countries) are given primaquin to destroy gametocytes which they may harbor, whether or not they had the clinical disease, to prevent them from returning to the homeland as carriers of chloroquine-resistant *P. falciparum*. It is to be hoped that this program will be carried out effectively. The treatment of acute chloroquine-resistant malignant malaria does not end at the battlefront. There will be other battles with *P. falciparum* as well as with other malarial parasites.

What has yet to be established in military medicine is where the battle lines of national defense should really be drawn, and whether the same full and prompt support of research in problems of national medical importance do not have a broader spectrum than is usually recognized and should not be applied to a more extensive horizon of natural enemies of mankind than a group of highly specific exotic tropical diseases. But in any event, the current military program of this country has solved a problem in malaria which will benefit all mankind: to date, our most important victory in Vietnam.

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Carbon Monoxide and Human Health

John R. Goldsmith and Stephen A. Landaw

Carbon monoxide (CO), a colorless, nonirritating gas, is generated by incomplete combustion. Its presence is a ubiquitous index of affluence, since it occurs in industry, in tobacco smoke, in household heating, and in motor vehicle exhaust. Because of the contribution of motor vehicle exhaust, carbon monoxide is one the most important of urban atmospheric pollutants.

To prevent adverse effects on human health as exposures to CO increase, adequate programs and policies must be adopted. Their formulation will require deliberate scientific judgment based on adequate information and the consideration of certain hypotheses, which are reviewed here.

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Sources of Exposure

Urgency is given the development of such policies by the large and rapidly growing number of motor vehicles, whose pollutants now have made the quantum jump from being a problem in the immediate vicinity of traffic to being a problem affecting the entire community. For example, in New York City *each day*, automobile traffic alone produces 8.3 million pounds (3.8 million kilograms) of CO; each car emits about 1/6 pound of CO per mile of travel at 25 miles (40 kilometers) per hour and about ⅓ pound per mile of travel at 10 miles per hour (*1*). An estimated 20 million pounds of CO per day were emitted by motor vehicles in Los Angeles during 1967.

In urban areas dependent on automobiles for commuting, a common pattern is observed. There is a relatively high peak of CO pollution in the morning and a flatter peak in the evening. A single day-long peak is observed in downtown New York City (*2*), reflecting saturation levels of traffic.

The first generation of exhaust control devices now required on new cars has reduced CO emissions, but the effectiveness of these systems is known to diminish as the vehicles are used. Since motor vehicle use is expected to increase by 70 percent by 1980, even 70-percent control—the goal of the existing program—would not produce an improvement over the present situation even if that goal were attained.

Carbon monoxide occurs in high concentration in cigarette smoke (> 2 percent), but an estimate of the average concentration in smoke inhaled into the lung is about 400 parts per million (0.04 percent).

The magnitude of exposure to CO from smoking has been estimated in a population of longshoremen (*3*) examined prior to the work shift and during a time when there was little community air pollution. The results therefore reflect primarily the effects of smoking. Exposure estimates were based on measurements of CO in expired air after the individual had held his breath for 20 seconds. Ringold *et al.* (*4*) have shown this to be a valid way to estimate the concentration of carboxyhemoglobin (COHb, the complex of carbon monoxide with hemoglobin in

the body) without drawing blood samples. The results are shown in Table 1; 5.9 percent of COHb is the median value for moderate cigarette smokers who inhale. The relatively low levels in pipe smokers and cigar smokers are due to the fact that less smoke is inhaled when tobacco is used in these forms. Inhaling clearly increases the uptake of CO.

In an extensive survey of occupational exposure to CO (*5*) covering 136,422 employees in Maryland and 25,122 in Utah it was reported that, respectively, 12.0 and 13.8 percent of employed persons had occupations in which there was a likelihood of exposure as defined by measurably increased levels at the work place or by the occurrence of toxic reactions. This survey is now out of date, but it seems likely that a sizeable proportion of the current work force has a significant occupational exposure.

The present maximum allowable atmospheric concentration, or threshold-limit value, for occupational exposure in industry is 50 parts per million, for 8 hours. The limit was reduced from 100 parts per million in 1964 because of new evidence of possible adverse effects, mostly on the central nervous system, from exposures in the range of 50 to 100 parts per million (*6*).

Various forms of indoor combustion may emit CO, and a number of deaths each year are due to intoxication from this source. For example, the Michigan State Department of Public Health recently called attention to the risks of CO exposure associated with gas-fired baseboard heaters. A number of these had to be recalled by the manufacturer as potential health hazards (*7*). Open fires and charcoal braziers produce a substantial amount of CO (*8*). Possibly some of the reported seasonal variation in COHb concentrations (*9*) may be attributable to household heating devices.

Table 1. Proportion of smokers and median concentrations of expired CO in a population of longshoremen ($N = 3311$). [California State Department of Public Health]

Category*	Median concentration (parts per million) of CO measured in expired air	Median percentage of carboxyhemoglobin estimated from regression
Never smoked (23.1)	3.2	1.2
Ex-smoker (12.1)	3.9	1.4
Pipe and/or cigar smoker only (13.4)	5.4	1.7
Cigarette smoker		
Light smoker (half pack or less) (13.0)		
Inhaler	17.1	3.8
Noninhaler	9.0	2.3
Moderate smoker (more than half pack or less than 2 packs) (31.3)		
Inhaler	27.5	5.9
Noninhaler	14.4	3.6
Heavy smoker (2 packs or more) (7.0)		
Inhaler	32.4	6.8
Noninhaler	25.2	5.6

* Values in parentheses are percentages of study population by smoking pattern.

Mechanism of Carbon Monoxide Effects

The major effect of CO depends upon its ability to impair oxygen transport by blood, through two distinct mechanisms. First, since the affinity of human hemoglobin is 210 times greater for CO than it is for oxygen, a small quantity of CO can reversibly inactivate a substantial percentage of the oxygen-carrying capacity of the blood. Second, COHb interferes with the release of the oxygen carried by the hemoglobin molecule (*10*). The resulting shift in the oxyhemoglobin dissociation curve is shown in Fig. 1.

Such a shift in oxyhemoglobin dissociation means that the avidity of hemoglobin for oxygen is increased. At high partial pressures of oxygen, such as occur in the pulmonary capillaries, the oxygen content is nearly maximal and is unlikely to be increased very much by this shift. However, at the tissue level, where the oxygen content of the capillary blood has been reduced to approximately 40 percent of saturation, the shift can substantially decrease the oxygen tension supplying the tissues. This shift is known to increase the hazard of CO toxicity at high concentrations of COHb (around 40 percent) as compared to an equivalent reduction of blood oxygen by hypoxia or altitude. More accurate measurements are needed on the effect of COHb in the 0- to 20-percent range on oxygen transport to the different tissues.

In general, the signs and symptoms of acute CO toxicity depend on the proportion of hemoglobin which is combined with CO. This is a function of the

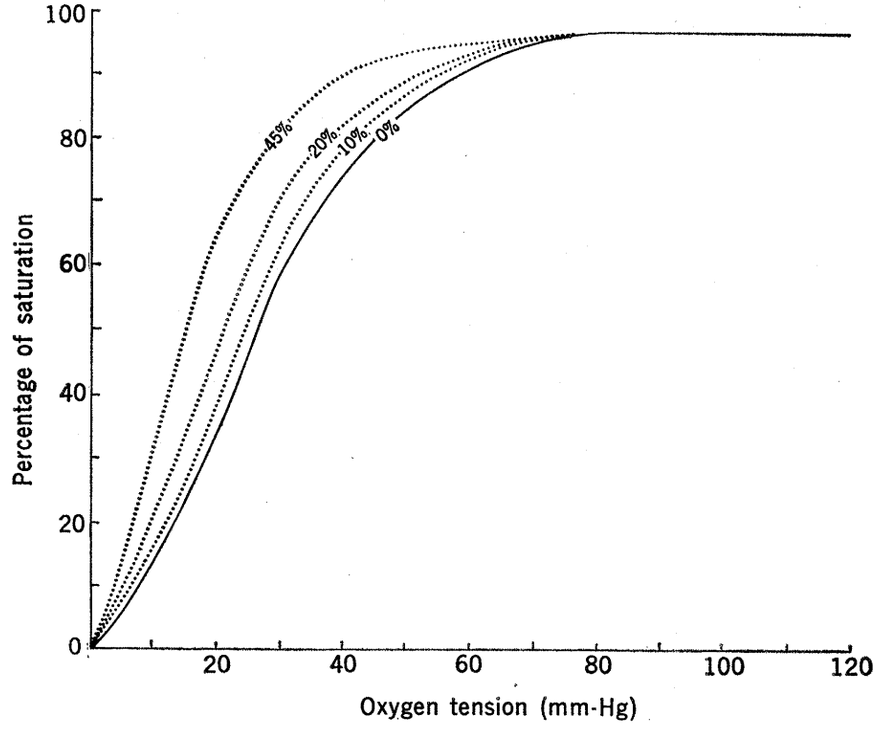


Fig. 1. The oxyhemoglobin dissociation curve is shown for COHb concentrations of 0, 10, 20, and 45 percent. The ordinate gives percentages of saturation of hemoglobin with oxygen for the remaining available binding sites in the hemoglobin, when equilibrium exists over the physiological range of oxygen tensions (*10*).

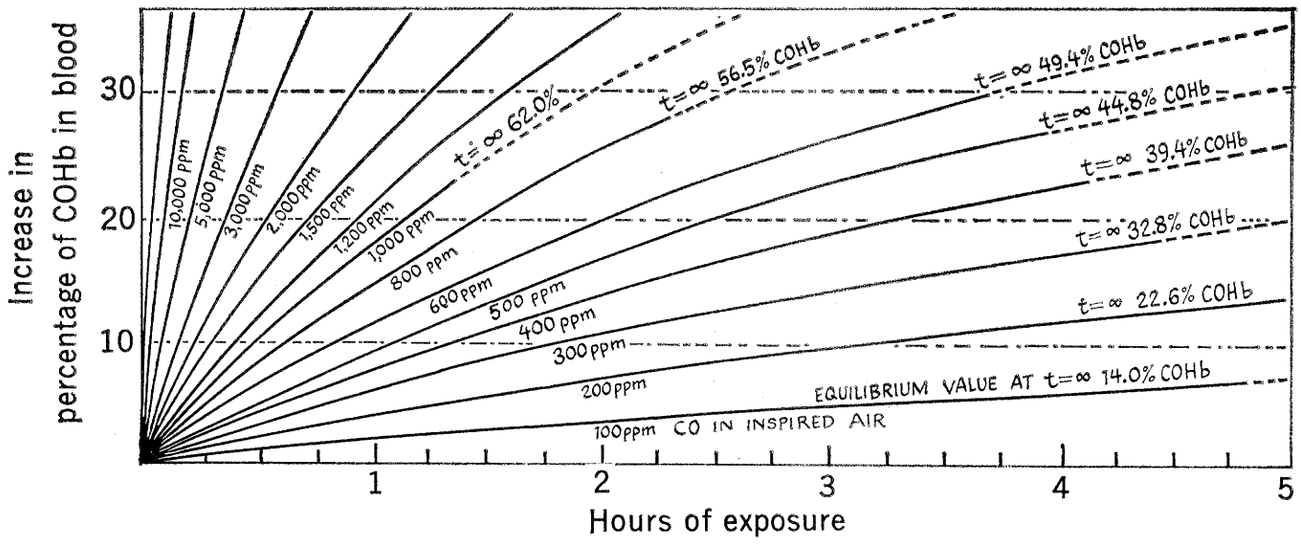


Fig. 2. The accumulation of carboxyhemoglobin (COHb) in resting males resulting from different amounts of CO in the inspired air and different durations of exposure. The COHb equilibrium values are shown for "infinite" exposure times. [Forbes, Sargent, and Roughton (*12*)]

concentration of the CO in the inhaled air and the volume of air breathed per minute. Carbon monoxide is excreted almost entirely from the capillaries of the lung, in the expired air, after dissociation of the COHb complex. The half-time of excretion for low concentrations is from 2 to 4 hours. With continual fixed exposure to CO, an equilibrium concentration of COHb is approached. The rate at which equilibrium is reached is determined principally by the rate of respiration. For continuous exposures to concentrations of less than 100 parts per million (*11*), the California State Department of Public Health has derived, from published data, the equation

$$\text{CO} \times 0.16 = \%\ \text{of COHb} \qquad (1)$$

where the concentration of CO (in parts per million, by volume) times 0.16 equals the percentage of COHb at equilibrium.

At low concentrations this equilibrium relationship is not reached for several hours. Forbes, Sargent, and Roughton studied the rate of uptake of CO for exposures at concentrations of from 100 to 2000 parts per million (*12*) (see Fig. 2). On the basis of these data, the California State Department of Public Health has used, for shorter exposures to concentrations higher than 100 parts per million, the equation

$$\text{CO} \times KT = \%\ \text{of COHb} \qquad (2)$$

where CO is the concentration of carbon monoxide, in parts per million; T is the exposure time, in hours; and K is a constant which varies with the ventilation rate, which in turn depends on the level of physical activity. K is 0.018 when the individual is at rest (ventilation, 6 liters per minute) and 0.048 when the individual is engaged in light work (ventilation, 18 liters per minute). Equation 2 is valid for exposures to concentrations in excess of 100 parts per minute, a preexposure COHb concentration of less than 5 percent, and increases in COHb concentration of up to 7 percent.

Since the effect of CO is an impairment of transport of oxygen to the tissues, at high altitudes, and in other situations where oxygen tensions are low, the effects of a given concentration of CO will be correspondingly more severe. The recommended CO threshold-limit value for work at 5000 to 8000 feet (1500 to 2400 meters) is only 25 parts per million (*6*).

The population group most susceptible to the adverse effects of atmospheric CO, according to the California State Department of Public Health, includes persons with severe anemia or impairment of circulation to vital organs of the body. It has been predicted that, in such individuals, community exposures which produce a 5-percent concentration of COHb, added to the burden attributable to occupational and smoking exposures, could increase mortality and morbidity rates. This COHb level can be produced by average exposures to a CO concentration of 30 parts per million for 8 hours, which is a sufficient time for equilibrium to be reached. (Equation 1 yields an increase in COHb of 4.8 percent, to which the natural background level must be added.) This exposure (a concentration of 30 parts per million in 8 hours) was adopted by the Department as an air quality standard at the second or "serious" level (the level likely to lead to insidious or chronic disease or to significant alteration of important physiologic function in a sensitive group). Confirmation of the prediction concerning morbidity and mortality will require study on a scale wider than has so far been attempted. This is discussed further below.

In a recent review (*12a*) Dinman expressed the view that it would be "the better part of discretion to consider dropping the 8-hour community level from 30 parts per million to a level of 20 ppm for that period."

Since the State of California first set air quality standards for CO, in 1959, there have been three developments which suggest the need for reevaluation. They are (i) an increase in knowledge concerning endogenous CO production and CO metabolism, (ii) clearer definition of the effects of CO on selected functions of the nervous system, and (iii) improvement of methods for epidemiologic study of possible CO effects. We briefly review these advances.

Endogenous Carbon Monoxide Production: Recent Findings

Although numerous reports appeared in the world's literature in the late 19th century asserting that a combustible gas was present in the blood and breath of man and other mammals (*13*), it was

not until 1945 that Roughton and Root (*14*) demonstrated conclusively that there was a small, but measurable, amount of CO in normal human blood. Later, Sjöstrand (*15*) confirmed these findings and showed that, in nonsmokers, the CO concentration was higher in expired air than in inspired air, thus demonstrating that CO is actually produced within the body. He estimated CO production to be approximately 0.5 to 1.0 milliliter per hour in the normal adult female, values which are in close agreement with those now accepted.

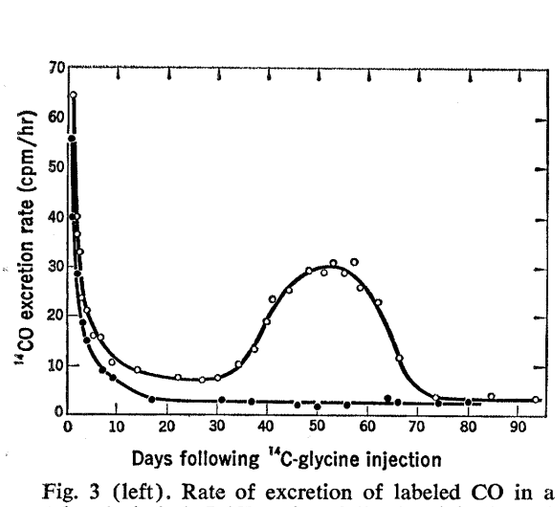
Sjöstrand also noted that endogenous production of CO was greater in patients with hemolytic anemia, extensive trauma, and transfusion reactions, and also following certain surgical procedures (*15, 16*). He further demonstrated that solutions of hemoglobin and myoglobin, on standing, liberated CO, and that maximum production of CO corresponded to the CO binding capacity of the original solution (*17*). These findings suggested that CO production was intimately associated with the decomposition of hemoglobin. In vivo and in vitro production of CO thus appeared to occur when a cyclic tetrapyrrole (heme) was decomposed to a linear tetrapyrrole (bilirubin) by the loss of a one-carbon fragment at the alpha-methene position (*18*). Libowitzky and Fischer (*19*) had been unable to recover the missing alpha-methene carbon in vitro as either formic acid or formaldehyde. Sjöstrand's suggestion that the missing carbon atom was oxidized to CO was later confirmed and amplified by Ludwig, Blakemore, and Drabkin, in 1957, using labeled heme (*20*).

Engstedt (*21*) showed that, in persons with no exogenous exposure, there was a high positive correlation between COHb concentrations and both reticulocyte count and fecal stercobilin production, and a negative correlation between such concentrations and the survival of red cells labeled with chromium-51. The measurement of endogenous production of CO is now recognized to be clinically useful in the diagnosis of hemolytic states.

Recently, Coburn, Forster, and their co-workers published a series of papers concerned with the accurate determination of CO production in animals and man, utilizing a rebreathing method (*22–25*). They showed that normal man produces approximately 0.4 milliliter of CO per hour, and that the rate is increased in various hemolytic states. They noted, however, that the normal rate of endogenous production of CO is higher by about 20 to 30 percent than the rate calculated from the known amounts and turnover rates for circulating red-blood-cell hemoglobin (*23*). Earlier studies of bile pigment metabolism (*26*) had shown that there were sources of bile pigments distinct from the breakdown of heme derived from circulating red-blood-cell hemoglobin. These sources were postulated to be (i) catabolism of myoglobin heme; (ii) catabolism of heme-containing enzymes (cytochromes and catalase, for example); (iii) excess production of heme in marrow and other sites; (iv) production of bilirubin through anabolic pathways; (v) early death of red blood cells within the marrow or shortly after release (ineffective erythropoiesis); and (vi) scarf of hemoglobin around the extruded nucleus of the normoblast (*27*).

White, Coburn, *et al.* (*28*), and Landaw and Winchell (*29*), injecting glycine-2-^{14}C as a label of the alpha-methene carbon atom of heme, recovered in expired air, during the first few days, labeled CO in an amount which was of the correct order of magnitude to account for this excess CO. A similar process has been demonstrated in liver slices (*30*) in vitro, demonstrating that nonhemoglobin hemes are important sources of bile pigment. Schwartz, Ibrahim, and Watson (*31*), Berlin (*32*), and Landaw (*33*), using hypertransfused animals in which erythropoiesis was nearly 100 percent suppressed (Fig. 3), estimated that about 40 percent of the early-appearing bile pigment (and CO) was due to catabolism of nonhemoglobin hemes. Recently, direct evidence of increased CO production in states associated with ineffective erythropoiesis has been obtained by Landaw (*33*) and by White *et al.* (*34*). On the basis of studies performed at the University of Pennsylvania, Coburn developed a schematic presentation of CO metabolism, shown in Fig. 4.

Patients undergoing anesthesia produce CO concentrations within rebreathing anesthesia circuits which often exceed 50 to 100 parts per million (*35*) —higher than the threshold-limit value for industrial workers. To prevent impairment of oxygenation, Middleton



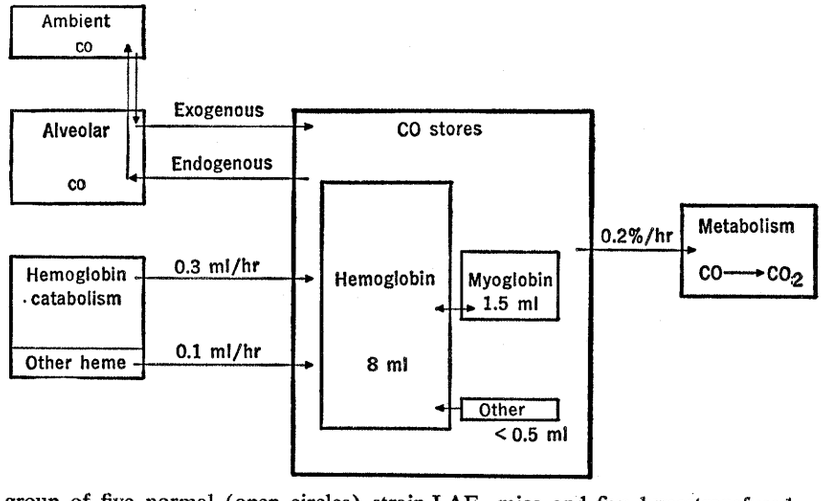


Fig. 3 (left). Rate of excretion of labeled CO in a group of five normal (open circles) strain-LAF$_1$ mice and five hypertransfused (closed circles) LAF$_1$ mice, following injection of glycine-2-^{14}C. Only the downslope portion of the "early peak" is shown. Note that in the hypertransfused mice, in which erythropoiesis was completely suppressed, the "late peak" is entirely absent, a finding which identifies this component with the destruction of labeled, senescent red blood cells. The "early peak" is still present, although its magnitude is approximately two-thirds that for normal animals, indicating that this fraction of the "early peak" is due to catabolism of nonhemoglobin hemes. [Landaw (*33*)] Fig. 4 (right). Schematic representation of variables that influence body stores of CO. [From Coburn (*22*), with permission]

et al. suggested that closed rebreathing systems be opened and flushed periodically during the operative procedure in order to remove this excess CO. Increased COHb concentrations, due to both normal and abnormal hemolysis, were also seen in newborn infants (*36*). The endogenous production of CO in these newborns led to increased COHb concentrations (as high as 12 percent), implying markedly impaired oxygen transport function.

Among physicians concerned with problems of undersea warfare it had long been known that CO arising from internal combustion engines, tobacco smoke, and other exogenous sources was an important contributor to atmospheric pollution in submarines. For this reason catalytic burners were provided to oxidize CO to harmless CO_2. This process helped make longer underwater operations practicable. Production of CO was also noted in other closed systems that contained men or animals but no other known CO sources. Toxic or fatal CO levels were frequently encountered in animal experiments when the CO was not specifically removed. This unexpected situation pointed to the animals themselves as important sources of CO pollution. Greater attention was then turned toward the endogenous production of CO in closed systems being developed for use in space flights and undersea exploration (*37*).

In a recent experiment with four men confined for a 14-day period to a closed system having a volume of 28 cubic meters, CO concentration had increased to 19 parts per million at the end of the study. The rate of endogenous production of CO, calculated from the rate of increase of atmospheric CO, is 0.37 milliliter per hour per man (*38*), a value in extremely close agreement with values obtained by Coburn *et al.* (*25*).

It is conceivable that the animal-plant cycles proposed for use on long space flights to produce oxygen and remove waste products will themselves be a source of CO, as a result of the decomposition of chlorophyll, the green respiratory pigment of plants, which contains a cyclic tetrapyrrole structure similar to heme. Mature leaves have been shown to produce large quantities of CO, presumably from degradation of this pigment (*39*).

The fate of atmospheric CO is not entirely known, but it has been suggested that a true CO cycle exists in nature, since CO can be produced by plants and by many lower animal species (*40*), can be utilized for metabolic purposes in certain bacteria and plants (*41*), and may be oxidized to CO_2 at slow rates in animals and man (*42*).

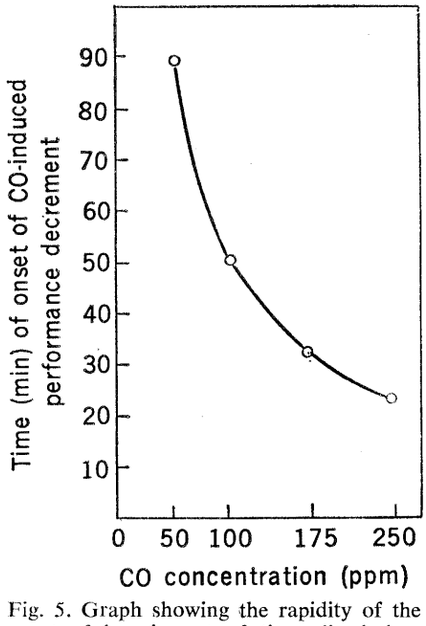


Fig. 5. Graph showing the rapidity of the onset of impairment of time discrimination by small concentrations of CO. When time of onset is plotted against CO concentration, this appears to be an almost perfectly negatively-accelerated function. When a reduction in correct responses equal to two standard deviations from the mean performance in an uncontaminated atmosphere was used as a criterion, an interval of 90 minutes, in an atmosphere of 50 parts of CO per million, was sufficient to produce a significant decrement in performance. For higher concentrations of CO, the needed interval was much shorter. [Beard and Wertheim (*45*), with permission]

Table 2. Coronary-heart-disease mortality ratios (with respect to rates observed in nonsmokers, set at 1.0), by age, for current smokers of cigarettes, by number of cigarettes smoked daily. The ratios are based on deaths from coronary heart disease reported over a 4-year period among 441,000 men. They show that rates of death from coronary heart disease are higher among men who smoke cigarettes than among men who do not, and that the mortality ratios for this disease generally increase with increased intensity of cigarette smoking. The highest mortality ratios are observed in the 45- to 54-year age group; ratios decrease with advancing age in each intensity category. [Data from Hammond (*59*)]

Age of subject	Nonsmokers	Smokers		
		Fewer than 10 per day	10–19 per day	More than 20 per day
<45*				
45–54	1.0	2.4	3.1	3.2
55–64	1.0	1.5	1.9	2.0
65–74	1.0	1.3	1.6	1.6
75–84	1.0	1.2	1.4	1.1

* No subjects available in this age group.

Effects of Low Concentrations on the Central Nervous System

In work done during World War II on the effects of CO on visual threshold, MacFarland, Roughton, and their colleagues detected an effect at a COHb concentration of about 5 percent (*43*). Schulte studied the effect on firemen of exposure to low concentrations of CO (*44*). He evaluated pulse rate, respiratory rate, changes in blood pressure, and neurologic reflexes and conducted a battery of psychomotor tests. On some of these tests, significant changes in response were found after exposure to CO. For some of the tests, variations in performance were found at COHb levels well below 5 percent, possibly even at levels as low as 2 percent. Schulte predicted that similar studies in a larger group of subjects might show significant variations in performance at even lower COHb levels. However, at the lowest COHb levels there was a somewhat erratic change in response as concentrations were increased, a fact which casts some doubt on the validity of this prediction. In any event, the tests used are rather complex and are not readily related to other types of behavior.

Beard and Wertheim (*45*) have reported distinct effects upon the ability to perceive differences in the duration of auditory stimuli among healthy subjects exposed for 90 minutes to CO in concentrations as low as 50 parts per million (Fig. 5). In supplementary tests to determine whether the effect was due to impairment of hearing or to impairment of temporal discrimination, the subjects were asked to estimate time intervals of 10 and 30 seconds; these tests showed that discrimination was impaired, not hearing. The results for the test subjects were significantly different from those for controls following exposure of the test subjects to CO concentrations as low as 50 parts per million for 45 minutes. Such an exposure could have produced COHb concentrations of less than 2 percent. We can only speculate upon the importance to driving performance of the capacity to estimate a 1-second interval to within an eighth of a second. It would seem sufficiently important to warrant testing to find whether similar levels of CO, commonly occurring in heavy traffic, are capable of influencing vehicular operations. Such effects should be detectable by epidemiologic methods.

Epidemiologic Study of the Effects of Carbon Monoxide on Human Health

Most epidemiologic studies have dealt with occupationally exposed groups (*46*). There are few epidemiologic data concerning effects likely to be observed in sensitive persons; individuals with severe anemia or critical vascular insufficiency are unlikely to be working in traffic tunnels, steel mills, or parking garages. Specific effects observed have generally been limited to increased levels of COHb and the disputed "chronic carbon monoxide poisoning" syndrome (*9*, *47*, *48*).

Grut (*9*), studying drivers of vehicles propelled by "producer-gas" in wartime Copenhagen, alleged that 46 percent of 721 drivers had "chronic CO poisoning" characterized by fatigue, headache, irritability, dizziness, disturbed sleep, and other symptoms. Some subjects had abnormal neurological symptoms. Lindgren (*48*) examined two groups of workmen, one group occupationally exposed, the other group not occupationally exposed but otherwise comparable. He found no higher frequency of symptoms and signs typical of so-called chronic CO poisoning in the exposed group than in the control group. The choice of the phrase "chronic CO poisoning" seems inappropriate, as it fails to distinguish between long-lasting effects of acute toxic exposures and a possible indolent process with a slow evolution, dependent on long-term exposure.

Table 3. Median concentrations (in parts per million) of expired CO for nonsmokers and for current smokers of cigarettes, by age of subject and by number of cigarettes smoked daily, from results obtained in the longshoreman study of Table 1. [California State Department of Public Health]

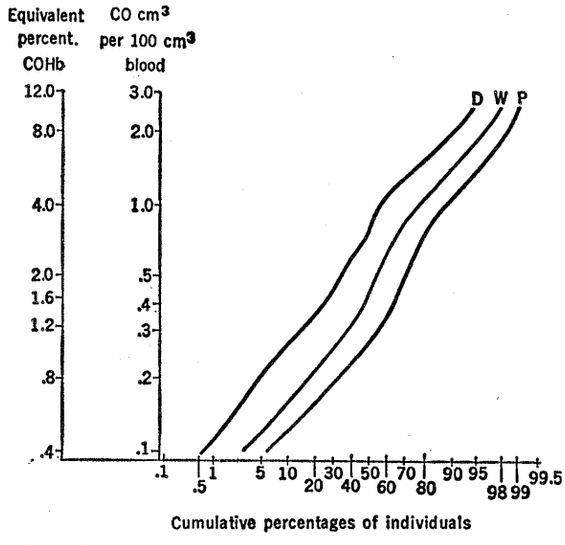
Age of subject	Non-smokers	Smokers		
		Fewer than 10 per day	10–39 per day	> 40 per day
< 45	3.6	18.9	30.6	34.2
45–54	3.6	12.6	27.0	34.2
55–64	3.6	17.1	25.2	27.0
65–74	3.6	12.6	16.2	*
75–84	3.6	*	14.4	*

*No value cited for populations of less than 10 individuals.

Accordingly, we feel that the data most relevant to the question of acute reactions in the general population would be data which show whether there are CO-associated increases in such relatively frequent events as motor vehicle accidents or in fatality rates for persons with myocardial infarction. Analyses of such data pose a number of difficult logical and statistical problems. In the case of motor vehicle accidents, there are fluctuations in traffic, visibility, the condition of vehicles, and driver exposure to alcohol and drugs. In the case of fatalities from myocardial infarction, the extent of the infarction, medical care, the use of oxygen, age, and sex may produce effects that would be difficult to control. Effects of CO derived from cigarette smoking must be considered as well as CO from community exposures.

Long-term effects of CO exposures are particularly difficult to evaluate. It is generally agreed that high-level exposures can produce tissue damage of the central nervous system and myocardium, but it is unclear whether low-level exposures can lead to impairment of these vital tissues. The central-nervous-system effects are essentially due to anoxia (*49*). The mechanism of myocardial effects is less certain. In at least one reported case, toxic levels of CO produced myocardial infarction in a 33-year-old man (*50*).

Animal exposure studies, with continuous or intermittent long-term exposure to a CO concentration of 50 parts per million, have given conflicting results suggesting that, in at least some species, changes in myocardial function can occur. For example, Stupfel *et al.* (*51*) find a transiently diminished QRS-complex amplitude in the electrocardiogram of the unanesthetized rat exposed continuously to a CO concentration of 50 parts per million. Musselman *et al.* (*52*), using the same exposures, observed no electrocardiographic or other changes in dogs, rats, or rabbits. But Lindenberg *et al.* (*53*) obtained significant results on exposing 15 dogs to a CO concentration of 50 parts per million for 6 weeks; seven of the dogs were exposed for 6 hours a day for 5 days a week, the others continuously. All showed electrocardio-



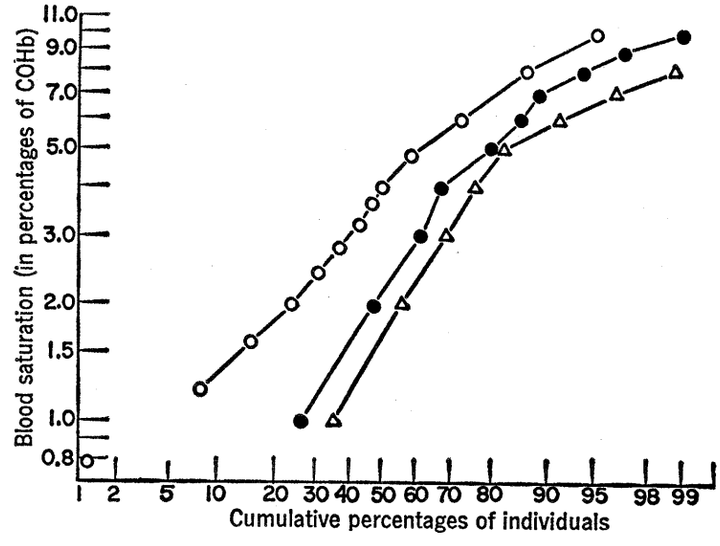


Fig. 6 (left). Concentrations of CO in the blood of (D) motor-vehicle drivers responsible for traffic accidents, (W) workmen showing evidence of occupational exposure to CO, and (P) private individuals believed to have been exposed to town gas or combustible gases containing CO. These are cumulative curves obtained from the results of Chovin's 5-year study. In all, more than 7000 samples were examined. [Chovin (*46*), with permission.] Fig. 7 (right). Percentages of COHb in the blood of (circles) 597 drivers responsible for traffic accidents in Paris (the same series as group D, Fig. 6), studied by Chovin (*46*); (solid circles) 100 drivers involved in traffic accidents in Detroit, studied by Clayton *et al.* (*57*); (triangles) 84 pedestrians involved in traffic accidents in Detroit, studied by Clayton *et al.* (*57*).

Table 4. Relationship between case fatality rate for patients with myocardial infarction and ambient CO concentration, by day of week, based on data from a 1958 hospital admission study for the Los Angeles area. [California State Department of Public Health]

Day	High-pollution area		Low-pollution area	
	Mean case fatality rate per 100 admissions	Correlation* coefficient for case fatality rate and CO concentration	Mean case fatality rate per 100 admissions	Correlation* coefficient for case fatality rate and CO concentration
All days	27.3	.161†	19.1	—.003
Weekdays	25.8	.161†	18.4	.050
Weekends	31.7	.280†	22.0	—.112
Sunday	29.3	.070	22.8	.002
Monday	26.3	.057	11.7	.081
Tuesday	24.5	.057	21.8	.206
Wednesday	24.7	.192	24.1	.228
Thursday	29.4	.164	18.4	—.131
Friday	24.3	.346‡	23.5	—.133
Saturday	34.0	.482‡	21.2	—.192

*Correlation between x', the arc sine transformation of the case fatality rate (arc sine $[(x+1)/(N+1)]^{\frac{1}{2}}$ + arc sine $[x/(N+1)]^{\frac{1}{2}}$, where x is the number of deaths and N is the number of admissions), and log CO (area averages). †Significant at the 1-percent level. ‡Significant at the 5-percent level.

graphic changes and, at autopsy, dilatation of the right side of the heart, with scarring of the heart muscle in some cases and fatty degeneration in others. Astrup *et al.* (*54*) have shown that exposure to CO concentrations of 200 to 350 parts per million increased atheromatous processes in cholesterol-fed rabbits.

These experimental data suggest that exposure to low concentrations of CO may have a role in the development of human heart disease. This becomes an important question for epidemiologic study.

This inference from acute toxicologic and experimental studies is strengthened by the abundant data linking cigarette smoking to coronary heart disease (*55*). The age-specific excess mortality is related to the amount of smoking and is reversed when subjects stop smoking. The relative excess decreases in older smokers, in a fashion paralleling the decrease in COHb levels as estimated from expired air. Tables 2 and 3 show the parallelism of COHb levels and excess mortality from coronary heart disease. We suggest that the role of CO in coronary disease be tested by comparing the smoking history with the COHb level as a predictor of occurrence of heart disease in large-scale prospective studies. Such studies will require a determination of the stability of the COHb level in individuals over a considerable period.

Since high levels of COHb imply increased respiratory absorption of other ingredients of tobacco smoke, comparisons with populations having high CO exposures from sources other than smoke will be needed. These populations could be most readily found in employee groups—for example, groups of firemen, traffic policemen, toll booth workers, and metallurgical workers. The histories of the longshoremen referred to in Table 1 are being followed in a search for a possible association of COHb levels with subsequent morbidity and mortality.

Methods for Studying Possible Acute Reactions

The complex temporal patterns of traffic accidents and CO exposure pose a formidable difficulty for conventional correlation analysis, since CO concentrations will be positively correlated with traffic density and probably with accidents. Ury (*56*) has developed a helpful nonparametric approach which should avoid this difficulty. From data for Los Angeles, pollutant levels and accident frequencies for each hour of each day of the week are tabulated. The data for adjacent weeks are then compared. If—to take an example—the CO level for 7 to 8 a.m. on Monday of week 13 of the year is lower than that for 7 to 8 a.m. on Monday of week 12 and the accident frequency for the same period is also less for week 13 than for week 12, a plus is scored. Had both the pollutant level and the accident frequency been higher for week 13 than for week 12, a plus would also have been scored; that is, a plus indicates concordant changes. If, however, a difference in CO level has a sign opposite to the sign for a difference in accident frequency, a minus is scored. If either the pollutant levels or the accident frequencies have identical values in adjacent weeks, a zero is scored. The pluses, minuses, and zeros are then cumulated for all pairs of weeks and tested by sign test statistics against random probability estimates. Pooling of the results not only permits a statistical inference for the set of data but makes it possible to isolate the contribution of different days, hours, seasons, and so on. Computer programs are now being developed for the many comparisons needed. The comparisons will be applied to 4 years of pollutant and accident data for Los Angeles.

Another approach to the accident problem is obviously that of measuring the COHb concentrations in persons involved in accidents. Chovin (*46*) made a study which showed (Fig. 6) that drivers thought to be responsible for accidents had substantially higher COHb concentrations than workers being examined for possible occupational exposure to CO, and that both groups had higher COHb concentrations than private individuals possibly exposed to CO from household devices. In this study, exposures from smoking could have a biasing effect; in future studies, smoking histories should be obtained. If CO exposure from smoking has an effect on accidents, more smokers should be found in the accident-involved driver group than in an appropriate control population. Clayton and his associates (*57*) also studied accident-involved drivers and found that they had higher COHb levels than pedestrians involved in traffic accidents. However, as may be seen in Fig. 7, the accident-involved drivers studied by Clayton had lower COHb levels than the drivers thought to be responsible for accidents in Chovin's series.

Cohen, Deane, and Goldsmith (*58*) have analyzed data for 3080 persons with myocardial infarction admitted to 36 Los Angeles hospitals, in relation to average levels of CO for the Los Angeles area. Case fatality rates were found to be associated with the CO level on the day of admission; there was a low but statistically significant correlation coefficient for all days and for weekdays. No significant associations were found between CO levels and the number of admissions. Since CO levels increase in winter, because of low average inversion height, and since there is a tendency for death rates also to in-

crease in winter, it is possible that a correlation could be spurious, being due to the effect of time of year on both case fatality rates and CO levels. A possible effect of autocorrelation was avoided by analyzing days of the week separately. All the significant associations involved patients in hospitals thought to be located in areas of relatively high pollution (Table 4). A temporospatial strategy was applied to test the hypothesis that the differences between case fatality rates in high-pollution and low-pollution areas was greatest in weeks when CO levels were high. It was felt that this procedure should reduce the effect of time of year on the correlation. Of the 13 weeks with the highest mean CO concentrations, a significant number (12) showed higher case fatality rates in high-pollution-area hospitals than in low-pollution-area hospitals. This was not the case for quartiles of weeks with lower mean CO concentrations. This result was obtained by the relatively insensitive sign test and was confirmed by the Wilcoxon matched-pairs signed-ranks test. Cohen *et al.* conclude that an association may exist between atmospheric CO pollution and case fatality rates from myocardial infarction. Obviously, in future tests of this association it would be desirable to obtain smoking histories and data on COHb concentrations at the time of admission of the patients to the hospital.

Further study of these problems will require the collection of a large number of data, since there is a complex temporal fluctuation, both of the exposure and of the underlying process.

Summary

Exposures to CO are widespread. For the U.S. urban population, cigarette smoking is probably the most important source, followed in importance by motor vehicle exhaust, occupational sources, and home heating and cooking devices. The median COHb concentration for one-pack-a-day cigarette smokers who inhale is 5.9 percent—a concentration sufficient to imply a serious threat to health in persons with underlying vascular insufficiency. This level of exposure may account for some of the excess mortality from cardiovascular disease observed among cigarette smokers. Community air pollution may produce COHb concentrations in nonsmokers similar to those observed in smokers, and the effects of these concentrations will be greater at high altitude.

Endogenous production of CO from heme catabolism has been abundantly documented. Such production provides a tool for the study of hemolytic disorders, is a hazard to infants in respirators and to men in submersibles and space capsules, and may add to the risk of closed-circuit anesthesia.

Low and commonly occurring CO exposures may impair accurate estimation of time intervals as well as the performance of more complex psychomotor tasks. A possible role of CO in motor vehicle accidents is suggested by data which show higher levels of COHb in drivers involved in accidents than in policemen and in other occupationally exposed populations. In Los Angeles an association of CO pollution and case fatality rates in patients with myocardial infarction has been observed.

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