91st Congress, 2nd Session, 10.

Vogel JA, Gleser MA, Wheeler RC, Witten BK. 1972. Carbon monoxide and physical work capacity. Arch Environ Health 24:198–203.

Wasserman K, Hansen JE, Sue DY, Whipp BJ. 1986. Principles of Exercise Testing and Interpretation. Lea & Febiger, Philadelphia, PA.

Weiser PG, Morrill CG, Dickey DW, Kir TL, Cropp GJA. 1978. Effects of low-level carbon monoxide exposure on the adaptation of healthy young men to aerobic work at an altitude of 1,610 meters. In: Environmental Stress: Individual Adaptations (Folinsbee LJ, Wagner JA, Borgia JF, Drinkwater BL, Gliner JA, Bedi JF, eds.). Academic Press, Orlando, FL.

Special Reports

Title	Publication Date
Gasoline Vapor Exposure and Human Cancer: Evaluation of Existing Scientific Information and Recommendations for Future Research	September 1985
Automotive Methanol Vapors and Human Health: An Evaluation of Existing Scientific Information and Issues for Future Research	May 1987
Gasoline Vapor Exposure and Human Cancer: Evaluation of Existing Scientific Information and Recommendations for Future Research (Supplement)	January 1988

Research Reports

Report No.	Title	Principal Investigator	Publication Date
1	Estimation of Risk of Glucose 6-Phosphate Dehydrogenase-Deficient Red Cells to Ozone and Nitrogen Dioxide	M. Amoruso	August 1985
2	Disposition and Metabolism of Free and Particle-Associated Nitropyrenes After Inhalation	J. Bond	February 1986
3	Transport of Macromolecules and Particles at Target Sites for Deposition of Air Pollutants	T. Crocker	February 1986
4	The Metabolic Activation and DNA Adducts of Dinitropyrenes	F.A. Beland	August 1986
5	An Investigation into the Effect of a Ceramic Particle Trap on the Chemical Mutagens in Diesel Exhaust	S.T. Bagley	January 1987
6	Effect of Nitrogen Dioxide, Ozone, and Peroxyacetyl Nitrate on Metabolic and Pulmonary Function	D.M. Drechsler-Parks	April 1987
7	DNA Adducts of Nitropyrene Detected by Specific Antibodies	J.D. Groopman	April 1987
8	Effects of Inhaled Nitrogen Dioxide and Diesel Exhaust on Developing Lung	J.L. Mauderly	May 1987
9	Biochemical and Metabolic Response to Nitrogen Dioxide-Induced Endothelial Injury	J.M. Patel	June 1987
10	Predictive Models for Deposition of Inhaled Diesel Exhaust Particles in Humans and Laboratory Species	C.P. Yu	July 1987
11	Effects of Ozone and Nitrogen Dioxide on Human Lung Proteinase Inhibitors	D.A. Johnson	August 1987
12	Neurotoxicity of Prenatal Carbon Monoxide Exposure	L.D. Fechter	September 1987
13	Effects of Nitrogen Dioxide on Alveolar Epithelial Barrier Properties	E.D. Crandall	October 1987
14	The Effects of Ozone and Nitrogen Dioxide on Lung Function in Healthy and Asthmatic Adolescents	J.Q. Koenig	January 1988
15	Susceptibility to Virus Infection with Exposure to Nitrogen Dioxide	T.J. Kulle	January 1988
16	Metabolism and Biological Effects of Nitropyrene and Related Compounds	C.M. King	February 1988

Copies of these reports can be obtained by writing to the Health Effects Institute, 215 First Street, Cambridge, MA 02142.

Research Reports

Report No.	Title	Principal Investigator	Publication Date
17	Studies on the Metabolism and Biological Effects of Nitropyrene and Related Nitro-polycyclic Aromatic Compounds in Diploid Human Fibroblasts	V.M. Maher	March 1988
18	Respiratory Infections in Coal Miners Exposed to Nitrogen Oxides	M. Jacobsen	July 1988
19	Factors Affecting Possible Carcinogenecity of Inhaled Nitropyrene Aerosols	R.K. Wolff	August 1988
20	Modulation of Pulmonary Defense Mechanisms Against Viral and Bacterial Infections by Acute Exposures to Nitrogen Dioxide	G.J. Jakab	October 1988

Copies of these reports can be obtained by writing to the Health Effects Institute, 215 First Street, Cambridge, MA 02142.

The Health Effects Institute (HEI) is an independent nonprofit corporation that is "organized and operated . . . to conduct, or support the conduct of, and to evaluate research and testing relating to the health effects of emissions from motor vehicles." It is organized in the following ways to pursue this purpose.

INDEPENDENCE IN GOVERNANCE

The Institute is governed by a four-member Board of Directors whose members are Archibald Cox (Chairman of the Board), Carl M. Loeb University Professor (Emeritus) at Harvard University; William O. Baker, Chairman (Emeritus) of Bell Laboratories and Chairman of the Board of Rockefeller University; Donald Kennedy, President of Stanford University; and Charles Powers, Partner, Resources for Responsible Management.

TWO-SECTOR FINANCIAL SUPPORT

The Institute receives half of its funds from the United States government through the Environmental Protection Agency, and half from the automotive industry. Twenty-seven domestic and foreign manufacturers of vehicles or engines contribute to the Institute's budget in shares proportionate to the number of vehicles or engines that they sell.

THE HEI RESEARCH PROCESS

The Institute is structured to define, select, support, and review research that is aimed at investigating the possible health effects of mobile source emissions. Its research program is developed by the Health Research Committee, a multidisciplinary group of scientists knowledgeable about the complex problems involved in determining the health effects of mobile source emissions. The Committee seeks advice from HEI's sponsors and from other sources prior to independently determining the research priorities of the Institute.

After the Health Research Committee has defined an area of inquiry, the Institute announces to the scientific community that research proposals are being solicited on a specific topic. Applications are reviewed first for scientific quality by an appropriate expert panel. Then they are reviewed by the Health Research Committee both for quality and for relevance to HEI's mission-oriented research program. Studies recommended by the Committee undergo final evaluation by the Board of Directors, who review the merits of the study as well as the procedures, independence, and quality of the selection process.

THE HEI REVIEW PROCESS

When a study is completed, a final report authored by the investigator(s) is reviewed by the Health Review Committee. The Health Review Committee has no role either in the review of applications or in the selection of projects and investigators for funding. Members are also expert scientists representing a broad range of experience in environmental health sciences. The Committee assesses the scientific quality of each study and evaluates its contribution to unresolved scientific questions.

Each Investigator's Report is peer-reviewed, generally by a biostatistician and three outside, independent reviewers chosen by the Review Committee. At one of its regularly scheduled meetings, the Review Committee discusses the Investigator's Report. The comments of the Committee and the peer reviewers are sent to the investigator, and he or she is asked to respond to those comments and, if necessary, revise the report. The Review Committee then prepares its Report, which includes a general background on the study, a technical evaluation of the work, a discussion of the remaining uncertainties and areas for future research, and implications of the findings for public health. After evaluation by the HEI Board of Directors, the HEI Research Report, which includes the Investigator's Report and the Review Committee's Report, is then published in monograph form. The Research Reports are made available to the sponsors, the public, and many scientific and medical libraries, and are registered with NTIS.

All HEI investigators are urged to publish the results of their work in the peer-reviewed literature. The timing of the release of an HEI Research Report is tailored to ensure that it does not interfere with the journal publication process.

HEI HEALTH EFFECTS INSTITUTE 215 First Street, Cambridge, Massachusetts 02142 (617) 491-2926

Research Report Number 21 **December 1988**