III. BIOLOGIC EFFECTS OF EXPOSURE TO CARBON MONOXIDE

Carbon monoxide (CO) is an odorless, colorless, tasteless gas which is an active reducing agent for chemicals at elevated temperatures, but is principally encountered as a waste product of incomplete combustion of carbonaceous material. A summary of the physical properties is presented in Table I. The best understood biologic effect of CO is its combination with hemoglobin (Hb) to form carboxyhemoglobin (COHb), thereby rendering the hemoglobin molecule less able to bind with oxygen. This action of CO results in more persons succumbing each year to acute CO poisoning than to any other single toxic agent, except alcohol.[6]

Extent of Exposure

With the single exception of carbon dioxide (CO_2), total emissions of CO each year exceed those of all other atmospheric pollutants combined. In 1968 it was estimated that 102 million tons of CO were released into the atmosphere by the major sources of emission.[4] Over one-half of this amount (58 percent) was produced by the gasoline-powered internal combustion engine. Specified industrial processes accounted for approximately 10 percent of the total. A summation of CO emission estimates for 1968 by specific industrial processes is presented in Table II.

From Table II it can be observed that large amounts of CO are emitted from petroleum refineries, iron foundries, kraft pulp mills, sintering mills, lampblack plants and formaldehyde manufacturers. Major sources of CO production within the first four industries have been identified as the cupola in the iron foundry, the catalytic cracking units in the petroleum refineries, the lime kilns and the kraft recovery furnaces in the kraft paper mills, and the sintering of blast furnace feed in sintering plants.

Aside from the above major industrial processes which produce large quantities of CO, there are numerous operations (arc welding, automobile repair, traffic control, tunnel construction, etc.) where the occupational exposure for a worker to CO can be considerable. In fact any industrial process or operation where incomplete combustion of carbonaceous material occurs may easily be of consequence as concerns occupational exposure to CO.

Historical Reports and Theoretical Considerations

Man's intimate association with carbon monoxide as a true environmental hazard began with his discovery of fire. Since that time his technological history has been one of advancement by means of incomplete combustion. The seriousness of exposure to high concentration of CO has been realized since the earliest medical writings. The Greeks and Romans used exposure to CO as a means of execution of criminals and committing suicide.[7]

Priestly discovered the chemical composition of CO in the late 18th century and in 1895 Haldane[8] demonstrated the important relationship involving CO, hemoglobin and their saturated product, carboxyhemoglobin (COHb), on physiologic processes.

Since the time when Douglas and the Haldanes[9] formulated the basic laws governing the interactions of CO and oxygen (O_2) with hemoglobin it has been understood that CO combines with the reduced hemoglobin molecule much more readily than does oxygen, when the two are simultaneously present in a breathing mixture. These investigators placed the affinity constant (M) for the equation:

$$\frac{[COHb]}{[O_2Hb]} = \frac{M \times P_{CO}}{P_{O_2}}$$

within the range, 220 to 290 and later investigations have generally confirmed this range, although at a slightly lower level, under conditions of complete hemoglobin saturation by oxygen and CO.[10-13] Briefly, the affinity constant may be expressed as the number of moles of oxygen which must be present with each mole of CO in order to maintain an equal saturation of hemoglobin. While CO actually combines less rapidly with reduced hemoglobin than does oxygen, the tenacity of the binding between CO and hemoglobin is some 200 to 300 times that of oxygen. This saturation of hemoglobin by either oxygen or CO occurs in four steps involving intermediates with four equilibrium constants:

$$Hb_4 + X \underset{k_1}{\overset{k'_1}{\rightleftharpoons}} XHb_4 \qquad K_1 = \frac{k'_1}{k_1}$$

$$XHb_4 + X \underset{k_2}{\overset{k'_2}{\rightleftharpoons}} (X)_2Hb_4 \qquad K_2 = \frac{k'_2}{k_2}$$

$$(X)_2Hb_4 + X \underset{k_3}{\overset{k'_3}{\rightleftharpoons}} (X)_3Hb_4 \qquad K_3 = \frac{k'_3}{k_3}$$

$$(X)_3Hb_4 + X \underset{k_4}{\overset{k'_4}{\rightleftharpoons}} (X)_4Hb_4 \qquad K_4 = \frac{k'_4}{k_4}$$

In the above equations, X represents either oxygen or CO with a different equilibrium constant for each equation. It has been determined that in both cases K_4 is much higher (18 to 50 times higher) than K_1, K_2, or K_3 because k'_4 is much greater than k_4.[4,14] Under these circumstances the last ligand to bind to hemoglobin (K_4 equation) dissociates much more readily than it binds.[15] The differences between the four constants depend on intra-molecular forces occurring as a result of the interactions of each

ligand with the others, or with other portions of the hemoglobin molecule. Hence, the effect is an allosteric one resulting in conformational changes in the hemoglobin molecule. These differences in reaction rates affect the dissociation of oxygen or CO from hemoglobin such that, as can be observed in Figure 1, the shapes of the respective dissociation curves are sigmoidal rather than parabolic, as is the case with myoglobin, which possesses only one heme group with a single dissociation constant.[16] Likewise the dissociation curve for COHb-O_2Hb tends to be parabolic, indicating the effect of CO upon the dissociation of the remaining O_2 molecules. Although the constant may be as high as 245 or as low as 135 depending upon, among other things, the blood pH and amount of reduced hemoglobin present,[17,18] the generally accepted figure of 210* is applicable only for human hemoglobin.[10] Each species has a particular value for the affinity constant because the composition of hemoglobin molecules varies between species.[19] The M value for a species remains relatively constant, dependent on the physiological conditions mentioned above. Both Rodkey[13] and Killick,[20] however, have reported individual variations in the value of M.

Because the tissue partial pressure of oxygen (P_{O_2}) (approximately 40 mm Hg in mixed venous blood) occurs at a steep portion of the curve, under normal physiologic conditions oxygen is rapidly dissociated from hemoglobin resulting in a tissue saturation which is maintained with a large oxyhemoglobin reserve near the lower end of the curve. This reserve is the result of the large value for K_4, which permits dissociation only at the upper portion of curve under normal physiologic conditions.[21]

*Rodkey[13] has recently placed this figure at 218.

The difference in the partial pressure of oxygen (P_{O_2}) between freshly oxygenated arterial blood (P_{O_2} = 100 mm Hg) and mixed venous blood (P_{O_2} = 40 mm Hg) represents a release to the tissues of approximately 5 milliliters O_2/100 milliliters blood.[16] A shift of the steep portion of the oxyhemoglobin dissociation curve to the left would tend to change the release of oxygen to the tissues appreciably.

While the dissociation curve shifts to the right, allowing for a more efficient dissociation of oxygen to the peripheral tissues under conditions of reduced ambient oxygen tension (hypoxic hypoxia), just the opposite situation occurs during exposure to CO (anemic hypoxia).[4,16,19,21] The leftward shift during CO exposure occurs because of the much greater affinity of CO for hemoglobin and in spite of the fact that the amount of oxygen in physical solution in the blood remains near normal.[4] The oxygen content of the blood is not only lowered during exposure to CO, but the shift of the oxyhemoglobin dissociation curve to the left decreases the amount of remaining oxygen that is made available to the tissues. Both mechanisms serve to effectively lower the tissue P_{O_2} and hence can create a generalized tissue hypoxia. Dinman[21] has suggested that the great affinity of hemoglobin for CO was, evolutionarily speaking, of a definite survival advantage since this mechanism permits the expedient removal of endogenously-produced CO resulting from heme catabolism.

It has been demonstrated that following an initial exposure to CO, animals become less susceptible to subsequent exposure(s).[4] On the other hand it has also been demonstrated that mice which survived one episode of exposure to a high concentration of CO succumbed during a subsequent exposure to the same concentration.[22] If acclimatization to CO occurs, then it is

possible many of the physiologic mechanisms facilitating acclimatization would be similar to those which aid in acclimatizing the animal to hypoxia.[16,23,24] Indeed, it has been demonstrated in animals that such similar acclimatory mechanisms as polycythemia and increased hematocrit and nemoglobin occur during both hypoxic hypoxia and CO-induced hypoxia. Whether there is a separate, distinct factor involved in the acclimatization of man to CO remains to be seen, although there is some evidence to the contrary.[22]

Quite apart from acclimatization is the question of the existence and mechanism of chronic CO poisoning.[25] Some investigators believe that if this condition occurs it is the result of the accumulated effects of repeated acute episodes and not merely a continuous insult by low levels of CO.[26,27]

Since complete acclimatization to ambient concentrations of CO may not be possible, biological alterations occurring during exposure to CO become suspect as indicators of possible deleterious effects. The same would still be true should acclimatization to CO occur. This reasoning has even led some investigators to believe that death resulting from acute CO intoxication may not be caused solely by simple asphyxia[22,28-32] but also by some toxic effect exerted by CO per se.

Among the most subtle of known physiologic alterations are those which involve shifts in compartmental concentrations of trace metals. New techniques (e.g., atomic absorption and anodic stripping voltametry) now allow for the detection of very minute amounts of these important entities, and changes in their departmental concentrations during the course of various disease states, including chronic CO exposure, have been documented.[33,34] Difficulties involved in determining the significance of findings and in the extrapolation of findings to the whole organism have,

so far, somewhat undermined the potential values of these techniques. However, the fact that most of the eight or ten essential trace metals participate, physiologically, either as co-factors or activators of enzymes underscores the importance of determining their aberrations in vivo. In fact, any condition precipitating changes in enzyme activity or concentration merits very close scrutiny, and the activity of several enzymes has been found to be altered during CO exposure.[35-38]

At the other end of the spectrum of alterations occurring in the animal organism as a result of exposure to CO are changes in behavioral patterns. There is evidence to suggest that certain behavioral changes induced in the whole animal via CO exposure are indications of subtle physiologic alterations occurring within the organism, the elaboration of which is beyond the detectable range of present physiologic techniques. Thus the work of several investigators has suggested that such quantities as time discrimination,[39] visual vigilance,[40] choice response tests,[30] visual evoked responses,[41,42] and visual discrimination thresholds[29,35] can be altered at levels of COHb below 5 percent. The results of these tests often must be evaluated in the light of very highly specific test conditions which may have included distractions that could have easily altered the responses. It is also possible that the motivational attitude of the experimental subject may have been sufficient to alter results.

Attempts to correlate behavioral changes with damage to the central nervous system (CNS) have produced conflicting results, although acute exposure to high concentrations of CO has consistently produced brain lesions.[43] The general trend has been the finding of less severe CNS damage as the concentration of CO and length of exposure are decreased.

At CO concentrations of 100 ppm some investigators have found cerebral cortex damage in dogs, especially along the course of blood vessels, while other investigators have detected no direct damage but have discovered that the glial cells were mobilized,[44] a condition which usually occurs only during the course of disease. It has been suggested, however, that CNS damage, when it does occur, may be secondary to cardiovascular damage.[44]

Although the concentration of myoglobin when compared to that of hemoglobin is small, nevertheless, it has been implicated by several investigators as an important factor during CO exposure[45,46] and hypoxia.[47] Myoglobin has approximately 16 percent the oxygen-carrying capacity of an equal quantity of hemoglobin and accounts for only approximately 20 percent of the body's total CO capacity,[16] but its existence as an extravascular carrier of oxygen prompted Wyman[45] to compare the "translational diffusion" of oxygen into the cell via myoglobin with the pumping of oxyhemoglobin via the heart throughout the body. Exposure to CO may decrease the oxygen-carrying capacity of myoglobin with the formation of carboxymyoglobin (COMb), which is analogous to the formation of COHb from hemoglobin. The affinity constant (M value in Haldane equation) for myoglobin, however, is only 40, compared with 210 for hemoglobin.[48] This proposed mechanism of facilitated oxygen transport within the myocardium under normal conditions could lead to yet another deleterious consequence during CO exposure. Ayres[49] suggested that a state of oxygen debt might develop in cardiac muscle tissue where the myoglobin has become deoxygenated since, according to Wittenberg,[50] an estimated 50 to 90 percent of the oxygen reaching the muscle mitochondria during heavy work is carried by myoglobin.

As mentioned earlier in this report it has been confirmed that an endogenous source of CO exists as a product of heme catabolism.[51,52]

When an α-methylene bridge in the heme portion of hemoglobin is broken during the catabolic process, a molecule of CO is released.[51] It has been estimated that this production amounts to approximately 0.3 to 1.0 milliliter(ml)/hour with an additional 0.1 milliliter(ml)/hour resulting from a similar catabolic process involving other heme-containing compounds (e.g., myoglobin and cytochrome and catalase enzymes).[6,53] This endogenous production of CO, which gives rise to approximately 0.5 to 0.8 percent COHb, would not be expected to be of important physiologic consequence per se since the hypothesized mechanism has evolved with man, but its removal would merit due consideration in a closed system such as a submarine or a space capsule. Also, in the determination of total CO exposure this quantity must be included as "base line" COHb.

Cardiovascular Effects of CO

The critical importance of cardiovascular involvement during exposure to CO is becoming increasingly evident.[6,28,49-60] While the brain has a higher requirement for oxygen than the heart, in contrast to the cerebral circulation the coronary circulation must supply an even increased amount of oxygen during periods of generalized tissue hypoxia; since under these circumstances the heart is forced to increase both its rate and its output in order to meet the normal oxygen demands of the body.[49] This increase in myocardial activity demands an increased oxygen supply to the myocardium which must be met by the coronary circulation. Under hypoxic conditions increased oxygen supply to the peripheral tissues can be accommodated by increased blood flow (via vascular dilatation) and/or increased oxygen extraction by the tissues. As mentioned earlier the peculiar dissociation characteristics of O_2Hb permits an oxygen reserve which is used at reduced

P_{O_2}. The myocardium under these circumstances appears only to increase the flow of blood rather than to extract an additional amount of oxygen from the coronary circulation. While the peripheral tissues normally extract only 25 percent of the oxygen content of the perfusing arterial blood during resting conditions, the myocardium extracts 75 percent, thus leaving the mixed venous blood only 25 percent saturated. This mechanism has the overall effect of maintaining the myocardial oxygen tension at a higher level than would be present in other muscle tissue and thus insures a continual aerobic metabolism, even under hypoxic duress. In terms of oxygen tension, the mixed venous blood of the peripheral tissues is approximately 40 mm Hg while the mixed venous blood of the coronary circulation is only 20 mm Hg. In the presence of COHb (and the shift to the left of the oxyhemoglobin dissociation curve), however, the arterio-venous difference can only be maintained by an increased flow in the coronary circulation. In an individual with diminished coronary circulation because of coronary heart disease, however, this situation may result in a decrease in the mixed venous oxygen tension of the myocardium precipitated by an inability to maintain the normal arterio-venous gradient. This hypoxic effect is further enhanced, as mentioned above, by an increase in cardiac rate and output as a general response to peripheral tissue hypoxemia. A person with diminished coronary circulation caused by coronary heart disease, consequently, may be constantly near the point of myocardial tissue hypoxia.

Ayres[49] attempted to demonstrate the redox state of the myocardium during CO exposure via a biochemical assay procedure. His technique involved determination of extraction ratios in humans of pyruvate and lactate from perfusing coronary circulation following exposure to 50,000 ppm

of CO for 30 to 120 seconds. Glucose can be converted to pyruvate under anaerobic conditions via glycolysis, but the fate of pyruvate from that point depends largely on the redox state of the cell. With adequate oxygenation pyruvate will be converted to acetyl coenzyme A and from thence it can be oxidized via the citric acid cycle. If there is inadequate oxygenation, however, pyruvate will be converted to lactate, a terminal product in animal anaerobic metabolism, and both can be transported to the liver for oxidation, should the redox state of the liver be adequate. In Ayres' experiments, measurements were made of the extraction ratios of pyruvate and lactate by myocardial tissue from the coronary circulation of patients with coronary artery disease as well as with patients with non-coronary heart disease. Normally the myocardium extracts both of these metabolites from the coronary circulation for purposes of oxidation as mentioned above. When appreciable COHb (mean = 8.7 percent) was present, however, not only did the myocardium fail to extract either of these two substances, it actually produced both. The production of lactic acid in the myocardium at any time indicates the existence of a state of tissue hypoxia, and a prolonged state of hypoxia is detrimental to cell function with the possible consequence of cell death. When Ayres compared coronary blood flow in patients with coronary artery disease and in patients with noncoronary heart disease, he found that although extraction of pyruvate decreased in both groups, the coronary blood flow increased only in the patients with noncoronary heart disease. Although lactate was produced in the myocardium in both groups, this change from lactate extraction was statistically significant only in the patients with coronary artery disease.

Recent investigations have been reported by Adams, Erickson, and Stone [58] concerning the effects of low concentrations of COHb on coronary

blood flow, myocardial oxygen consumption and cardiac function in conscious dogs, breathing a 1500 ppm carbon monoxide air mixture through a tracheostomy. This exposure to CO increased the COHb slightly less than 1 percent per minute. At 5 percent COHb (control levels of COHb in the same animals were 1 percent) there was a significant increase in coronary blood flow of 13 percent. During the exposure to CO, there was a significant decrease in the arterio-venous difference in oxygen content across the heart and in myocardial oxygen consumption. The arterial oxygen content decreased, while the coronary venous oxygen content increased. Arterial and coronary sinus P_{O_2} remained constant. Left atrial pressure decreased slightly, but there was no significant change in the left ventricular pressure or maximum left ventricular dP/dt. Myocardial oxygen consumption, which increases with hypoxic hypoxia, thus supporting the net increase in energy expenditure by the myocardium, results from an increase in coronary flow and a decrease in coronary sinus oxygen saturation, which compensates for the decrease in the quantity of oxygen available. As documented by the investigators, however, the coronary flow response during exposure to CO may not be adequate, since the oxygen consumption decreases. This phenomenon may be associated with the hyperbolic shift to the left of the oxyhemoglobin dissociation curve, resulting in an increase in the coronary venous saturation.

The interaction of CO and hypoxic hypoxia on coronary flow was studied in seven dogs using the same methods.[58] Coronary flow increased 38 percent during exposure to 10 percent oxygen. There was a 13 percent and 24 percent increase in coronary flow with 5 percent and 10 percent COHb, respectively. Exposure to 10 percent oxygen in the presence of 5 percent and 10 percent COHb, however, resulted in a 51 percent and 67 percent increase in coronary

flow, respectively. These results document the additive effect of CO and altitude hypoxia on coronary blood flow.

Lewey and Drabkin[44] exposed dogs to 100 ppm CO for 5 3/4 hours a day, six days a week for eleven weeks. The mean daily COHb levels were approximately 20 percent. Although no electroencephalographic (EEG) changes were noted by the investigators, the animals were observed to suffer from psychomotor disturbances and at autopsy, cerebral cortical damage, which tended to follow the course of blood vessels, was observed in all animals. In this study one animal, which had the posterior coronary artery ligated for some time prior to the study, demonstrated the most severe cerebral damage and also had severe myocardial alterations. The investigators suggested that "...an inadequate functioning heart increases the general risk in CO poisoning, and may be responsible for a higher degree of brain damage." Utilizing the same exposure regime as Lewey and Drabkin,[44] Ehrich, Bellet, and Lewey[60] found electrocardiographic (EKG) alterations in dogs exposed to 100 ppm for eleven weeks, which produced a COHb of 21 percent.

When Lindenberg and co-workers[59] exposed fifteen dogs both continuously and intermittently to 50 ppm of CO for six weeks they observed pathologic EKG's in ten animals, pathology of the heart in seven animals and pathology of the brain in six animals.

Separate studies by Musselman[24] and Jones[61] were conducted at 50 ppm CO and demonstrated no significant cardiovascular alterations occurring in various experimental animal species used in the experiments. Recently Theodore, O'Donnell, and Back[62] exposed several species of animals to CO concentrations of 400 ppm CO for 71 days and then to 500 ppm CO for the 97 remaining days of a 168-day continuous exposure period. On gross examination of the CNS and the heart, none of the larger animals used in the

experiment (e.g., monkey, dog) demonstrated any changes. However, there was a marked increase in both hemoglobin concentration and RBC. The COHb levels reached 38 percent in the monkeys and 39 percent in the dogs. Although several species of animals were used by the investigators in the above experiments, only the canine was used in all investigations. It is very interesting in this regard, then, that when Ayres[63] acutely exposed canines and human CHD patients to concentrations of CO sufficient to produce significant myocardial changes, the lowest level of COHb at which such alterations were observed was only 6 percent in humans but was 25 percent in the dogs. It appears that the canine may be able to tolerate a much higher level of COHb than is the human before significant myocardial changes occur.

Jaffe[64] has emphasized the relationship between CO poisoning and an elevated titer of serum lactic dehydrogenase as an indicator of myocardial damage. He speculated that "...even 'normal' amounts of carbon monoxide may operate as the last straw in precipitating coronary attacks." When rats were exposed to 500 ppm CO for four hours Lassiter, Coleman, and Lawrence[65] observed a statistically significant aberration in the plasma lactic dehydrogenase isoenzyme distribution which was considered to be highly indicative of myocardial damage. The COHb level in the animals at termination of exposure was <40 percent.

The relationship between chronic cigarette smoking and increased risk of coronary heart disease (CHD) is undeniable,[66] as is the fact that cigarette smoking causes increased exposure to CO. A CO concentration of 4 percent (40,000 ppm) in cigarette smoke, which will cause an alveolar concentration of 0.04 to 0.05 percent (400 to 500 ppm) will produce a COHb concentration 3 to 10 percent.[6,67-69] Goldsmith[70] estimated that the cigarette smoker is exposed to 475 ppm of CO for approximately six minutes per cigarette.

In a review article on CO and human health, Goldsmith and Landaw[71] stated that the COHb level in the one-pack-a-day cigarette smoker is 5.9 percent, which they say is a sufficient concentration to impose a serious health threat to persons with underlying vascular insufficiency. In another paper these two investigators used a regression analysis of expired air samples from 3,311 longshoremen and found a COHb of 6.8 percent in two-pack-a-day smokers and 1.2 percent COHb in nonsmokers. They believed that the high level in the nonsmokers, above the 0.5 to 0.8 percent normally present as a result of endogenous production, was accounted for by occupational exposure.

In a study by Kjeldsen[57] COHb levels of both smokers and nonsmokers were compared from 934 "CHD-free" persons. The mean COHb was 0.4 percent for nonsmokers and 7.3 percent for cigarette smokers who inhaled. In addition, the mean level of COHb for all 416 smokers in the study, regardless of inhalation habits or number of cigarettes smoked, was 4.0 percent.

A similar study is presently being conducted to determine the range of COHb in the American public by Stewart and Peterson.[72] The presently available data, from Milwaukee, has demonstrated that the mean COHb levels for nonsmokers is 1.33 ±0.85 percent and for smokers is 4.47 ±2.52 percent.

Pirnay and co-workers[73] provided evidence, based on CO immobilization of 15 percent of hemoglobin, which they state confirms the hypothesis that there is a circulatory limitation upon maximal oxygen consumption and that decreases in maximal oxygen consumption seem to result from a reduction in oxygen transport capacity. This hypothesis has important implications for the cigarette smoker and nonsmoker alike who have CHD and who are occupationally exposed to CO. Based upon this data the imposition of mild to

moderate exercise upon such individuals during CO exposure could have very detrimental repercussions.

In an epidemiologic survey involving approximately 4,000 middle-aged males, who were kept under medical surveillance for 8 to 10 years, Doyle and co-workers[74] found that one-pack-a-day smokers had about a three-fold greater risk of myocardial infarction than did nonsmokers, or former smokers.

The finding that death rates for ex-smokers were no higher than for nonsmokers prompted Bartlett[16] to state that the effect of cigarette smoking on this particular pattern is completely reversible when an individual ceases to smoke. He concluded that smoking caused a myocardial hypoxemia by some acute, reversible process, which was probably unrelated to the formation of hard, irreversible, atherosclerotic lesions and that CO would fit such an epidemiologic pattern very well. He further stated, however, that other components of cigarette smoke, including nicotine, may be responsible for this pattern and that the question, in his estimation, remained unsolved.

Astrup, Kjeldsen, and Wanstrup,[75] reporting on an investigation in progress in 1970 in which 1,000 randomly chosen individuals were examined for evidence of arteriosclerotic disease, demonstrated a clear relationship between this disease and high COHb levels after smoking. They further stated that it is very likely "...that it is the inhalation of CO in tobacco smoke that is, in part, responsible for the much higher risk of smokers to develop coronary heart disease and other obliterating arterial diseases in comparison to that of nonsmokers."

Chevalier, Krumholz, and Ross[67] found when the COHb of nonsmokers was increased, via CO exposure to 5 percent CO (50,000 ppm), such that their levels of COHb were the same as those observed in cigarette smokers (greater than 4 percent), that the nonsmokers developed an increased oxygen debt with

exercise and a reduced pulmonary diffusing capacity at rest. These findings were similar to those observed in smokers. The investigators implied that in persons with approximately 4 percent COHb the same amount of work is accomplished by means of increased metabolic rate. Or stated differently, a worker with approximately 4 percent COHb can maintain a particular level of activity only at the expense of an increase in metabolic rate.

Bartlett[16] made a significant observation that CO in ambient air and CO from cigarette smoke are not additive as concerns their biologic effect because each represents an independent source of CO. He suggests that, because of this, smokers may be the least susceptible individuals to increases in COHb during exposure to low concentrations of CO since their levels of COHb, already high, would not be increased by the exposure. The author admitted, however, that the rate of excretion of CO for the cigarette smoker is decreased during ambient CO exposure and this would increase the long-term average COHb levels in the presence of ambient CO.

In evaluating the exposure of patients who have coronary heart disease with angina pectoris to CO sufficient to produce a COHb level of 5 percent, Dinman[21] stated that while a small additional decrease in the oxygen saturation of the blood brought about by mild exercise might be feasible, "...the degree of blood oxygen desaturation demanded with 10 percent COHb loading is rather severe."

Anderson and co-workers[76] recently exposed normal young males and clinically normal middle-aged males to 100 ppm of CO for four hours which resulted in COHb levels at the end of that time of 5 to 9 percent. During exposure the two groups were subjected to 85 percent submaximal treadmill exercise testing while ECG monitoring and several cardiac function measurements were recorded. Statistical differences in the measured parameters

were observed only in the older group of subjects. The investigators stated that "...low-level CO exposure may augment the production of exercise-induced myocardial ischemia in persons with preexisting subclinical heart disease, contribute to the development of myocardial dysfunction, and may lead to an increased incidence of arrhythmias in such persons." They further stated that these findings in clinically normal persons would be more pronounced in persons with overt ischemic heart disease (e.g., angina pectoris or myocardial infarction). The investigators further said that arrhythmias observed in the older group may explain the observations of Cohen, Deare, and Goldsmith[77] concerning the increased case fatality rates for persons with acute myocardial infarctions during periods of increased ambient levels of CO as well as explain the increased incidence of sudden death in smokers.

In a study conducted by Knelson,[78] seven patients with clinically diagnosed angina pectoris, who suffered daily from frequent angina pains, were exposed, at rest, to 50 ppm and to 100 ppm CO for separate four-hour periods. The patients, all cigarette smokers, refrained from smoking for eight to ten hours prior to being exposed to CO. The mean COHb prior to exposure was 1.32 ±0.30 percent. Following four-hour exposure periods the mean COHb levels were 3.01 ±0.34 percent in the patients exposed to 50 ppm CO and 4.65 ±0.58 percent in those exposed to 100 ppm CO. Each patient served as his own control and was continuously monitored before, during and after a double-blind exposure period. Immediately after the exposure period each patient exercised on a treadmill and the time to angina pain and the duration of the pain were recorded. The investigator reported a statistically significant difference ($p < 0.01$) in the time to onset of

pain in the patients exposed to 50 ppm for four hours. The same level of significance was also found for the patients exposed to 100 ppm although the differences of results between the two regimes were not significantly different. The other parameter measured, duration of pain, was statistically significant ($p < 0.05$) only for the patients exposed to 100 ppm CO. Again the differences of results between the lower and higher exposures were not significant. Knelson concluded, using this particular protocol of exposure, that patients with angina pectoris who were exposed to CO and then exercised experienced pain earlier and pain lasted longer, than when these same patients were exposed to ambient air.

An interesting set of data has been produced recently by Horvat and co-workers[79] concerning the effect of oxygen breathing on the threshold of angina pain in patients with confirmed coronary heart disease. The investigators first determined the angina threshold while the patients breathed air by increasing the heart rate via right atrial pacing. Patients were then, unknowingly, switched to 100 percent oxygen and the heart paced to the previously determined angina threshold. Angina pain did not occur in nine of eleven patients. Associated with this improvement was increased lactate extraction from an average of -17 ± 15 to $+18 \pm 10$ percent ($p < 0.025$). In four of six patients lactate production turned to lactate extraction, in six of seven patients S-T abnormalities in the EKG were improved as well as improvement in pulsus alternans in three of five patients.

These data present significant evidence that oxygen breathing permits the heart to do more work before coronary insufficiency develops. They also indicate the validity of the approach used by Knelson in determining

the time to onset of angina pain in patients exposed to CO. Each investigation, in fact, complements the other concerning the parameter of angina pectoris.

The important implications of these studies for the cigarette smoker with angina pectoris is all too clear. Thus, based on cardiovascular alterations which could prove to be of severe physiologic consequences for persons with CHD, a significant portion of who are in the worker population, it seems advisable that levels of COHb in excess of 5 percent should be avoided.

Neurophysiologic and Behavioral Effects of CO

The clinical effects on the central nervous system (CNS) of CO poisoning have been extensively reported. In general, increasing COHb levels result in a corresponding depression of the CNS showing a progression from slight headaches at 10-20 percent COHb, coma with intermittent convulsions at 50-60 percent, and death at 70 to 80 percent COHb. In contrast, the subclinical effects on the CNS of low level CO exposures are less well documented. This section will review the histopathological, neurophysiological, and behavioral effects of such low-level to moderate CO exposures, and evaluate the significance these findings may hold for occupational safety and health considerations.

Histopathological Effects

Lewey and Drabkin exposed six dogs to 100 ppm of carbon monoxide for 5 3/4 hours per day, six days per week, for a period of eleven weeks. The mean COHb level was found to be approximately 20 percent. The animals were sacrificed three months after the end of the exposure. Distinct histopathologic changes were found in the cerebral cortex and included infarction,

degenerative changes, formation of cysts, gliosis, perivascular infiltration, loss of myelin and softening of the white matter. The basal ganglia showed the severest damage with loss of cells and demyelinization. No changes were seen in the electroencephalogram (EEG) or in peripheral nerves. The question has been raised as to whether or not all the changes reported by Lewey and Drabkin were artifacts of post-mortem changes peculiar to dogs.

In contrast, Lindenberg and co-workers[59] exposed dogs to 100 ppm CO for twenty-four hours per day, seven days a week, for six weeks (1-1/2 times as much carbon monoxide as in the Lewey and Drabkin study). Lindenberg found areas of pathologic changes in the heart and the brain on histologic examination of the dog brains.

Musselman and co-workers[24] exposed dogs, rabbits and rats to 50 ppm of CO for three months. Gross histologic examination of the CNS revealed no histopathologic effects.

Shul'ga[80] exposed rats to 25-27 ppm of CO eight hours daily for ten weeks. Histologic examination of the brains of these animals revealed focal destruction of nerve cells in the cerebral cortex, abnormalities of the Purkinje cells with pyknosis of cells, and completely disintegrated nerve cells in the spinal cord. The results of Musselman are at variance with those of Shul'ga and are difficult to reconcile.

Neurophysiological Effects

Several studies have been reported concerning searches for subclinical effects of low levels of carbon monoxide exposure using such objective electrophysiological measures as spontaneous electroencephalograms (EEG), visual evoked responses (VER), sleep patterns, and conditioned electrocortical reflexes.

Dinman[81] failed to observe any gross EEG changes in humans after their exposure to CO concentrations that produced about 27 percent COHb. Grudzinska[82] examined the EEG's of sixty workers occupationally exposed to not more than 100 ppm of CO. A group of thirty workers not exposed to CO served as a control group. COHb levels in the exposed group averaged 7 percent and for the control group 3 percent. A higher proportion of flat, low-voltage tracings with diminished alpha rhythm was found in the EEG's of the exposed group ($p < 0.01$). These data are difficult to interpret and include subjective assessments of "scanty alpha." The experimental design may not have been double blind. Sluijter[83] described a decrease in the amplitude of alpha activity at COHb levels of 29 percent. In workers chronically exposed, with COHb levels of 10-20 percent, Zorn[84] showed an instability in the fundamental frequencies in the EEG's of the workers. Lindenberg and co-workers,[59] on the other hand, failed to show EEG changes in laboratory animals, except in the presence of high COHb levels that also produced marked cardiovascular alteration and severe brain damage.

Dinman[81] suggested that analysis of spontaneous EEG records does not appear to promise consistent or reproducible results at low levels of CO exposure. However, it was pointed out that the EEG analyses could be improved by use of new computational methods unavailable at the time the reviewed studies were performed.

Another approach for assessing the effect of carbon monoxide on the CNS involves the use of photic stimulation and computer averaging of the resulting visual evoked responses (VER). The report of Xintaras and co-workers[41] suggests that changes of the evoked photic response in the rat following exposure to 100 ppm of CO for two hours were analogous to

those effected by use of drugs known to depress the CNS. The COHb levels were not measured. By contrast, at levels of 22 percent and 37 percent COHb, analysis of human photic responses with similar techniques by Dinman[81] did not reveal changes in VER latency or amplitude. Hosko,[42] however, reported that COHb saturations greater than 20 percent effected two changes in the human VER. One was an increase in the amplitude of the 2-3-4 wave complex, a change also noted by Xintaras to occur in the rat VER.[41] The second change noted by Hosko in the VER was a CO-induced negative-going shift involving late waves of the VER, which according to Hosko may be associated with general CNS depression. Rhythmic after-potential changes in the VER were also reported by Helmchen and Kunkel[85] following CO exposure.

Another approach to EEG measurement involves the analysis of a subject's sleep patterns. Sleep patterns are known to be extremely sensitive to changes in CNS conditions. The study of O'Donnell, Chikos, and Theodore[86] demonstrated changes in sleep patterns during the first three hours of CO exposure. The authors estimate that COHb concentration in the blood was probably not higher than 8 percent and possibly much lower. O'Donnell reported trends in his data that suggest a general reduction in nervous system activation, i.e., less light sleep, more deep sleep, and less mobility between stages of sleep. Johnson[87] reported that rats exposed to 100 ppm of carbon monoxide for six hours per day for ten days exhibited a general decrease in the overall amplitude of visual evoked responses recorded during sleep.

That CO may cause extinction of conditioned reflexes was studied by Shul'ga,[80] who failed to demonstrate an effect on conditioned electrocortical reflexes in two subjects inhaling about 16-17 ppm CO. COHb levels were not reported.

Behavioral Effects of CO

The effects of CO on behavior have been researched by several investigators interested in the effects of CO on the CNS. Specific behavioral tests have involved measures of perception, psychomotor function, and cognitive ability. In the context used here, behavior is defined as the way a subject acts in response to a stimulus.

(a) Animal Studies

Goldberg and Chappell[88] found evidence of a behavioral deficit for two-hour exposures to 200 ppm CO in the bar-pressing performance of trained rats. The behavioral tests utilized in separate controlled studies included the following: (a) the number of continuously reinforced bar presses made in one hour of testing, (b) the number of nonreinforced bar presses made in one hour, (c) the number of responses made in one hour when the probability of reinforcement was 30 percent. The effect of CO was to decrease the number of bar-pressing responses in all three behavioral tests. The maximum decrement was found to be 33 percent for continuously reinforced bar presses. No COHb determinations were obtained for the rats.

Beard and Wertheim[39] investigated the behavioral effects on rats of CO concentrations ranging from 100 to 1000 ppm. The behavioral test was a differential reinforcement of low rate of response (DRL) bar-pressing schedule. For this schedule the subject refrained from pressing the bar for a predetermined fixed time (the delay time) in order to receive a food reinforcement. The authors found that when the DRL delay time was 30 seconds, a 100 ppm CO exposure of eleven minutes duration effected a decrease in DRL response rate equal to two standard deviations below the control rate. When the DRL delay time was ten seconds, forty minutes of 100 ppm CO exposure

were required to achieve the same effect. No COHb measurements were obtained for the animals during CO exposure.

Back[62] initiated in 1967 a series of experiments to ascertain the effects of continuous, long-term, low-level CO exposure on the behavior of adult rhesus monkeys. The study examined the effect of CO on operant avoidance behavior in monkeys utilizing both continuous and discrete avoidance tasks. The avoidance tasks required the subjects to press switches at selected times in order to avoid electrical shock. Continuous CO exposures ranging from 50 ppm for 105 days (mean COHb = 3.7 percent) to 400 ppm for seven days (mean COHb = 30.1 percent) produced no significant effect on avoidance behavior. Under these exposure conditions (i.e., 50 and 400 ppm) humans would be expected to reach COHb levels of 8.4 and 41 percent, respectively.

(b) Human Studies

One of the earliest studies to report a systematic investigation of the effects of CO on human behavior was conducted by Forbes, Dill, and DeSilva.[89] Eight normal men were given simple performance tests of reaction time, binocular vision, and hand-eye coordination that simulated tasks required of automobile driving. No performance decrements were observed, even though the COHb levels reached 45 percent. A later study concerning the effect of CO on automobile driving behavior was reported by Ray and Rockwell,[90] who investigated the effect on performance of COHb levels of 0, 10, and 20 percent in three subjects. The subjects drove a specially instrumented automobile over a prescribed route while maintained at a constant COHb level. Performance tasks performed while driving included the following: estimation of ten-second time intervals, estimation of half-mile distances, taillight brightness discrimination, vehicle velocity detection, peripheral detection of an oil pressure warning light, and vehicle handling performance.

A COHb level of 10 percent was found to cause a decrease in mean time estimation and increases in distance estimation variance, mean and variance of response time for taillight discrimination, and mean and variance of velocity response times.

Several investigators have reported the effects of CO on brightness discrimination. McFarland and co-workers[29] used a visual discriminometer to test effects of CO on visual thresholds of human male subjects ranging in age from 16 to 25 years. The subjects were required to indicate the lowest intensity of brief red light flashes that could be discerned when presented against an illuminated background. It was found that the visual threshold increased as COHb levels increased; an increase of 12 percent occurring at a COHb level of 5 percent. This finding was repeated by Halperin and co-workers[35] in a subsequent report. The effect of CO on brightness discrimination was also utilized by Horvath, Dahms, and O'Hanlon,[40] who were interested in the effects of CO on vigilance. Ten male subjects were trained to discriminate one-second duration light pulses on the basis of stimulus brightness. The subjects were required to attend to the vigilance task for one hour. It was found that COHb level of 6.6 percent significantly impaired vigilance, causing a maximum decrement in performance of approximately 28 percent.

Schulte[30] investigated in 49 male adults the effect of COHb levels ranging up to 20 percent on a variety of physiological and behavioral tests. The behavioral tests included the following: color stimulus response, letter stimulus, plural noun underlining, static steadiness, arithmetic test, and t-crossing test. No correlation was found between COHb levels and any of the physiological tests or reaction time on the simple choice

response tests. Effects of CO (significant at the 0.001 level) were observed on the following: number of errors in letter response, color response, arithmetic, and t-crossing tests; and increases in the time required to complete the arithmetic, t-crossing, and plural-noun underlining tests. Examination of Schulte's data indicates that these effects occur for COHb values as low as 5 percent.

Several reports exist concerning the effect of CO on timing (temporal) behavior. Beard and Wertheim[39] reported that exposure to CO concentrations between 50 and 250 ppm caused a progressive deterioration in the ability of eighteen subjects (young college students) to discriminate auditory stimuli on the basis of stimulus duration. The behavioral task consisted of presenting to the subject a "standard" tone of one-second duration, followed by a second tone which was varied randomly in eighteen steps between 0.675 and 1.325 seconds. The subject indicated by lever press his judgment of the second tone's duration. An impairment in time discrimination behavior was found for a ninety-minute 50 ppm exposure, which yields an estimated COHb value of 2.5 percent. In a later report Beard and Grandstaff[91] described a study in which subjects were required to estimate in the absence of any external clues a specified length of time, which was either ten or thirty seconds. It was observed that an eighty-minute 50 ppm CO exposure impaired estimation of thirty-second lengths of time. A corresponding effect was not observed if the time interval to be estimated was ten seconds.

In contrast to the findings previously described concerning time discrimination and visual perception, other investigators have been unable to demonstrate comparable behavioral effects of CO. Stewart and Peterson[92] could demonstrate no effect of an eight-hour 100 ppm CO exposure (which

produced COHb levels of 11-13 percent) on hand and foot reaction time, hand steadiness, coordination, orthorator visual tests, or a time estimation-hand reaction time test. The latter test required the subject to estimate the duration of stimuli that persisted for 1, 3, or 5 seconds.

A series of investigations performed at Wright-Patterson Air Force Base, Ohio failed to demonstrate any effects of CO on human behavior under the test conditions. Theodore, O'Donnell, and Back[62] and Mikulka, O'Donnell, and Heinig[93] exposed subjects to 0, 50, and 125 ppm CO for three hours, yielding mean COHb levels of 0.96, 2.98, and 6.64 percent respectively; they found no effect of CO on time estimation of ten-second intervals, performance on a critical instability tracking task, or tasks taken from the Pensacola Ataxia Battery. Three subjects were subsequently exposed to 250 ppm CO for three hours (mean COHb = 12.4 percent) with no effect on performance. O'Donnell, Chikos, and Theodore[86] found no effects in four subjects at COHb levels of 12.7 percent on critical flicker frequency, mental arithmetic, tracking, time estimation, and time discrimination. The results on tracking are in conflict with those of Trouton and Eysenck[94] who reported impairment in control precision and multiple limb coordination at COHb levels of approximately 5 percent.

Conflicting results have been reported concerning the effects of CO on critical flicker frequency (CFF) estimation. Lilienthal and Fugitt[32] found CFF impairment at COHb levels of 5-10 percent (at an altitude of 6000 feet). Vollmer, King, and Birren,[95] Guest, Duncan, and Lawther,[96] and O'Donnell, Chikos, and Theodore[86] could demonstrate no effect of CO on CFF for COHb levels of 22, 10, and 12.7 percent respectively.

A review of the literature concerning the effects of CO on the CNS and behavior indicates a general lack of agreement concerning results. The behavioral data in particular reveal conflicting results when the data for a given behavioral measure, e.g., time estimation, from different studies are compared.[39,62,86,92,93] A number of possible explanations have been offered in an attempt to account for the variation in results. Possible considerations include the following: the lack of control of the motivational level of the subjects, certain physical and psychological aspects of the exposure test situation, the purity of the CO exposure gas, and the lack of control of experimenter bias (single blind versus double blind). Because of such factors, it is difficult to compare results from different laboratories, since no one study exactly replicates any other in terms of experimental design. It is felt that the findings of McFarland[29] and Halperin[35] concerning visual perception, Horvath[40] concerning vigilance, Schulte[30] concerning cognitive function, Beard[39,91] concerning time discrimination, Ray and Rockwell[90] concerning driving behavior, and Trouton and Eysenck[94] concerning limb coordination provide evidence for the behavioral effects of low-level CO exposures. These studies suggest a COHb level of 5 percent as a reasonable value in terms of providing the worker protection against adverse behavioral effects due to CO exposure.

Epidemiologic Studies

Many epidemiologic studies have been conducted which have related a source of CO with demonstrable biologic effects. A great many of such studies have been concerned with the gross physiologic effects and clinical symptoms associated with acute exposure to high concentrations of CO. The effects on humans of exposure at high concentrations of CO and the manifestation of

clinical symptoms resulting from such exposure episodes are quite predictable. It is generally understood that exposure to a particular concentration of CO will render inactive a portion of the oxygen-carrying capacity of the blood. This combination of CO with hemoglobin to form carboxyhemoglobin (COHb) is the best understood biologic activity of CO. The more subtle biologic effects of CO exposure which occur at lower concentrations have been detailed earlier in this chapter.

Several studies of epidemiologic importance have been conducted on occupationally-exposed individuals and are worthy of mention. In a survey conducted by Cohen and co-workers[97] on border inspectors at the U.S.-Mexican border, they found significant increases in COHb in both smokers and non-smokers which were correlated with high ambient CO concentrations. Concentrations of CO as high as 170 ppm for an hour were encountered in this study. Although COHb levels were not determined, individuals engaged in light to moderate activity during exposure at this concentration of CO for an hour could be expected to reach a COHb level of approximately 8 percent. In another study Cohen[77] found a significant correlation between higher levels of ambient CO and the case fatality rate of individuals hospitalized with acute myocardial infarction. Ramsey[98] found that parking garage employees experienced COHb levels in excess of 10 percent following a workday in which the CO concentration averaged almost 60 ppm. Ramsey stated that the occupational exposure in this study was more instrumental in producing the elevated COHb levels than was smoking. Breysse and Bovee,[99] measured the COHb of workers exposed to CO emissions from the operation of gasoline-powered fork lift trucks and demonstrated elevated COHb levels in excess of 10 percent. These investigators stated that the cigarette smoking

habits of the workers made a significant contribution to their levels of COHb and that below CO concentrations of 50 ppm the contribution of smoking will be more important than that from the working environment. Likewise, Buchwald[100] has shown that cigarette smoke normally made a more significant contribution to COHb levels of garage and service station operators than did ambient CO concentrations.

A long-term mortality study of steelworkers by Lloyd and co-workers[101] determined the specific mortality ratios (SMR) of observed deaths to expected deaths for 53 work areas within the steel industry. The 1953 study involved over 58,000 employees. Four of the 53 work areas (janitors, machine shops, mechanical maintenance assigned, and sheet finishing and shipping) demonstrated a statistically significant excess of deaths over those expected. One area, the carpenter shop, had a statistically significant deficit in mortality. Statistically significant excesses in deaths due to heart disease were found for janitors and mechanical maintenance assigned employees. The SMR for blast furnace workers, for deaths due to all causes, was 92. This indicated a slight deficit in the number of expected deaths. The same trend was found for open-hearth workers (SMR = 95) while coke plant workers had a slight increase (SMR = 104). Neither of the last two trends were statistically significant. All three of these areas are known to produce significant exposure to CO.

Lloyd and co-workers noted that while certain areas (e.g., janitors) had an excess of deaths due to heart disease, other areas had a deficit in this specific cause of mortality.

In attempting to determine why an apparent selection for health should have been more likely among steelworkers dying from heart disease, it was

suggested that such persons may have been more likely to migrate between work areas. Thus, employees exhibiting symptoms of cardiac insufficiency (e.g., shortness of breath) may move to less physically demanding jobs on their own. Similarly, employees with CHD who return to work following an attack are often returned to less physically demanding jobs (e.g., janitors and mechanical maintenance). As a result the investigators indicate that selection for health may have been more important than environmental factors in explaining the excess in mortality from heart disease among janitors and mechanical maintenance personnel. If this suggestion is correct, then the work areas from which those employees dying from heart disease migrated would not be expected to show similar increases in deaths from heart disease. For example, if these employees migrated from the areas aforementioned that produce significant exposure to CO, then those areas would be expected to have a lower SMR for heart disease. Although this rate for those areas was not published in the paper, because of statistical insignificance, the SMR for all deaths in those areas, as mentioned, did not demonstrate trends which were statistically significant.

Based upon this study, then, it would not seem possible either to infer or to deny that occupational exposure to CO at the three work places in question resulted in an excess of deaths due to heart disease.

More information is needed concerning daily exposure of workers, engaged in various levels of activity, to specific sources of CO within their working environment and the correlation of such information to both smoking habits and to nonoccupational exposure.

Regardless of CO source, however, the rate of CO excretion from the blood is dependent upon the concentration in the ambient air, and for smokers with elevated COHb levels who are occupationally exposed to CO, their excretion of CO will be proportionally delayed.

Because the recommended standard for occupational exposure to CO is designed to protect employees with CHD, it is necessary to characterize the extent of this disease among the general worker population.

Friedberg[102] has defined CHD to represent clinical heart disease due to lesions of the coronary arteries. However, the term, CHD, is generally used to refer to the process of atherosclerosis of the coronary arteries leading to disturbances in the myocardial blood supply. It is in this latter context that the term applies in the criteria document.

It is an established fact that each year more persons in the U.S. die from CHD than from any other disease.[103] Coronary atherosclerotic heart disease is the most common form of cardiac disease in adults in the U.S.[104] During the Korean War autopsies performed on young soldiers, with an average age of twenty-two years, revealed that 77.3 percent had gross pathologic evidence of CHD.[104] A study[105] of autopsies in a stabilized population of 30,000 revealed that CHD was the cause of death in 40 percent of the males.

Friedberg states:[102]

> "The diagnosis of coronary (atherosclerotic) heart disease refers to clinical manifestations and not to the mere presence of atherosclerotic lesions. Extensive pathologic lesions may be present but cannot be diagnosed unless they produce overt clinical manifestations or are revealed by coronary angiography."

In most cases the first clinical manifestation of CHD is expressed[106] either as the angina pectoris syndrome or as frank myocardial infarction.

According to the Framingham, Massachusetts, study conducted by the USPHS,[107] CHD was first manifested in one-sixth of the cases of CHD as sudden death.

Brest[106] states that it has been estimated that in the U.S., more than 500,000 persons sustain silent infarctions each year. He further cites various prospective epidemiologic studies[106] which indicate that, annually, approximately 1 percent of all white middle-aged males in the U.S. will develop clinical CHD. He further stated that after age twenty it would be virtually impossible to delineate a control group "without atherosclerosis."

It is clearly evident from these statements that the general worker population in the U.S. is composed of a very significant number of persons with CHD. Since the detection of such persons in the absence of overt clinical symptoms is virtually impossible, it is necessary to assume that the average worker has asymptomatic CHD; especially when his first clinical symptom may be sudden death.

Correlation of Exposure and Effect

The signs and symptoms of acute CO poisoning are well known and easily recognized. These may include headache, nausea, vomiting, dizziness, drowsiness, and collapse. The gross clinical manifestations of CO poisoning at various levels of blood saturation have been well documented. The correlation of ambient CO concentrations with bodily uptake has been continuously studied since Douglas and the Haldanes first formulated the basic laws concerning the combination of CO and oxygen with hemoglobin. Although the correlation between exposure and effect is understood, at least in terms of symptomatology, in the case of acute exposure to high concentrations of CO, exposures to low concentrations of this gas, at and below 100 ppm, have often produced conflicting results.

From the studies presented earlier in this chapter it is obvious that disagreement exists concerning the effects of CO on several biologic parameters as well as concerning the exposure conditions during which specific biologic aberrations occur. Often different investigators in attempting to repeat the work of others have failed to produce the same experimental results under supposedly identical exposure conditions. This has been true for epidemiologic, neurophysiologic,[41,44,59] cardiophysiologic[24,44,59,63,78] and behavioral[39,62,91] studies. On such occasions it is necessary to examine very carefully the circumstances surrounding a particular set of experimental conditions. Thus, while several investigations[24,44,49,59,62] have rendered conflicting data concerning alterations of the myocardium during exposure of animals to low concentrations of CO (50 ppm and 100 ppm), Ayres[63] has shown that the dog (which was used in several of the above studies) may be less susceptible to CO than man. Hence, extreme care must be used in the extrapolation to man of any alterations observed in the canine myocardium during exposure to 50 ppm of CO. An eight-hour exposure to 50 ppm of CO would produce approximately 7.5 percent COHb in an individual engaged in light activity. Earlier work by Ayres[49] in which he discovered that lactate was produced in the myocardium of patients with coronary artery disease during acute exposure to concentrations of CO sufficient to produce a COHb content of less than 9 percent provides metabolic evidence of myocardial hypoxia occurring under this regime. His finding that in patients with coronary artery disease the coronary blood flow did not increase at this level of COHb saturation, although it did increase in controls, serves to further underscore the possible consequences for an individual with coronary heart disease (CHD) who is carrying less than 9 percent COHb. Furthermore, it

must be emphasized that these coronary patients were at rest and were not subjected to exercise. The consequences of this additional stress were documented earlier in the study by Knelson.[78] His discovery that the time to onset of pain was diminished in cigarette smokers with angina pectoris during exercise immediately following exposure to 50 ppm of CO for four hours (average COHb of 3.0 percent), provides considerable evidence that workers with CHD, and particularly those with CHD who smoke, should not be exposed to concentrations of CO which will produce a level of COHb in excess of 5 percent.

Similarly, the effects of CO on behavior are not in complete agreement. As mentioned previously, several mechanisms have been suggested to possibly account for the differing results. These suggestions can be summarized by noting that no one study has completely replicated the experimental design of any previous study that indicated a behavioral impairment due to CO exposure. For this reason the reports by McFarland,[29] Halperin,[35] Horvath,[40] Schulte,[30] Beard,[39,91] Ray,[90] and Trouton[94] concerning the effect of CO on behaviors ranging from vigilance to cognitive function are sufficient to suggest possible safety hazards for the worker exposed to CO. A review of the above studies indicates that a value of 5 percent COHb should not be exceeded if these behavioral effects are to be avoided.