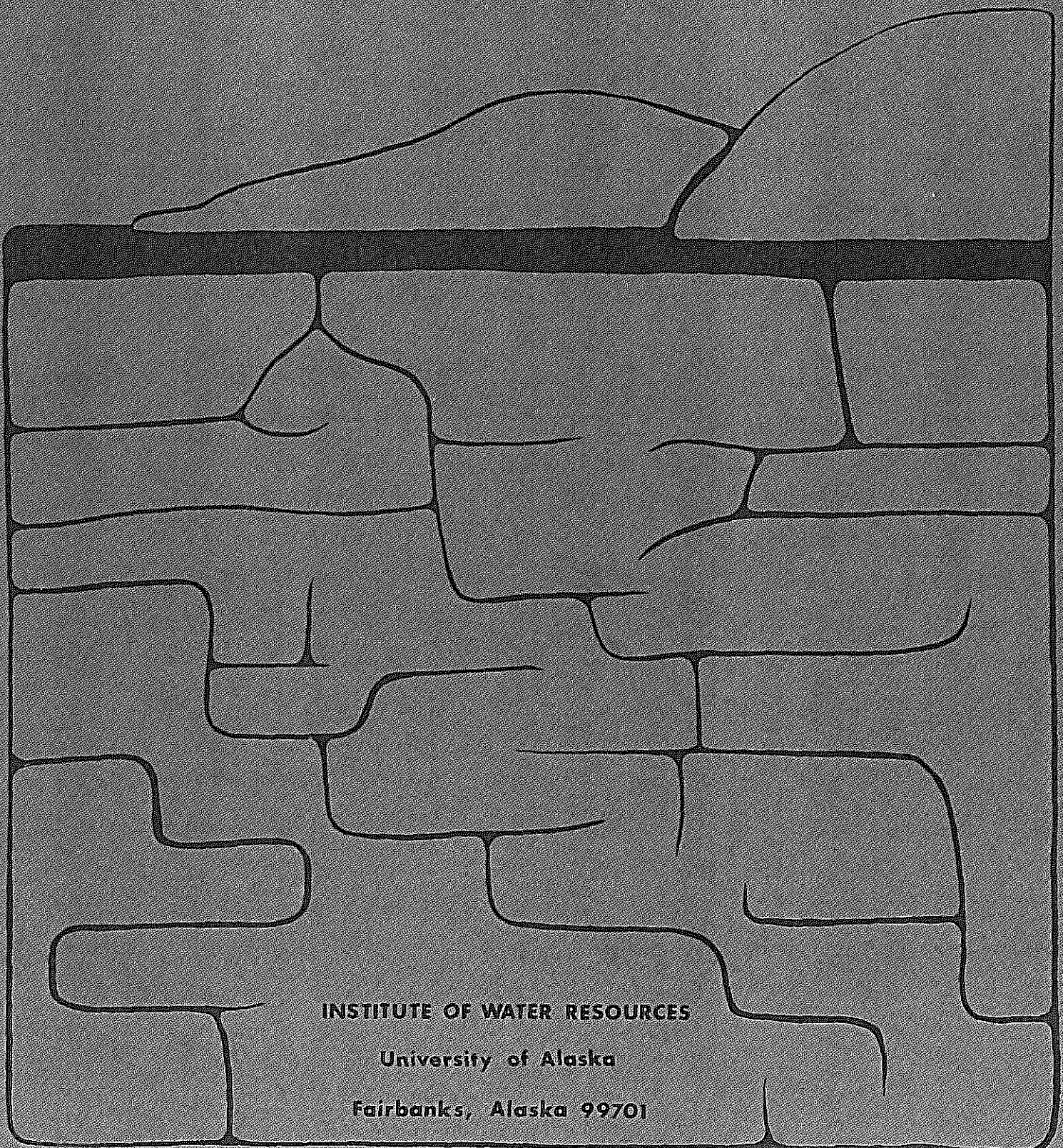# CARBON MONOXIDE EXPOSURE
AND HUMAN HEALTH

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CARBON MONOXIDE EXPOSURE AND HUMAN HEALTH

Carbon monoxide exposure and human health
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ACKNOWLEDGEMENTS

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PREFACE

In the late 1960's and early 1970's, the City of Fairbanks, Alaska, was identified as having a serious carbon monoxide air pollution problem. It was later learned that not only was the problem serious but that it may be as severe as, if not worse than, the ambient air carbon monoxide concentration anywhere in the United States. This determination, of course, brought the regulatory officials flocking to Fairbanks and, perhaps, rightfully so. Subsequently many committee meetings and public hearings were held. A portion of the community responded by saying that there was no carbon monoxide problem, that the Federal standards were incorrect, and that the regulatory agency (EPA) was simply a part of the Federal bureaucracy.

During the ensuing turmoil over an air pollution control program, a Fairbanks North Star Borough Health Study Committee was formed under the guidance of Ken MacKenzie, Director of Environmental Services. At least two significant results have emanated because of the committee's work. The first of these is a preliminary report dealing with carboxyhemoglobin levels in the blood of Fairbanks donors[1]. The second is this report which is a review of the literature concerning acute and chronic carbon monoxide concentration effects on human health. This report resulted largely from the efforts of Richard Joy who at the time was a graduate student in the Program of Environmental Quality Engineering and Science at the University of Alaska.

Quite recently several publications have shed some light on the subject of this paper. Stewart *et al.* (1974)[2] reported in August of 1974 on a national survey conducted from 1969-1972 for carboxyhemoglobin (COHb) levels in 29,000 blood donors of various segments of the American population. The most signi-

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1. Harding, R. (1974). Preliminary Report from Fairbanks Memorial Hospital Laboratory on Carboxyhemoglobin Levels, prepared for Fairbanks North Star Borough Environmental Services, 4 pp.

2. Stewart, E.D., *et al.* (1974). Carboxyhemoglobin levels in American blood donors. JAMA, 229:1187-1195.

ficant findings of this survey were that the national average COHb was about
1.4 percent and that 45 percent of all non-smokers tested had COHb saturations
greater than 1.5 percent. These findings are very important in view of the
fact that the existing primary carbon monoxide standard of 9 parts per million
for 8 hours will result in a COHb content of approximately 1.5 percent in a
normal, resting man. The findings suggest that excessive CO exposure is wide-
spread and occurs regularly. In September of 1974, the Coordinating Committee
on Air Quality Studies (National Academy of Sciences and National Academy of
Engineering)[1] issued their report which reviewed the national ambient air qua-
lity standard for carbon monoxide. Their review contains the following:

1. On the basis of the new data base, there is no reason
   to relax the existing carbon monoxide standard of 9
   ppm for 8 hours. . . .

2. . . .populations with coronary arterial disease and
   the other groups. . .are so numerous and so widely
   distributed in the population that protection from
   adverse effects of carbon monoxide in these groups
   requires general control of the air quality in the
   community.

3. . . .it is impossible to state whether this standard
   provides a margin of safety.

The report also noted that no population group could be identified that
would be adversely affected if the statutory standards are met; and it
also made note of possible synergism or antagonism with other air pollutants.

The two national studies presented some fairly startling data and con-
firmed the need for the existing ambient air carbon monoxide standards. In
late 1974, the preliminary report on COHb in the blood of Fairbanks donors
was issued and included some results at least as startling as those of the
national survey. The Fairbanks study included about 150 COHb analyses and

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1. National Academy of Sciences and National Academy of Engineers,
   Coordinating Committee on Air Quality Studies, prepared by the Panel on
   Carbon Monoxide (1974). "Air Quality and Automobile Emission Control -
   Summary Report," Washington, D.C., U.S. Govt. Printing Office, Vol. 1,
   pp. 26-33.

the average percent COHb for the nonsmokers was about 2.4%. Greater than 85 percent of Fairbanks' nonsmoking blood donors have COHb levels exceeding 1.5% (compared to 45% nationally). However, the preliminary nature of this first investigation and, thus, the need for confirmation of the findings are recognized.

The primary objective of this report is to provide detailed information on the health effects of carbon monoxide. With this information, the community can judge for itself what action is deemed necessary to maintain or improve the health of its residents.

INTRODUCTION

CARBON MONOXIDE PROBLEM

Carbon monoxide (CO) is a colorless, odorless, poisonous gas which is formed when carbon is burned in an atmosphere deficient in oxygen. Although it is present naturally in the air in very small quantities, the chief sources of carbon monoxide are man's incomplete combustion processes. These processes include stationary sources such as power and heating plants and industrial processes, but the major man-made sources of carbon monoxide are mobile: the cars, trucks, and buses on our roads.

High-level, short-term exposures to carbon monoxide can cause death in humans. Experimentation begun around 1900 thoroughly documented the effects of this acute exposure to carbon monoxide. Exposure to very low levels of this gas will not cause death but does have many subtle effects. The effects of low-level, long-term (chronic) exposure are not nearly as well understood as high-level effects. Concern over the chronic effects of this gas has greatly increased in the past few years as people have become more and more aware of the air pollution problems in their communities and the possible effects of carbon monoxide on their health. As a result, much more research is now being conducted on this problem.

BACKGROUND

Fairbanks, Alaska, is a relatively small city (1970 U.S. Bureau of Census Population of 14,771 and a surrounding urbanized population of 30,000) located in the central portion of the state. Beginning in 1969, carbon monoxide measurements revealed very high levels of this pollutant in the ambient air of the city, especially during the winter months. Also, a recent random sampling of Fairbanks blood donors showed higher values of carboxyhemoglobin (COHb) than anywhere else in the United States.

There are several reasons for the high carbon monoxide levels present in the air in Fairbanks. Temperature inversions are present in more than 60 percent of all of the nighttime atmospheric soundings and in more than 80 percent of both the day and night soundings in December and January. These inversions are unusual in that they begin at ground level and extend upward to as high as 1,500 feet, are among the strongest in the world, and persist for unusually long periods of time.

The characteristics of these inversions are due to some special circumstances of the Fairbanks area during the winter:

1. In the winter the sun's rays are at such an angle and are visible for such a short time each day that there is very little energy input to the ground.

2. The snow-covered ground emits more heat than it receives.

3. During much of the winter there are no clouds present which otherwise could reflect the radiative heat emitted from the ground back to the earth.

4. There is little wind in the Fairbanks area which, if present, might break the inversion by promoting mixing. The absence of wind, in addition to the presence of hills on three sides of the town, helps stabilize the inversion.

5. The steepness of the inversion, three times as much as that of the Los Angeles area, also increases its stability.

Due to the frequency and stability of these inversions, any pollutants originating in the Fairbanks area become trapped and stagnate in the ambient air. As the Fairbanks population and its attendant number of automobiles has risen so has the carbon monoxide levels in the air during these inversions. It is now necessary to know whether or not chronic exposure (low-level and long-term) to carbon monoxide is hazardous to human health.

OBJECTIVES

In order to help determine the answer to this question, a literature review of the effects of both chronic and acute exposure to carbon monoxide has been prepared. This was felt to be necessary in view of the fact that:

1. no comprehensive and up-to-date review of this subject exists, and

2. a controversy currently exists as to whether or not the carbon monoxide levels in the Fairbanks air are detrimental to human health, and whether or not the ambient air standards for carbon monoxide established by the U.S. Environmental Protection Agency (EPA) are appropriate.

Abstracts of the literature reviewed are contained in the appendices of this paper. These abstracts are provided as a source of additional information for readers possessing a technical knowledge of the subject. A summary of the literature reviewed is presented herein.

BIOCHEMISTRY (1-15)[1]

The main effect of carbon monoxide on human health results from the reaction of CO with the hemoproteins, mainly the hemoglobin which is present in blood and which is the transport mechanism by which oxygen is taken from the lungs and distributed to all the tissues of the body. In the reaction of CO with hemoglobin, carboxyhemoglobin (COHb) is formed at the following rate:

$$\text{change \% COHb} = \frac{\text{ppm CO x minute volume x exposure time}}{46.5 \text{ x blood volume}}$$

where:

    ppm = parts per million
    minute volume - total volume of air breathed per minute
    blood volume - total volume of blood in the body (8)[1]

The carbon monoxide attaches to the hemoglobin molecule in competition with the oxygen, forming carboxyhemoglobin rather than oxyhemoglobin. Hemoglobin's affinity for carbon monoxide is more than 200 times greater than its affinity for oxygen (14). This attachment of carbon monoxide to the hemoglobin results in a decrease of the oxygen-carrying capacity of the blood.

Another effect of the formation of carboxyhemoglobin is the shift of the oxyhemoglobin dissociation curve. This shift, shown in Figure 1, reflects a decreased oxygen tension of the blood. This means that the diffusion of oxygen from the blood to the tissues is slowed (1).

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1. Numbers in parentheses refer to bibliographical references.
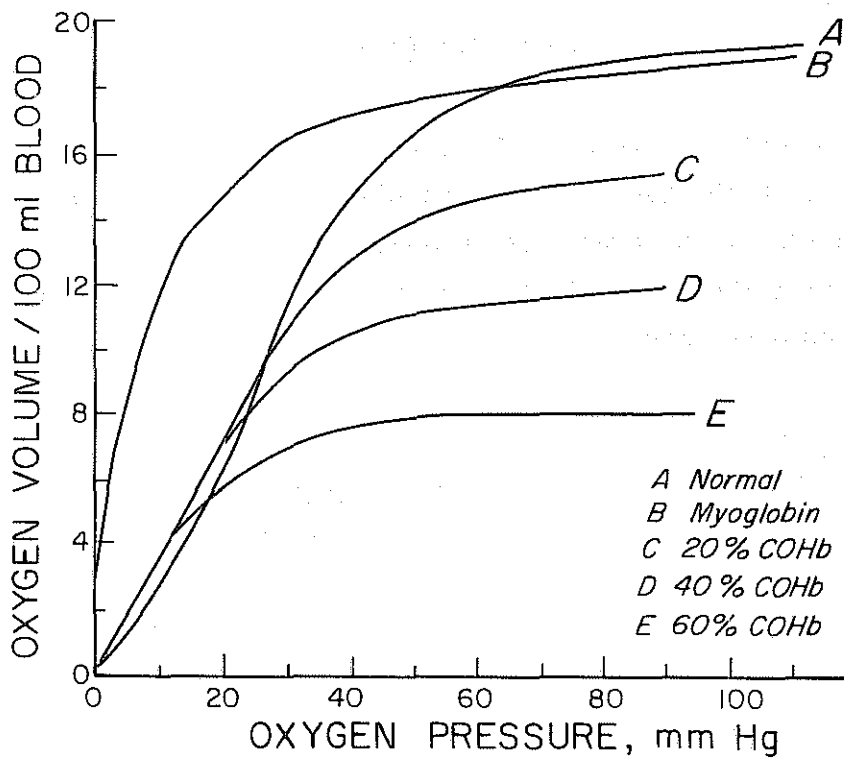
Figure 1: Oxyhemoglobin Dissociation Curves for Adult Hemoglobin, Myoglobin, and for Three Concentrations of COHb.(1). Oxygen volume, ml per 100 ml blood versus oxygen pressure, mm Hg.

Besides the reaction with hemoglobin, carbon monoxide also combines with other substances in the human body. These include the combination of CO with myoglobin, a muscle protein known to bind and store oxygen, and certain iron-containing enzymes. The combination of CO with these substances inhibits tissue enzyme activity (1). Other effects of CO intoxication include a temporary rise of the blood sugar, increased breakdown of body sugar (glycolysis), and an increase in the acid content of the blood (acidosis) (9).

Carbon Monoxide Poisoning (16-35)

When carbon monoxide combines with hemoglobin it can reduce the oxygen-carrying capacity of the blood to that of water, thus producing a deficiency in the supply of oxygen reaching the tissues of the body which can be sufficient to cause death. Death can occur at carboxyhemoglobin levels as low as 40 percent in otherwise healthy persons (22). Common sources of carbon monoxide include gas furnaces, fires, and gasoline engine fumes (26).

Symptoms of carbon monoxide poisoning include headache, nausea, vomiting, and drowsiness followed by coma and death (26). Even when there is apparent recovery the victims may experience long-term effects. In one study, persons examined five years after an acute exposure to carbon monoxide experienced organic disturbances, intellectual impediments, neurologic abnormalities, and/or various other symptoms of impairment of the nervous system (35).

Treatment of this poisoning is possible and can involve various methods including respiratory resuscitation (using inhalation therapy with such gases as pure oxygen, carbogen, and hyperbaric oxygen), cardiovascular resuscitation, and drug therapy with vitamin C, hexaphosphene, and cocarboxylase (20). Hyperbaric oxygen therapy (the breathing of oxygen at a pressure greater than one atmosphere) seems to be the most encouraging method of treatment at the present time (28).

Unintentional carbon monoxide poisoning is a frequent contributor to motor vehicle accidents which result in death. Such accidents are often erronesously attributed to driver fatigue, drowsiness, or inattention and should be investigated more closely to determine the role of possible carbon monoxide poisoning (17).

Cardiac Impairment (36-41)

Acute carbon monoxide concentrations lead to aberrations in the electro-cardiograms of exposed individuals. These electrocardiographic variations indicate abnormal functions of heart tissue but usually disappear completely after exposure is discontinued (37). However, there are cases in which these changes continue indefinitely (41). They are due to both the anoxemic (reduction of the blood oxygen content below normal physiological levels) action of carbon monoxide and to a cytotoxic action shown by increases in transaminases (39). If such damage may be done to a healthy heart, an already impaired myocardium may suffer irreparably under similar conditions.

Etiological and Epidemiological Studies (42 44)

There is the possibility that, after acute exposure to carbon monoxide, a person might seem to recover and regain good health, only to die eventually due to the exposure episode (42). A significant number of the people who do recover from the poisoning exhibit impaired memory functions and deterioration of personality. The level of deterioration correlates significantly with the degree of exposure to carbon monoxide prior to treatment (44).

Nervous System Effects (45-57)

The central and peripheral nervous system is also affected by acute carbon monoxide exposures (49). Electroencephalographic changes also occur. (An electroencephalograph is an instrument that records the electrical activity of the brain). Lesions can occur in both the central nervous system (47) and the peripheral nervous system (56). Anoxia (reduction of oxygen in the body tissues below normal physiological levels) due to carbon monoxide poisoning also produces effects on the nervous system (47). The occurrence of Parkinsonism following acute poisoning is common (57).

Tissue and Blood Chemistry (58-62)

The introduction of high levels of carbon monoxide into the bloodstream results in an inhibition of reflex vasoconstrictor responses despite the presence of normal arterial oxygen tension (59) as well as resulting in an inhibition of oxygen consumption in most of the body's tissues (61). It appears that carbon monoxide exposure also causes increased capillary permeability to protein (60).

One interesting finding is that, following inhalation of carbon monoxide, only the erythrocytes exposed to the gas in the lungs were carboxylated and the carboxyhemoglobin wasn't redistributed between the erythrocytes during blood circulation. Thus the hypoxic (low oxygen content or tension) insult to an individual erythrocyte was not related to the carboxyhemoglobin saturation as determined on whole blood; therefore, this insult may be much greater than is shown merely by the percent of carboxyhemoglobin in the blood (58).

Another very important aspect of carbon monoxide in the bloodstream is that it passes readily through the placenta in a pregnant woman (62). We must, therefore, be concerned with fetal exposure to carbon monoxide concentrations. Several other studies have resulted in similar findings and are discussed later in this paper (156, 171, 176).

Visual Effects (63)

Little information is available related to visual impairment effects of carbon monoxide (63, 73). Carboxyhemoglobin levels above 20 percent produced changes in the visually evoked response similar to those found in animals. A more comprehensive coverage of visual effects is presented later in the section on "Chronic Concentration Effects on Human Health" (194-199).

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Air Quality Standards (64-71)

In setting air quality standards we must decide at what level the car-
bon monoxide concentration is "safe" to humans. In order to decide this, it
is necessary to examine two questions.

In the United States we have accepted a certain degree of dependence
upon the protective mechanisms operating in the homeostatic and compensatory
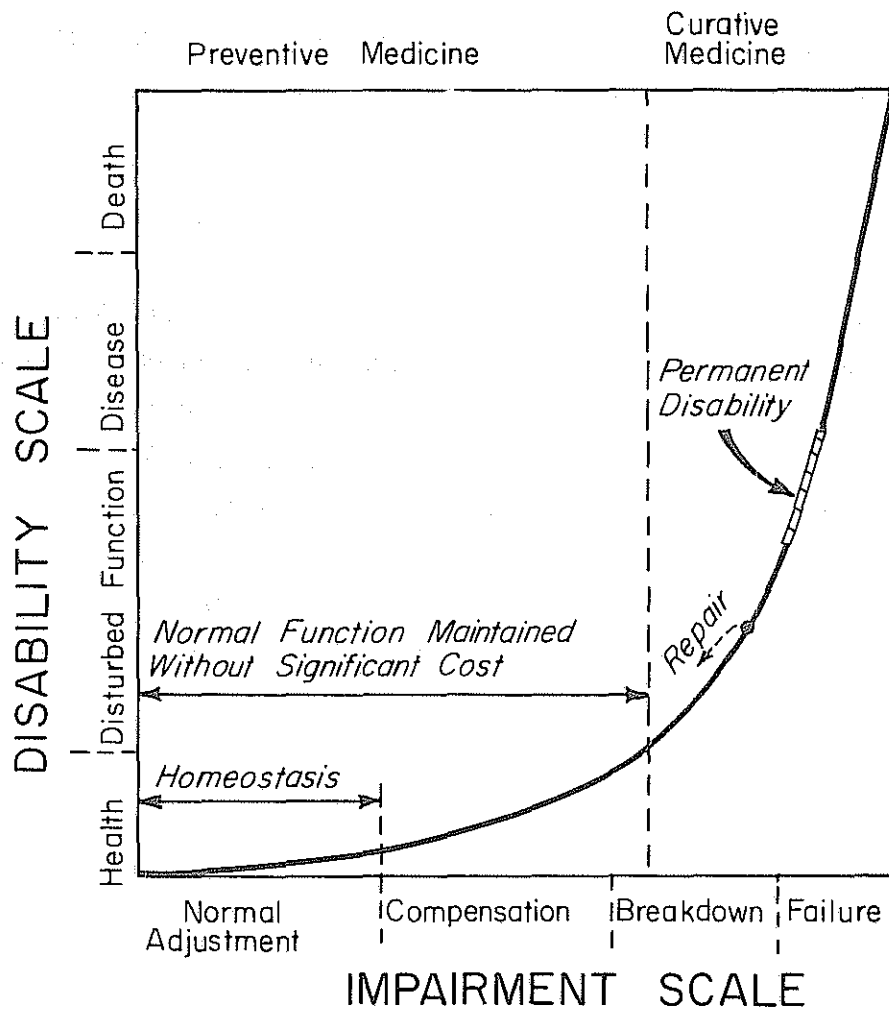zones of the curve in Figure 2. (Figure 2 is a general graph descriptive of

Figure 2: *Functional Impairment versus Degree of Disability Due to
Environmental Stress (71).*

damage due to various environmental factors. The graph may be interpreted to describe the effects of increasing amounts of COHb on the human body.) It is believed that these protective mechanisms can be drawn upon safely and repeatedly as long as they are not overloaded. In the U.S.S.R. however, the standard is set so as to make no demands on these protective mechanisms. This is done to allow these mechanisms to be held in reserve for emergency needs in unexpected encounters with environmental stresses (70). Thus, the first of these two questions - which approach is correct? Or is there a third approach, perhaps a happy medium, which is better than both of the others?

The other question is this - what percentage of the people must be affected by a pollutant before it is judged to affect the entire population? Do we set the standard at a level at which only persons with high sensitivity to the pollutant are affected, or should we set it higher, with regard to economic considerations (67)?

Figure 3 shows that the proportion of population judged to be affected by a pollutant increases as lesser effects are used to determine the proper standard. Therefore, if "pollutant burdens" are used in the determination of air pollution standards, 100 percent of the population may be affected at low concentrations, whereas if "morbidity" is used for these criteria a smaller proportion of the population is assumed to be affected at these same low concentrations. So, by lowering the standard, thus allowing less pollutant, we not only ensure protection for those individuals with sensitivity to carbon monoxide, we also increase the proportion of the population that we assume to be affected in some manner by carbon monoxide.

The current United States standard of 9 parts per million carbon monoxide for eight hours would produce about 2% carboxyhemoglobin in the average

person. Exposure to 10 to 15 parts per million for eight hours has resulted in impairment of time interval discrimination (64). However, other studies have given different results.
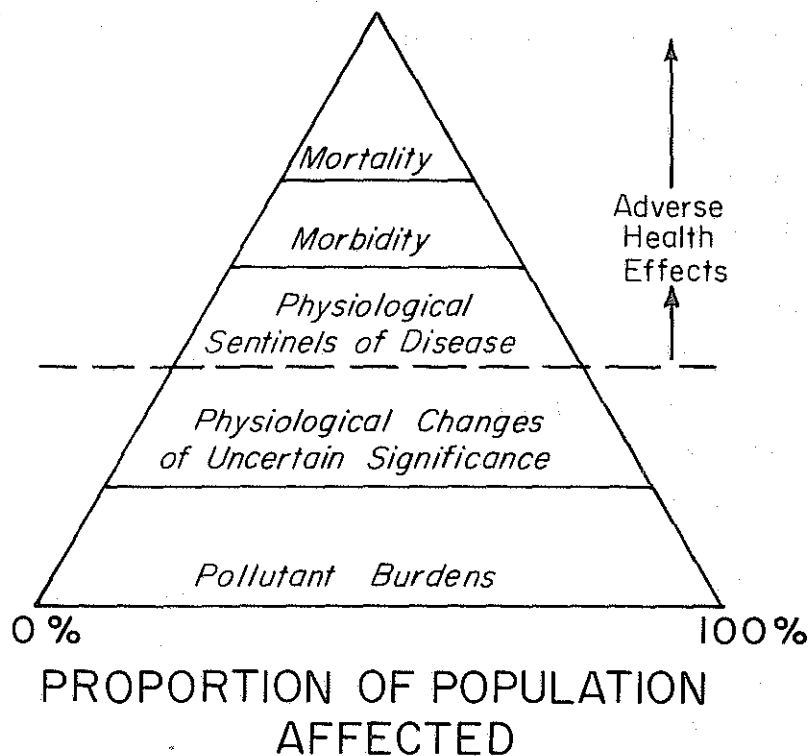

Figure 8: Proportions of Population Experiencing Adverse Health Effects at a Theoretical Pollutant Level (23).

Behavioral Impairment (72-104)

The results of experiments on the effects of chronic carbon monoxide exposure on behavioral functions are varied. Researchers have found impairment of several behavioral functions. The main question is the level of carbon monoxide in the bloodstream at which this impairment begins to occur. Some have not found any impaired function below 12% carboxyhemoglobin (73). Others have found no threshold below which there are no effects (74). The majority of researchers favor the latter view. Again, the question is not how low a concentration we must achieve to avoid impairment, but rather how much impairment we are willing to tolerate.

This variation in experimental results may be accounted for by differences in testing procedures and by the stressing effect of monotony involved in some of the tests. We are inclined to agree with the majority of researchers in classifying the studies which find effects only at higher levels of carboxyhemoglobin as special cases which do not represent the findings as a whole.

There is an indication that the effects of carbon monoxide on behavioral functions may be more severe when a person is already resisting the stressful effects of monotony (87). Is there a possibility that the stress of cold in Fairbanks during the winter may have a similar effect? If so, then the high concentration of carbon monoxide present during the winter may have a greater effect than would like concentrations under laboratory conditions. The effects caused by stress cannot be separated because physiological and psychological tests will identify changes but not their causes. Most of these other stresses can't be controlled whereas the level of carbon monoxide in the air can (89).

Some of the effects on performance produced by carbon monoxide exposure include changes in visually evoked responses, prolongation of reaction time, and manual coordination impairment (73). Degradation also occurs in estimation of time intervals (83) discrimination of forms and color, ability to perform arithmetic problems, and t-crossings (87). Driving skills, such as brake reaction time, night vision, glare vision, glare recovery, hand-steadiness, and depth perception all deteriorate slightly (104).

Cardiac Impairment (105-112)

Chronic exposure to carbon monoxide leads to cardiac impairment in healthy subjects. It not only hastens the development of arteriosclerosis, but also has a damaging effect on the myocardium (108). A decrease in the contractile capacity of the myocardium was noted in workers exposed to carbon monoxide for a number of years (112).

Carbon monoxide has a very important effect on patients with angina pectoris. Onset of angina during exercise occurs earlier and the duration of pain is prolonged due to the intake of small amounts (less than 10 percent carboxyhemoglobin) of carbon monoxide (105). Angina was also noted at a lower systolic blood pressure and heart rate for those individuals receiving CO (106). This raises questions about what levels of carbon monoxide are "safe" for cardiac patients.

After exposure to carbon monoxide, increases were observed in minute ventilation, cardiac output, peripheral oxygen extraction, and oxygen consumption (109). Figure 4 shows the increases in cardiac output as the concentration of carboxyhemoglobin is increased.
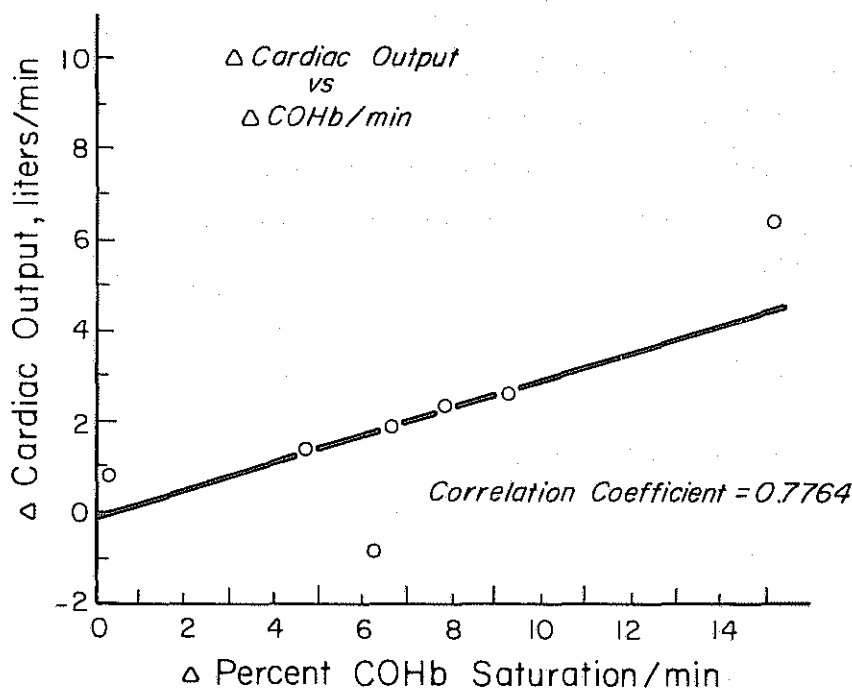
Figure 4: *Cardiac Output versus Increase in Percent COH_b Concentration per Minute.*

The heart is doubly burdened by the presence of carbon monoxide in the bloodstream. It not only has to increase its output so as to deliver more blood to the rest of the body in order to make up for the lower level of oxygen in the blood, but the heart in turn needs more oxygen to support its increased work load.

Etiological and Epidemiological Studies (113-121)

A number of studies have related carbon monoxide exposure to various physical manifestations. One study found that workers exposed to carbon monoxide had increased accident and illness rates (114). There is good evidence relating levels of carbon monoxide to mortality of patients hospitalized with myocardial infarction (115, 116) as well as relating the occurrence of automobile accidents to carboxyhemoglobin levels found in the driver's blood (116).

Nervous System Effects (122-127)

Chronic exposure to carbon monoxide appears not to cause distinct changes in the nervous system, but rather subtle and nonspecific changes such as inhibition of bioelectric activity in the brain (125). It seems to interfere with vestibular activity (123) and its initial effect is impairment of functions in the higher centers of the central nervous system in the area which controls some of the cognitive and psychomoter abilities (127). The effects on behavorial functions mentioned earlier are caused in part by subtle changes in the nervous system.

Occupational and Community Exposure (128-152)

As early as 1928, there was concern over community-level carbon monoxide exposure due to automobile exhaust (130). The articles abstracted show that many various occupational and community exposures now lead to increased carboxyhemoglobin levels in exposed subjects. People working in traffic,

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such as border inspectors (129), traffic policemen (131), parking garage employees (143), auto mechanics (147), and others (149). show high carboxyhemoglobin levels in their blood.

In looking at occupational and community exposure to carbon monoxide, there are three important factors to consider: [1] the proportion of people affected, [2] the magnitude of short- and long-term exposure in relation to the possibility of illness, and [3] the time-course of exposure in relation to the possible hazards (134). When setting community or occupational health standards. these three factors must be considered. Standards should not be established on the basis of a single exposure of one person, but rather on the continued exposure of a group of people, some healthy and some with medical problems.

In community exposure, the automobile is the chief source of carbon monoxide. The correlation coefficient between automobile traffic density and atmospheric carbon monoxide levels fluctuated between 0.75 and 0 95 in one study (137). Therefore, in attempting to reduce community carbon monoxide levels, the best method is to reduce emissions from automobiles, especially in Fairbanks where automobiles are the major source of carbon monoxide.

Tissue and Blood Chemistry (153-193)

During exposure to carbon monoxide in low concentrations, both the uptake and the elimination of this gas in the blood are rapid at first and then taper off (156) Figure 5 shows this effect for three concentrations of carbon monoxide in the inspired air. It takes three to four hours after exposure to eliminate one half the carbon monoxide in the blood (168).

As the carboxyhemoglobin level in the bloodstream increases, oxygen consumption (163), arterial oxygen tension (175), and venous oxygen tension (192) all decrease. This lowering of venous oxygen tension is probably the major effect of carboxyhemoglobin in the blood (169). Many other effects

occur during carbon monoxide exposure that are not well understood at this time, such as an increase of body temperature by approximately 0.5°C (181). More studies are needed before all the effects of carbon monoxide are known.
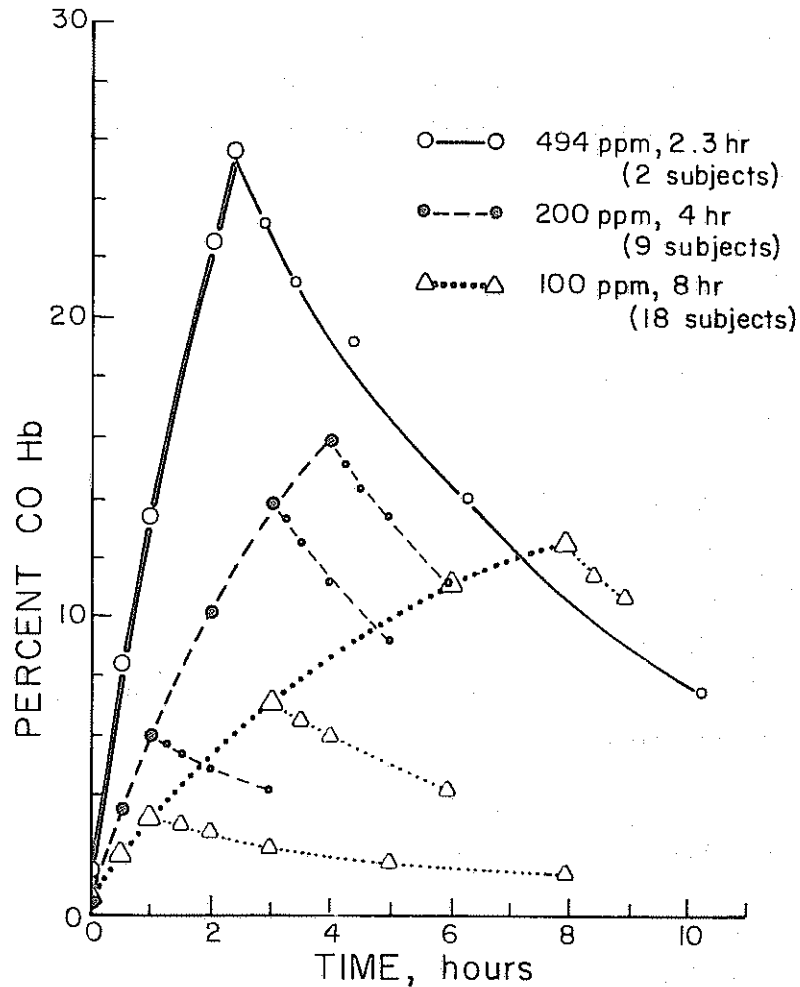
Figure 5: *Percent COHb During and Following CO Exposure for Healthy, Sedentary, Non-smoking Individuals.*

A certain amount of acclimatization does occur in that there is a decrease in the severity of symptoms during successive exposures to the same concentration of carbon monoxide (173). These frequent exposures alter the physiological reactions to carbon monoxide (188). This acclimatization may occur through mechanisms such as increased hemoglobin concentrations in

the blood (187), increased cardiac output, possibly increased capillary blood volume, and, perhaps, slightly increased volumes of pulmonary ventilation. However, these mechanisms increase the burden on the physical reserve (82). Thus we return to the question discussed earlier: what degree of impairment are we willing to accept? Another problem in discussing acclimatization is that most of the experiments on human acclimatization have been done only once and remain unverified (182).

An important effect which also occurs due to exposure to low-level carbon monoxide concentrations is a decrease in the oxygen-carrying capacity of both maternal and fetal blood (171). The decreased availability of oxygen is probably injurious to fetal tissues, but to what extent carbon monoxide per se is harmful remains to be determined (176). There is evidence that this exposure results in the birth of smaller babies and may have other effects on fetal development (156).

Visual and Auditory Effects (194-199)

Visual effects of low levels of carbon monoxide occur at blood concentrations as low as 3 percent carboxyhemoglobin (198) and produce an effect like that of a comparable decrease in percent oxyhemoglobin due to hypoxic anoxia (195). It appears that there may be an enzyme involved in the visual system which combines competitively with carbon monoxide and oxygen (194).

With regard to auditory effects, a threshold limit has not been defined. However, a significant percentage of people chronically exposed to carbon monoxide develop hearing impairments (197).

SUMMARY AND CONCLUSIONS

In discussing the effects of carbon monoxide, a distinction should be made between acute and chronic exposures. An acute exposure is a high-level, short-term episode which can result in immediate death due to a lack of oxygen reaching the tissues of the body. Death can occur at a level as low as 40 percent carbon monoxide saturation, or carboxyhemoglobin, in the bloodstream.

In contrast chronic concentrations are caused by low-level, long-term exposures, and usually result in carboxyhemoglobin levels below 20 percent, with a concentration of as low as 2 percent carboxyhemoglobin producing significant symptoms. This level produced behavioral impairments in the majority of studies, impairment which could be significant in tasks such as driving a car. In fact, some researchers indicate no threshold below which there are no effects, which means that any increase of carbon monoxide in the ambient air may be deleterious to human health. This behavioral impairment is caused, at least in part, by subtle changes in the nervous system.

The effect of carbon monoxide on the body is due mainly to its reaction with the hemoproteins, especially hemoglobin. Hemoglobin has an affinity for carbon monoxide of over 200 times that for oxygen. As carbon monoxide combines with hemoglobin it decreases the amount of oxygen in the blood available to the tissues, thus producing nearly the same effects as hypoxic anoxia. However, carbon monoxide also has lesser effects: one is the inhibition of certain tissue enzyme activity.

Due to the main direction of attack of carbon monoxide, people who may be particularly susceptible to low-level exposure are those already subject to a degree of hypoxia from altitude, anemia, or reduced cardiac output; or those with supernormal oxygen needs due to pregnancy, hyperthyroidism, or fever (156). Patients with heart disease may be very sensitive to this gas because they are doubly burdened. Not only is there less oxygen in the

bloodstream available to the heart, but the heart must also increase its blood output to provide the necessary supply of oxygen to the other tissues. Fetal development may also be affected by chronic exposure of the mother to carbon monoxide.

Due to the fact that there may not be a threshold concentration of carbon monoxide below which no effects occur, almost certainly the case for sensitive individuals, two questions must be answered in establishing an ambient air standard. First: what degree of impairment are we willing to live with; and second: how many people must exposure to low levels of carbon monoxide affect before such exposure is considered hazardous to the general public?

In our opinion, any level of impairment is too great and a safety margin in the human body is necessary in order to protect against unexpected environmental stresses. Therefore, in view of the information presented, the standards now officially adopted in the United States are not too strict and should not be repealed or diluted solely in the interest of economic considerations. The item of utmost concern is the health of every individual.

Especially in Fairbanks, where the levels of carbon monoxide in both the ambient air and the bloodstreams of residents are among the highest in the nation and where the winter cold places an additional stress on residents, these standards should be upheld in order to make Fairbanks a healthy place in which to live for all her people.

Finally, although the subject of this report is the effects of carbon monoxide on human health, we would be remiss in our objective if we did not mention other air pollutants including nitrous oxides, sulfur oxides, hydrocarbons, and particulates. Each of these pollutants can have an adverse effect on human health. Unfortunately, they are often found in combination with carbon monoxide and to date very little information has been reported concerning their synergistic effects. However, some researchers indicate that their effects are additive, or worse yet, that they may increase the

toxicity of each other when inhaled together. Therefore the adverse effects on human health due to carbon monoxide reported in this paper should, perhaps, be viewed as being conservative.

APPENDIX

ABSTRACTS OF LITERATURE REVIEWED

CONTENTS

Page

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    which indicates that oxygen is released to the tissues with great diffi-
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    equally dependent upon ventilation rate and diffusion capacity.

5. Joels, N., and Pugh, L.G.C.E. (1958). The carbon monoxide dissociation curve of human blood. *J. Physiol.*, 142:63-77.

Carboxyhemoglobin (COHb) and O_2Hb dissociation curves have been compared for the blood of 3 subjects of CO_2 pressures of 15,50 and 70 mm Hg and pH values of 7.50, 7.25, and 7.15, respectively. The affinity of hemoglobin for CO and O_2 varies only slightly between subjects, but is affected by changes in plasma pH and CO_2 pressure.

6. Lynch, S.R., and Moede, A.L. L972). Variation in the rate of endogenous carbon monoxide production in normal human beings. *J. Lab. Clin. Med.*, 79:85-95.

Significant variations occur in the rate of heme catabolism in normal human beings and these are reflected in fluctuations seen in the rate of endogenous CO production, the serum iron level, and the serum unconjugated bilirubin concentration.

7. Meda, E. (1964). Kinetics of the reaction of human hemoglobin with carbon monoxide. *Rass. Med. Ind. (Rome)*, 33:292-295. (French).

Results of studies on the kinetics of the reaction of human hemoglobin with CO were obtained using the "interrupted flow" method. The influence of temperature on the kinetics of the reaction was studied and the equation is given for calculating the rate constant.

8. Pace, N.; Consolazio, W.V.; White, W.A. Jr.; and Behnke A.R. (1946). Formulation of the principal factors affecting the rate of uptake of carbon monoxide by man. *Amer. J. Physiol.*, 147:357-359.

In man, the degree of blood saturation with CO after exposure is as follows:

$$\text{change in } \% \text{ COHb} = \frac{\text{parts CO} \cdot \text{minute volume} \cdot \text{exposure time}}{46.5 \text{ blood volume}}$$

This equation is valid for % COHb up to one-third the equilibrium value for air containing concentrations of 100-200 ppm of CO.

9. Pankow, D., and Ponsold, W. (1973). Biochemical aspects of carbon monoxide intoxication. *Z. Ges. Hyg. Ihre. Grenzgebiete (Berlin)* 19:321-330. (German).

The effects of long-term CO exposure on the properties and metabolism of haemoproteins, porphyrines, carbohydrates, amino acids, peptides, albumin, lipids, nucleic substances, acid, base and electrolyte metabolism, and stress are discussed. In particular, mention is made of increases of hemoglobin and erythrocyte protoporphyrin, serum iron level and serum globulin with simultaneous decreases of serum albumin, concentration of trace elements in liver fragments, and decrease of the liver benzopyrene hydroxylase activity. Acute CO intoxication is characterized by a drop of oxygen pressure and hemoglobin level, a temporary rise of the blood sugar, and increased glycolysis, glutathione concentration in the blood, and metabolic acidosis.

10. Saidel. G.M.; Militano, T.C.; and Chester, E.H. (1971). Pulmonary gas transport characterization by a dynamic model. *Resp. Physiol. (Amsterdam)*, 12:305-328.

A mathematical model is developed which describes and predicts pulmonary transport of CO. This model simulates CO uptake with normal subjects and those with chronic obstructive lung disease. With each subject, experiments are conducted at several levels of tidal volume and frequency.

11. Salhany J.M.; Mathers, D.H.; and Eliot, R.S. (1972). The deoxygenation kinetics of hemoglobin partially saturated with carbon monoxide. Effect of 2,3-diphosphoglycerate. *J. Biol. Chem.*, 247(21):6985-6990.

The deoxygenation rate of human hemoglobin solutions partially saturated with CO in the presence and absence of 2,3 diphosphoglycerate (2,3-DPG) were measured. The results indicate that 2,3-DPG has no effect on the release of the first oxygen from the fully liganded conformation but does affect the rate of removal of the second and subsequent oxygen molecules.

12. Schmelzer, U.; Steiner, R.; Mayer, A.; Nedetzka, T.; and Fasold, H. (1972). On the kinetics of the reaction of hemoglobin with CO. Flash-photolysis experiments. *Eur. F. ...*, 25(3):491-497.

Flash-photolysis measurements were performed on normal and on chemically modified human adult hemoglobin solutions. The observed data suggests that an all-or-none transition of the quaternary structure of hemoglobin accompanies the third step of the ligation process.

13. Stynes, D.V.; Stynes, H.C.; James, B.R.; and Ibers, J.A. (1973). Reversible binding of nitric oxide and carbon monoxide to iron porphyrins. Assessment of the role of protein in hemoglobin. *J. Am. Chem. Soc.*, 95(12):4087-4089.

Preliminary results on the equilibrium constants for the reversible binding of NO and CO to iron (II) protoporphrin IX and iron (II) tetraphenylporphrin in piperidine are presented. The competition between NO and CO indicates a greater amount of the NO complex is formed initially than that expected from the separate equilibrium constants, but on standing, the relative amounts of NO and CO complexes reach their expected equilibrium concentrations.

14. Sterz, H. (1963). On hemoglobinemia. *Medizinische Klinik*, 58:1705-1709.

Carbon monoxide (CO) has a 200 to 300 times greater affinity for hemoglobin (Hb) than oxygen, 0.1% CO in the air being sufficient to tie up half of the hemoglobin (Hb). Severe headache, restlessness, shaking, weakness, cramps, deep coma, and muscular paralysis followed by death may be caused by the paralysis of the breathing mechanism and by hemorrhage in the brain. Sixty percent COHb causes coma; 70 to 80 percent is fatal.

15. Tivnov, L.A.; Sokolova, T.; and Paribok, V.P. (1957). Duration of carbon monoxide excretion from the body. *Farmakol. i. Toksikol.*, 20:76-78, 1957. IN: Levine, B.S. (editor and translator): U.S.S.R.

Literature on Air Pollution and Related Occupational Diseases. A Survey. Vol. 7, 1962, pp. 262-264, CFSTI-TT-62-11103, U.S. Dept. of Commerce, Springfield, Va.

The authors investigated the rate of carbon monoxide excretion from the blood and the possibility of its being retained by the tissue, employing the labeled atoms method which is described.

ACUTE CONCENTRATION EFFECTS ON HUMAN HEALTH (16-63)

Carbon Monoxide Poisoning (16-35)

16. Anonymous (1970). Carbon monoxide poisoning. *Brit. Med. J.*, 3:180.

The best treatment for CO poisoning is the administration of hyperbaric oxygen, or 95% oxygen and 5% CO_2 with intravenous hypertonic mannitol as an alternate. Hyperbaric oxygen keeps the patient's tissues oxygenated at a time when his hemoglobin is not available to him for oxygen transport.

17. Anonymous (1963). Hundreds of motorists are killed by carbon monoxide. *Public Health J. (Johannesburg)*, 63:30-32.

Many deaths from CO fumes are included in that group dying from injuries sustained in car accidents commonly attributed to driver fatigue, drowsiness, or inattention. Incidence of deaths from CO in automobiles are cited. The blood of drivers should be tested for both alcohol and CO content.

18. Arena J.M. (1963). Carbon monoxide: Report from the Duke University poison control center. *North Carolina Med. J.*, 24:28-29.

This summarizes the effect of CO poisoning on the health of man and advises on respective treatments. There is a description of symptoms in relation to percentage of CO in the atmosphere, duration of exposure, and saturation of the blood.

19. Baker, S.P.; Fisher, R.S.; Masemore, W.C.; and Sopher, I.M. (1972).
     Fatal unintentional carbon monoxide poisoning in motor vehicles.
     Am. J. Public Health, 62(11):1463-1467.

     An attempt was made to determine how many persons die in motor vehicles
     as a result of unintentional CO poisoning. Synergism between alcohol
     and CO was a factor. Carboxyhemoglobin in the blood of the victims
     was measured. Suggested counter-measures include modification of future
     automobiles, detection and correction of defects in existing vehicles,
     and prompt oxygen therapy for victims found alive.

20. Beghe, R. (1964). Experiences in the treatment of acute carbon monoxide
     poisoning. *Rass. Med. Indust.*, 33:337-351. (French).

     Cases of acute CO poisoning treated in artificial-respiration wards
     are presented. A review is included of the therapeutic procedures
     during respiratory resuscitation (oxygen therapy), cardiovascular
     resuscitation, and drug therapy (Vitamin C, hexaphosphene, cocarboxy-
     lases). Antibiotics are also administered the CO-poisoned patients
     in order to pervent respiratory complications.

21. Bilchik, R.C.; Muller-Bergh, H.A.; and Freshman, M.E. (1971). Ischemic
     retinopathy due to carbon monoxide poisoning. *Arch. Opthalmol.*,
     86:142-144.

     Three subjects, exposed to 500 ppm of CO due to a defective gas heater,
     were hospitalized. Positive findings limited to the ocular fundi and
     indicative of tissue ischemia included retinal hemorrhages, cotton wool
     exudates, retinal edema, and papilledema. The ischemia resolved spontan-
     eously

22. Edgerley, P.H. (1971). Supplemental information estimating carbon
     monoxide exposure. *North American Rockwell Corp.*, MSC-17211, 17 p..
     National Aeronautics and Space Admin., TSP71-10319.

     Carbon monoxide combines with hemoglobin to reduce the oxygen capacity
     of blood to that of plain water. The cause of death due to CO exposure

is the result of a deficient oxygen supply to the tissues of the body. The effects of CO to produce hypoxia are additive with other causes of hypoxia, including increased oxygen demands on the body caused by exertion.

23. Hayhurst, E.R. (1926). Carbon monoxide and automobile exhaust gases. *Amer. J. Pub. Health*, 16:218-223.

The problem of discovering which symptoms are due to CO poisoning itself and which are due to the surrounding environment or previous condition of the victim is discussed. It is questioned whether or not asphyxia accounts for all the phenomena of CO poisoning, whether there are low-level effects, and if acclimatization takes place.

24. Jackson, R.C.; Bunker, N.V.; Elder, W.J.; and O'Connor, P.J. (1959). Case of carbon monoxide poisoning with complications. Successful treatment with an artificial kidney. *Brit. Med. J.*, pp. 1130-1134.

A case is described of CO poisoning with the following complications: skeletal muscle necrosis, probable myocardial necrosis, acute renal failure mental changes, and a radiculomyelitis of L 2-5. The literature concerning muscle necrosis and renal failure, with the neurological sequelae, is reviewed.

25. Johnson, D.M. (1961). Killer on our highway. *Good Housekeeping*, pp. 49 and 146-148.

Carbon monoxide causes many accidents and deaths on our highways. Examples are described and precautions and solutions are detailed.

26. McBay, A.J. (1965). Carbon monoxide poisoning. *New England J. Med.*, 272:252-253.

Symptoms of CO poisoning include headache, nausea, vomiting and drowsiness, then coma and death. The accumulation of the gas in human beings depends

on the concentration of CO in the air, duration of exposure, and rate and depth of respiration. Carbon dioxide is eliminated at a rate slower than that at which it is taken up.

27. Meigs, J.W., and Hughes, J.P.W. (1952). Acute carbon monoxide poisoning: An analysis of one-hundred-five cases. *Arch. Indust. Hyg. & Occupat. Med.*, 6:344-356.

An analysis of a study of 105 patients with acute CO poisoning showed several common symptoms, including skin lesions, excessive sweating, liver enlargement, and localized soreness. An attempt was made to correlate severity of poisoning with the degree of these symptoms.

28. Perret, C. (1973). The physiopathology and treatment of carbon monoxide poisonings. *Schweiz. Med. Wochenschir.*, 103(33):1161-1166. (French).

Intoxication by CO interferes with the tissue oxygen supply in various ways: decrease in available hemoglobin, alteration of the oxygen dissociation, and inhibition of cell respiration after fixation upon myoglobin and the cytochromes. The effects of simple oxygen therapy, carbogen and hyperbaric oxygen are discussed, with all clinical cases presented demonstrating the advantages of hyperbaric oxygen.

29. Peterson, J.E., and Stewart, R.D. (1972). Human absorption of carbon monoxide from high concentrations in air. *J. Am. Ind. Hyg. Assoc.*, 33(5):293-297.

Healthy males were exposed to high CO concentrations and the rate of rise of COHb in the blood was determined. This increase was accurately predicted by the relationship $\log (\% \text{ COHb/liter}) = 1.036 \log (\text{ppm of CO inhaled}) - 4.4793$.

30. Ramsey, T.L., and Eilmann, H.J. (1931-32). Carbon monoxide, acute and chronic poisoning and experimental studies. *J. Lab. & Clinical Med.*, 17:415-427.

Presented is a study of CO from a standpoint of the method of its production, its affinity for hemoglobin, its action upon being respired, the percentages of blood saturation in varying lengths of time according to the concentrations in the respired air, the symptoms and effects upon the body, possible methods of its elimination from the body, the production of chronic CO poisoning, and methods of treatment.

31. Rothschild, J.E. (1962). Carbon monoxide poisoning. *Amer. Pract.*, 13:213-218.

The author discusses the overall effect of CO on the health of man, and reports a case of acute CO poisoning in which he used exchange transfusion to treat the victim.

32. Stewart, R.D., *et. al.* (1973). Experimental human exposure to high concentrations of carbon monoxide. *Arch. Environ. Health*, 26:1-7.

Carbon monoxide was rapidly absorbed in healthy male humans exposed to high concentrations and the increase in percent COHb saturation in venous blood per liter of CO mixture inhaled was predicted by the equation, log (change % COHb/liter) = 1.036 log (ppm CO inhaled) - 4.4793.
The abrupt increase in COHb of 11.6% plus 9.1% saturation in two subjects produced the immediate onset of mild frontal headache.

33. Stewart, R.D., *et al.* (1970). Experimental human exposure to carbon monoxide. *Arch. Environ. Health*, 21:154-164.

Humans were exposed to CO at varying concentrations for different periods of time. No untoward effects were observed in sedentary males exposed to 100 ppm for eight hours. Exposures producing COHb saturations greater than 15% to 20% resulted in delayed headaches, changes in the visually evoked response, and impairment of manual coordination.

34. Vyskocil, J. (1957). "Neurohumoral regulation" in acute and chronic carbon monoxide poisoning. *Arch. Gewerbepathol. Gewerbehyg.*, 15:457-472.

In acute poisoning during the first few days there is leucocytosis, diminution in the eosinophil count, increase in blood sugar, glycosuria, and pathological values of the adrenalin and water tests. These findings usually disappear in about 14 days, but in other instances signs suggestive of damages to the central nervous system develop gradually. Congestion of the adrenals, pancreas, liver and spleen were found. Among the 29 persons who had for an average period of 8 years worked in an atmosphere containing CO, the findings were enlargement of the thyroid (38%), loss of hair (45%), diminution in potency (17%), pathological values in the adrenalin test (59%), and the water test (27%), and increase in blood sugar (41%)

35. Yukitake, A. (1971). *Clinical Investigation on Acute Carbon Monoxide Poisoning Due to Explosion in Miike Coal Mine Five Years After the Accident*. Translated from Japanese. McGregor and Werner, Inc., Washington, D.C., Fundus Systems, 14 pp.

Eighty-one percent of 829 persons affected by a carbon explosion in a coal mine were examined 5 years after the incident. Twenty-eight percent of the 671 people examined had organic disturbances, with 25% experiencing intellectual impediments, 12% with affected characteristics, 8% with neurologic abnormalities, and 4% with various nervous symptoms. The occurrence of residual symptoms can be related to CO concentrations and the duration of the exposure.

Cardiac Impairment (36-41)

36. Belza, J. (1955). Electrocardiographic changes following acute carbon monoxide poisoning. *Inaugural - Dissertation for the Degree of Doctor of Medicine*. P.G. Keller, Winterthur, Switzerland, p. 39.

The damaging influence on the myocardium as reflected in the clinical picture and electrocardiogram is examined. Frequency of pathological

changes in the EKG following acute CO poisoning are discussed, and
an attempt has been made to estimate the relation of the age factor
to the speed of electrocardiographic findings of impairment.

37. Colvin, L.T. (1927-28). Electrocardiographic changes in a case of
severe carbon monoxide poisoning. *Amer. Heart J.*, 3:484-488.

In the case studied, the EKG changes were due mainly to asphyxia.
These changes, suggesting damage to the ventricular muscle, disappeared
rapidly and completely. If such damage may be done to a healthy heart,
an already impaired myocardium might, under similar conditions, suffer
irreparably.

38. Cosby, R.S., and Bergeron, M. (1963). Electrocardiographic changes
in carbon monoxide poisoning. *Amer. J. Cardiol.*, 11:93-96.

Electrocardiograms were abnormal in 9 out of 10 patients with severe
CO toxicity. In two patients the EKG pattern didn't return to normal
for 4 years, and the clinical course was compatible with moderately
severe coronary artery insufficiency and myocardial damage. Anoxia,
toxic changes and true coronary ischemia secondary to shock may all
play a part in CO poisoning, depending on concentration, duration of
exposure, and presence or absence of shock.

39. Mainardi, M. (1964). Electrocardiographic alterations in cases of acute
intoxication from carbon monoxide. *Rass Med. Ind. (Rome)*, 33:420-
429. (French).

Electrocardiographic alterations in subjects with acute CO intoxication
are due both to the anoxemic action of CO and to a cytotoxic one shown
by increases in transaminases, in particular of lactic dehydrogenase,
even in instances where the damage was transient.

40. Middleton, G.D.; Ashby, D.W.; and Clark, F. (1961). Delayed and long-
lasting electrocardiographic changes in carbon monoxide poisoning.
Lancet, 1:12-14.

Two cases of CO narcosis are reported in which long-lasting changes
were seen in serial electrocardiograms taken up to 3 months after
exposure.

41. Shafer, N.; Smilay, M.G.; and MacMillan, F.P. (1965). Primary myocardial
        disease in man resulting from acute carbon monoxide poisoning.
        Amer. J. Med., 38:316-320.

This paper presents a case of myocardial damage resulting from acute CO
poisoning. In this case the patient remained symptomatic and showed
persistent changes on the EKG; the electrocardiographic patterns reported
prior to this consist of transient and reversible changes.

Etiological and Epidemiological Studies (42-44)

42. McConnell, J.W.; and Spiller, W.G. (1912). A clinicopathologic study
        of carbon monoxide poisoning. *J. Amer. Assn.*, 59:2122-2126.

Poisoning by CO is divided into three classes: acute, chronic, and
relapsing, the latter being apparent recovery from the poison, with
development of symptoms leading to death after a period of fair
health. Studied closely was the elapsed time between the initial
poisoning and the development of grave symptoms, the bilaterality
of the motor symptoms, the intense spasticity present, and the ab-
sence of distinct vasomotor or trophic symptoms.

43. Saita, G., and Lussana, S. (1971). Late coronary-cerebral syndrome of
        acute carbon monoxide poisoning. *Med. Lavora (Milan)*, 62(4):185-195.
        Translated from Italian. 17 pp.

A patient showed coronary changes with an EKG pattern of ischemia lesion
and decreased blood pressure for 24 hours (13 days after complete reco-
very from coma due to acute CO poisoning). The patient died in spite
of quick reversion to normal blood pressure and improvement of the EKG

changes. The coronary lesion would probably not have induced such severe and irreversible cerebral changes in the absence of pre-existent damage induced by acute CO poisoning.

44. Smith, J.S., and Brandon, S. (1973). Morbidity from acute carbon monoxide poisoning at three-year follow-up. *Brit. Med. J.*, 1 318-321.

Seventy-four survivors of acute CO poisoning were followed up for 3 years. Of 63 patients alive, 8 showed an improvement and 21 (33.3%) a deterioration of personality, and 27 (43%) reported a subsequent impairment of memory, with high correlation between these two effects. The level of consciousness on admission to the hospital in the acute phase of poisoning correlated significantly with the development of gross neuropsychiatric sequelae.

Nervous System Effects (45-57)

45. Bell, M.A. (1961). Subacute carbon monoxide poisoning. *Arch. Environ. Health*, 3:594-596.

Unexpected collapse or fainting upon mild to moderate effort is a clue to cerebral hypoxia possibly due to CO poisoning not revealed in the patient's initial history.

46. Borman, M.C. (1926). Carbon monoxide poisoning. Mental and neurological changes in a case of acute carbon monoxide poisoning with partial recovery. *Amer. J. Psychiatry*, 6:135-143.

A patient with CO poisoning showed widespread central nervous system (CNS) changes with apparent recovery, followed by mental and neurological disturbances with ultimate recovery. The chemical alterations in the blood and clinical tests thereof in CO poisoning are mentioned, along with anatomical changes in the CNS and various explanations for their occurrence.

47. Bour, H., and Ledingham, I. McA., ed. (1967). *Carbon Monoxide Poisoning*. Elsevier Publishing Company, Amsterdam, London and New York, 203 pp.

An in-depth discussion of the effects of acute CO poisoning on the nervous system documented with clinical data. The individual authors have studied such effects as brain lesions and anoxia as well as various treatments for CO intoxication.

48. Gilbert, G.J., and Glaser, G.H. (1959). Neurological manifestations of chronic carbon monoxide poisoning. *New England J. Med.*, 261: 1217-1220.

A patient with 20% COHb had anorexia, weight loss, a fluctuating organic mental syndrome, and recurrent episodes of loss of consciousness. Each attack was preceded by a period of dizziness and ataxia. After withdrawal from the source of exposure, serial electroencephalograms showed progressive clearing of focal and paroxysmal abnormalities, correlated with clinical improvement.

49. Guenther, K.D (1971). Chronic wrongly diagnosed CO intoxications with severe neurological symptoms. *Psychiat. Neurol. Med. Psychol. (Leipzing)*, 23(6):368-377. (Presented at the Tagung Der Berliner fuer Neurologie and Psychiatrie, Neuruppin, West Germany, July 7, 1970). (German).

A couple who were exposed alternately to subtoxic and toxic concentrations of CO for 2 to 3 weeks exhibited numerous neurological defects. Since CO intoxication may produce many symptoms in the peripheral and central nervous system, differential diagnosis is required. Electroencephalographic changes are also discussed.

50. Howse, A.J.G., and Seddon, H. (1966). Ischemic contracture of muscle associated with carbon monoxide and barbiturate poisoning. *Brit. Med. J.*, 1:192-195.

Four cases of ischemic muscle contracture associated with CO or barbiturate poisoning are reported. Ischemic nerve lesions occur, this condition almost certainly due to a combination of local pressure and general hypoxia.

51. Kirichinskava, I.A. (1958). Sequelae of severe carbon monoxide poisoning. *Soviet. Meditsina*, 22:152-154, 1958. IN: Levine, B.S. (editor and translator): *U.S.S.R. Literature on Air Pollution and Related Occupational Diseases. A Survey*. Vol. 5, 1961, pp. 115-119, CFSTI-TT-61-11149, U.S. Dept. of Commerce, Springfield, Va.

Carbon monoxide poisoning causes acute impairment to the central nervous system due to COHb formation and disturbed brain cell oxygen metabolism. Severe CO poisoning may follow a favorable course at first, but later can result in mental changes. Akinetic syndrome with symptoms of diffuse damage of the cerebral vessels is one reason for these changes.

52. Neubuerger, K.T., and Clarke, E.R. (1945). Subacute carbon monoxide poisoning with cerebral myelinopathy and multiple myocardial necrosis. *Rocky Mountain Med. J.*, 42:29-35.

Subacute CO poisoning in a 19-year-old girl led to death after 13 days. Autopsy revealed cerebral myelinopathy and myocardial necrosis. The significance of a low concentration of CO together with high atmospheric temperature is emphasized.

53. Paris, J. (1964). Study of the "excitation-duration" curves after occupational acute CO poisoning. *Rass Med. Indust.*, 33:275-291. (French).

Neuromuscular excitation curves after acute occupational intoxication from CO show hypoexcitability of the nerve with corresponding inversion of the nerve-muscle excitability ratio. The inversion of this proportion seems to render objective the subjective clinical syndrome of muscular asthenia and great weakness of the lower limbs that is observed after acute CO poisoning.

54. Ramsey, J.M. (1973). Effects of single exposures of carbon monoxide
    on sensory and psychomotor response. *Am. Ind. Hyg. Assoc. J.*,
    34(5):212-216.

    Two groups of subjects had their mean COHb increased by 7.61% and 11.22%,
    respectively. All subjects were given tests for depth perception, visual
    discrimination for brightness, reaction time to a visual stimulus, and
    flicker fusion discrimination. The only test showing significant deteri-
    oration was the reaction time test, with the decrement produced by each
    group essentially the same.

55. Raskin, N., and Mullaney, O.C. (1940). The mental and neurological
    sequalae of carbon monoxide asphyxia in a case observed for fif-
    teen years. *J. Nerv. & Mental Dis.*, 92:640-659.

    The mental and neurological sequelae of a patient who survived for 15
    years, a case of CO asphyxia is described. The patient developed
    Parkinson's syndrome, and the mental picture was one of involution
    melancholia. Also reviewed is literature of case studies of patients
    who survived CO poisoning for a few days or months.

56. Trozano, L., and Coscia, G.C. (1964). Readial paralysis in a case of
    acute carbon monoxide intoxication. *Rass. Med. Indust.*, 33:401-403.
    (French).

    Paralysis of the right arm in a patient acutely poisoned by CO persisted
    for 3 months, although no signs of central nervous systme distress were
    evident. This case demonstrated the occurrence of isolated lesions in
    the peripheral nerve trunks of the arm during acute CO poisoning.

57. Turner J.W.A. (1964). Parkinsonism: Aetiology and Treatment. *London
    Clin. Med. J.*, 5:41-49.

    The occurrence of Parkinsonism following acute CO poisoning can occur
    within 2 to 3 weeks of the poisoning. In a few cases there has been
    an interval of months, even up to a year or more before Parkinsonism

developed. Although the condition may become worse for some months, progressive deterioration over a number of years does not usually take place.

Tissue and Blood Chemistry (58-62)

58. Blackmore D.J. (1970). Distribution of HbCO in human erythrocytes following inhalation of CO. *Nature (London)*, 227(5256):386.

Following inhalation of CO only erythrocytes exposed to the gas in the lungs were carboxylated and COHb was not redistributed between erythrocytes during circulation. The hypoxic insult to individual erythrocytes wasn't related to the COHb saturation as determined on whole blood.

59. Heistad, D.D., and Wheeler, R.C. (1972). Effect of carbon monoxide on reflex vasoconstriction in man. *J. Appl. Physiol.*, 32(1):7-11.

Testing at levels of COHb of 4% (control), 19% and 25% showed that the hypoxia induced by CO causes an inhibition of reflex vasoconstrictor responses despite the presence of normal arterial oxygen tension.

60. Parving, H.H. (1972). The effect of hypoxia and carbon monoxide exposure on plasma volume and capillary permeability to albumin. *Scand. J. Clin. Lab. Invest.*, 30:49-56.

The transcapillary escape rate for albumin increased significantly during 3 to 5 hours exposure to CO. It is suggested that CO exposure causes increased capillary permeability to protein. No change in the plasma volume was found during CO exposure.

61. Schmitt, F.O., and Scott, M.G. (1934). The effect of carbon monoxide on tissue respiration. *Amer. J. Physiol.*, 107:85-93.

Carbon monoxide containing 21% O_2 produces definite accelerations of oxygen consumption with skeletal muscle, stomach, liver, spleen and

particularly with heart muscle, while at lower O_2 concentrations CO produces inhibition in all the tissues studied with the exception of liver, heart, and skeletal muscle. It seems that the catalyst of CO combination is light sensitive, and illumination causes partial recovery of respiration of CO-poisone tissues.

62. Woodruff, R.S. (1960). Carbon monoxide poisoning. *Med. Sci.*, 7:550.

A woman 5 months pregnant died of asphyxiation by CO. Her blood showed 65% COHb, while heart blood obtained from her fetus showed 40% COHb. It is evident that CO crosses the placenta readily.

Visual Effects (63)

63. Hosko, M.J. (1970). The effect of carbon monoxide on the visually evoked response in man. *Arch. Environ. Health*, 21:174-180.

Humans were exposed to varying amounts of CO. Carboxyhemoglobin levels above 20% produced changes in the visually evoked response similar to those described in animals. Carboxyhemoglobin levels up to 33% did not alter gross spontaneous electroencephalographic activity.

CHRONIC CONCENTRATION EFFECTS ON HUMAN HEALTH (64-199)

Air Quality Standards (64-71)

64. Anonymous (1970). *Air Quality Criteria For Carbon Monoxide*. Public
    Health Service, National Air Pollution Control Admin., Washington,
    D.C., U.S. Govt. Printing Office. 158 pp.

    Exposure of nonsmokers to 30 ppm of CO for 8-12 hours gives an equili-
    brium value of 5% COHb while 20 ppm gives 3.7% and 10 ppm gives 2%.
    Exposure to 50 ppm for 90 minutes, or 10-15 ppm for 3 hours results in
    impairment in time-interval discrimination and exposure to 30 ppm for
    8 or more hours can lead to impaired performance on other psychomotor
    tests and an impairment in visual acuity. Exposure above 30 ppm for 8
    or more hours produces physiologic stress in heart patients.

65. Council for the Living Environment (Japan), Committee on Carbon Monoxide
    Environmental Standard (1972A). Measurements of air pollution by
    carbon monoxide and its effects on the human body. *I. Taiki Osen
    Kenkyo (J. Japan Soc. Air Pollution)*, 7(4):671-694. (Japanese).

    Effects from exposure to CO include anemia, nausea, increase of COHb,
    damage to the nervous and circulatory systems, deterioration of brain
    function, anoxia, headache, fatigue, numbness, palpitation, and breathing
    difficulty. Sex and age of the patients, exposure duration, degree of
    coma, degree of atelectasis, congestion of air passages, constriction
    noted by decerebrization examination, body temperatures, survival time,
    direct cause of deaths, and other symptoms of CO poisoning are presented.

66. Council for the Living Environment (Japan), Committee on Carbon Monoxide
    Environmental Standard (1972B). Measurements of air pollution by
    carbon monoxide and its effects on the human body. *II. Taiki Osen
    Kenkyo (J. Japan Soc. Air Pollution)*, 7(4):695-743. (Japanese).

    The average COHb for people in polluted and nonpolluted areas was 4.27%
    and 2.79%, respectively. There was a correlation between COHb in blood

and CO concentration in the air. More than half the policemen in auto-
mobiles had above 10% COHb, and more than half of them on motorcycles
had above 20%. All showed higher levels in the winter.

67. Dinman, B.D. (1973). Discussion of papers of Drs. Bartlett and Horvath.
Presented at Conference on Health Effects of Air Pollutants, Assem-
bly of Life Sciences, National Academy of Sciences, National Research
Council, October 3, 4, and 5, 1973.

In setting an air quality standard we must decide what is the cutoff
level. If we make it low enough to protect patients with continuous
angina at rest, there may be "no threshold." Those with this condition
equal 0.02% of our population. So, what segment of the population are
we to protect, how much will this protection cost, and does this invest-
ment represent an optimal use of finite resources? To answer these
questions we must apply a cost benefit analysis.

68. Grut, A.; Astrup, P.; Challen P.J. R., and Gerhardsson, G. (1970).
Threshold limit values for carbon monoxide. *Arch. Environ. Health,*
21:542-544.

A COHb level of 13% may provide an increase in vascular permeability,
15% may enhance cholesterol uptake in intima and changes resembling
arteriosclerosis. The criteria for the threshold limit value should
not include subjective symptoms symptoms caused by fatigue or by
conditions outside the workplace alone. It should be below 13% COHb,
i.e. 50 ppm. (8% to 10% COHb in nonsmokers).

69. National Academy of Sciences, Committee on Motor Vehicle Emissions,
prepared by the Panel on Emission Standards (1973). *A critique
of the 1975 Federal Automobile Emission Standard for Carbon
Monoxide,* Washington, D.C., U.S. Govt. Printing Office. 60 pp.

A discussion of CO in the ambient air is presented. A method of com-
puting emission standards is shown and the calculations done, giving

an acceptable emissions limit for CO for 1975 three times as high as
that promulgated by EPA for 1975 vehicles. Appendix A is a summary
of the health effects.

70. Ryazanov, V.A. (1964). New data on limits of allowable atmospheric
         air pollutants. IN. Levine, B.S. (translator and editor): *U.S.S.R.*
         Literature on Air Pollution and Related Occupational Diseases. A
         Survey. U.S. Dept. of Commerce, CTS 64-11574, Washington, D.C.,
         Vol. 9, 1964, pp. 1-8.

Results show that 20 mg/m^3 CO had no effect on the reflex reaction of
brain biocurrents either directly or through the formation of condi-
tioned electrocardial reflexes. The maximal allowable single concen-
tration for CO when inhaled for a brief period of time had no effect
on humans. The average 24 hours concentration limit was lowered to
1 mg/m^3, retaining the previously adopted 6 mg/m^3 value as the limit
of allowable single CO concentration.

71. Vol'fson, Z.G. (1952). Limits of allowable concentration of carbon
         monoxide in atmospheric air. IN: Levine, B.S. (translator) and
         Ryazanova, V.A. (editor): *Limits of Allowable Concentrations of*
         Atmospheric Pollutants. U.S. Office of Technical Services,
         Washington, D.C., Book 1, 1952, pp. 56-64. OTS 59 21173.

The U.S.S.R. literature on CO is reviewed in this paper. Maximum
levels at which disturbances in the central nervous system are noticeable
are considered to be 20 to 30 mg/m^3 of CO. The population surveyed con-
sisted of children, the aged, sick, and generally feeble persons. The
maximal allowable limit of average CO concentration was recommended not
to exceed 2 mg/m^3 with the maximal single concentration of CO not to ex-
ceed 6 mg/m^3.

Behavioral Impairment (72-104)

72. Attwood, D.A. (1972). *The Use of a Secondary Task Paradigm to Determine the Effect of Elevated Levels of Carboxyhemoglobin on Human Psychomotor Performance.* Ohio State Univ., Columbus, Dept. of Industrial Engineering, Thesis (Ph.D.), Ann Arbor, Mich., Univ. Microfilms, Inc., 385 pp.

   Highway driving experiments were conducted concurrently with laboratory experiments and employed the same set of subjects. Studied were effects of CO intoxication on dual task performance, effects of CO on after-driving performance, eye movements, and human information-processing, and the relative effects of alcohol and CO intoxication on dual task performance. A summary of all test results with a general discussion of the results is included.

73. Baretta, E.E., *et al.* (1972). What's new with man's oldest poison? *Proc. Am. Petrol. Inst., Div. Refining,* Vol. 52:121. (Presented at the American Petroleum Institute, Division of Refining, Midyear Meeting, 37th, New York, May 8-11, 1972.

   Subjects were exposed to varying amounts of CO for periods sufficient to produce COHb saturation of 2-23%. Performance wasn't impaired below 12% COHb. COHb above 15-20% resulted in delayed headaches, changes in the visually evoked response, prolongation of reaction time, and impairment of manual coordination. Exposure to CO had no effect on time discrimination tests.

74. Bartlett, D., Jr. (1973). Effects of carbon monoxide on human physiological processes. Presented at Conference on Health Effects of Air Pollutants, Assembly of Life Sciences, National Academy of Sciences - National Research Council, October 3, 4, and 5, 1973.

   The uptake half-time for CO is about 2 hours. Adverse effects of CO on patients with angina pectoris have been shown and possibly, low

concentrations of CO affects fetal development. Carbon monoxide uptake
results in chemoreceptor stimulation and a decrease in the maximal rate
of O_2 consumption during heavy exercise, there being no evidence of a
threshold CO concentration below which the.e are no effects. The
question is not how low a concentration we must achieve to avoid impair-
ment, but rather how much impairment we are willing to tolerate.

75. Beard, R.R. (1969). Toxicological appraisal of carbon monoxide. *J. Air
    Poll. Control Assoc.*, 19:722-727.

    This is a critique of a Technical Report on Air Quality Criteria for
    Carbon Monoxide prepared by J.R. Goldsmith. The findings of this report
    are presented, including effects in the 1-5% and 5-10% COHb ranges. This
    paper summarizes the information gathered on low-level effects of CO up
    to 1969.

76. Beard, R.R., and Grandstaff, N.W. (1972). Carbon monoxide and human
    functions. Presented at the Fifth Rochester International Con-
    ference on Environmental Toxicology: Behavioral Toxicology. June
    7-9, 1972. (Unpublished).

    The effects of low levels of CO upon several cerebral functions in man,
    including perception, discrimination, memory, and complex cognitive pro -
    cesses was examined. Carbon monoxide produced a reduction in vigilance
    and an effect in performance on a task incorporating estimation of time
    and motion together, whereas a complex problem-solving test showed only
    marginal impairment. Spatial perception, digit span, and arithmetic
    performances were not consistently nor reliably altered.

77. Beard, R.R., and Wertheim, G.A. (1967). Behavioral impairment asso-
    ciated with small doses of carbon monoxide. *Amer. J. Pub. Health*,
    57:2012-2022.

    The effects of exposure to CO upon the ability to discriminate short
    intervals of time were studied. Degradation of performance was shown

after 90 minutes at 50 ppm, and at proportionately shorter times after exposure to higher levels up to 250 ppm.

78. Beard, R.R., and Wertheim, G.A. (1970B). Behavioral manifestation of carbon monoxide adsorption. *XVI Int. Cong. Occup. Health*, pp. 224-226.

Tests were conducted to determine the effect of low levels of CO on discrimination of short time intervals. The results show a degradation of discrimination as the CO concentration increases without any bottom threshold values.

79. Beck, H.G. (1937). Chronic CO anoxemia: Clinical syndromes. *Southern Med. J.*, 30:824-829.

This paper considers the more remote effects of acute CO poisoning and the effects of chronic poisoning produced by frequent and prolonged periods of exposure to sublethal amounts and describes the characteristic syndromes.

80. Beck, H.G. (1927). The clinical manifestations of chronic carbon monoxide poisoning. *Ann. Clin. Med.*, 5:1088-1096.

Severe chronic CO poisoning shows symptoms such as headaches, dizziness, muscular weakness, disturbances of gait, parasthesia, breathlessness on exertion, and nervous and emotional instability. The severity and clinical course of these symptoms depend upon the concentration of CO, frequency and duration of exposure, temperature and humidity, physical exertion, health of the individual, admixture of other poisonous gases and individual susceptibility.

81. Bjerver, K., and Goldberg, L. (1948). Alcohol tolerance in individuals with chronic producer-gas intoxication. *Quart. J. Stud. Alcohol*, 9:329-351.

The tolerance to alcohol in patients with chronic CO intoxication was the same as in healthy control subjects. No difference was found between the patients and the control subjects either in regard to the blood alcohol curve or in regard to alcohol tolerance.

82. Dubois, A.B. (1969). *Effects of Chronic Exposure to Low Levels of Carbon Monoxide on Human Health, Behavior, and Performance.* National Academy of Sciences, National Academy of Engineering, Washington, D.C., 66 pp.

Conclusions include: the importance of CO in the ambient air lies mainly in its ability to combine with hemoglobin (Hb), preventing that portion from combining with oxygen; the background level of COHB is about 0.4%, decreased mental function was shown at a level as low as 2% COHb above the background, and no threshold below which no effects occurred was found; adaptation to increased CO levels may occur through such things as increased Hb concentration in the blood, increased cardiac output, possibly increased capillary blood volume and perhaps slightly increased volume of pulmonary ventilation with these adaptive mechanisms themselves increasing the burden on physical reserves; people with some pre-existing medical conditions are more susceptible to the effects of increased CO levels, in particular when the condition involved an already reduced level of oxygen in the body; in persons with a cardiovascular condition the CO levels may result in a reduction of the oxygen delivered to the heart; exposures to low levels of CO are innocuous until the blood COHb level has been raised appreciably; and the CO present in cigarette smoke could theoretically by itself produce adverse health effects. Also discussed are tissue hypoxia, electroencephalographic data, other behavioral aspects, and epidemiological studies.

83. Goldsmith, J.F., and Landaw, S.A. (1968). Carbon monoxide and human health. *Science,* 162:1352-1359.

Frequent low CO exposure impairs accurate estimation of time intervals
as well as the performance of more complex psychomotor tests. Data
shows higher levels of COHb in drivers involved in accidents than in
policemen and other occupationally exposed subjects. In Los Angeles,
an association of CO pollution and case fatality rates in patients with
myocardial infarction has been shown.

84. Groll-Kanpp, E.; Wagner, H.; Havck, H.; and Haider, M. (1972). The action
    of low carbon monoxide concentrations on the alertness and computer-
    analyzed brain potential. Staub, *Reinhaltung Luft*, 32(4):186-188.
    Presented at the VDI (Verein Deutscher Ingenievre) Clean Air Mainte-
    nance Committee, Carbon Monoxide Symposium, Düsseldorf, West Germany,
    October 28-29, 1971 (German).

The effects of different CO levels on human brain function were studied
in an acoustic vigilance test. The impairment in performance was parti-
cularly high during the second half of the test period and was accele-
rated by the CO effect. Significant impairment of vigilance due to CO
occurred even in a concentration of 50 ppm.

85. Hanks, T.G. (1970). Human performance of a psychomotor test as a
    function of exposure to carbon monoxide. *Ann. N.Y. Acad. Sci.*,
    174:421-424.

No effect on performance of a critical tracking task, which is partly
a measure of driving ability, attributable to CO exposure was found.
An empirical relationship between pulmonary CO and blood COHb values
was observed, which is expressed as: % COHb = 0.146 x (observed pul-
monary CO level).

86. Hattori, H. (1971). Effects of air pollution on humans. Ryusan *(J.*
    Sulphuric Acid Assoc., Tokyo), 24(7):13-25. (Japanese).

Relationships between pollutant concentrations and specific symptoms
of health damages are reviewed with regard to CO. For CO the minimum

measurability by human reaction is 1 ppm, with exposure to 50 ppm for 45-90 minutes causing decrease in awareness of time, and the initial sign of influence on nerve centers occurring at 4-6 hours of exposure to 30 ppm or at 1 hour of exposure to 120 ppm.

87. Horvath, S.M. (1973). Effects of carbon monoxide on human behavior. Presented at Conference on Health Effects of Air Pollutants, Assembly of Life Sciences, National Academy of Sciences National Research Council, October 3, 4, and 5, 1973.

Affected at as low as 5% COHb are visual thresholds, ability to perform arithmetic problems, t-crossings, discrimination of forms and color, and judgment of short time intervals. Some have found several effects at low concentrations and others have not found any, the effects of CO on performance seeming to be most severe when individuals are already required to resist monotony's stressful effects.

88. Horvath, S.M.; Dahms, T.E.; and O'Hanlon, J.F. (1971). Carbon monoxide and human vigilance. *Arch. Environ. Health*, 23:343-347.

This study was conducted to determine whether CO causes deterioration of vigilance. Results showed that vigilance was impaired by breathing 111 ppm CO which raised the COHb level to 6.6%. Heart rates and minute ventilatory volumes were not affected.

89. Luederitz, P. (1972). The confirmable effects of carbon monoxide on the human organism. *Z. Ges. Hyg. Ihre Grenzgebiete (Berlin)*, 18(12):898-903. (German).

The inhaled quantity of CO depends on the emission concentration, on the duration of stay in the polluted atmosphere, and on the air quantity inhaled during this stay. A clear separation from the symptoms caused by stress isn't possible since physiological and psychological tests will determine changes but not causes. The only method for preventing effects on humans is the limiting of emissions.

90. McFarland, R.A. (1973). Low level exposure to carbon monoxide and
     driving performance. *Arch. Environ. Health*, 27:355-359.

Results indicate that 6% COHb has no effect on driving ability, and
that 11% and 17% do not appear to affect seriously this ability, as
measured by the tests in this study. However, certain significant
differences were found in some of the tests that suggest some decre-
ment in performance due to CO exposure.

91. McFarland, R.A. (1972). Low level exposure to CO and driving perfor-
     mance. *Preprint, American Medical Assoc.*, Chicago, Ill., 23 pp.
     (Presented at the Air Pollution Medical Research Conference,
     Chicago, Ill., October 2-3, 1972).

The finding that significantly more visual stimuli located 20 degrees
away from the center of fixation were not perceived in brief exposure
under 17% COHb, along with a progressive increase from the 0 through
11 to 17% levels, supports the hypothesis that CO adversely affects the
perception of stimuli in the peripheral field of view.

92. Mikulka, P.; O'Donnell, R.; Heinig, P.; and Theodore, J. (1970). The
     effect of carbon monoxide on human performance *Ann. N.Y. Acad.
     Sci.*, 174:409-420.

Results in this study indicate that 3 hours of exposure to 125 ppm CO
produce no effect in functioning, and, possibly, 200-250 ppm will pro-
duce no observable effect. Other studies reporting effects may attri-
bute such effects to sensory restriction effects. Most test exposures
are brief, however, and possibly prolonged exposures to equivalent COHb
levels may have very different effects on behavior.

93. O'Donnell, R.D.; Chikos, P.; and Theodore, J (1971A). Effect of carbon
     monoxide exposure on human sleep and psychomotor performance. *J.
     Appl. Physiol.*, 31(4):513-518.

After subjects were exposed to CO while asleep, no performance decrements from control conditions were found in any tests used. Although certain CO effects occur in sleep, these are not great enough to affect performance and that for healthy well-motivated umans these levels of CO don't produce decrements in the tests used.

94. O'Donnell, R.D. (1971). Recent research into the effects of low level carbon monoxide exposure on psychomotor performance in healthy humans. Inst. of Environmental Sciences, Mt. Prospect, Ill. *Proc. Inst. Environ. Sci. Ann. Tech. Meet.*, 17th, Los Angeles, Calif., pp. 266-269.

No degradation in psychomotor performance was observed, nor was there any major change in sleep patterns. Mean COHb levels ranged from 3-12%. Although the results can't be applied unequivocally to community standards, they indicate that a normal person can tolerate exposure to 50 ppm for 8 hours without disrupting psychomotor functions.

95. Pfrender, R.E. (1962). Chronic carbon monoxide poisoning. A critical resume. *Indust. Med. & Surg.*, 31:99-103.

Carbon monoxide combinations with other substances, pathological effects attributable to CO per se, and the nature and extent of adaptation to the gas are discussed. Pertinent literature is reviewed.

96. Ramsey, J.M. (1972). Carbon monoxide, tissue hypoxia, and sensory psychomotor response in hypoxaemic subjects. *Clin. Sci.*, 42(5): 619-625.

Anemic patients and those with emphysema were compared with normal subjects in respect to CO uptake and venous oxygen content. Patients with emphysema had a smaller increase in COHb and a smaller decrease in O_2 content than the others. All showed a significant diminution in reaction speed to a visual stimulus, but no significant changes in depth perception and brightness discrimination.

97. Ramsey, J.M. (1970). Oxygen reduction and reaction time in hypoxic and normal drivers. *Arch. Environ. Health*, 20:597-601.

Thirty young and thirty older, presumably hypoxic, drivers were exposed to an average of 38.1 ppm for 90 minutes while commuting. Correlation of both CO exposure with O_2 reduction and of O_2 reduction and time-solving were significant. In both groups, drivers were slower in reac-

98 Ray, A.M., and Rockwell, T.H. (1970). An exploratory study of automobile driving performance under the influence of low levels of carboxyhemo-globin. *Ann. N.Y. Acad. Sci.*, 174:369-408.

It is estimated that CO highway levels result in 8% of the nonsmoking drivers having above 7% COHb and 4% having above 14% COHb, assuming 2 or more hours exposure. This is supported by blood samples from accident victims. This study shows effects below 10% COHb, several effects being detrimental to driving performance. What levels of performance decrements are dangerous and what required preventive measures of action should be decided.

99. Sayers, R.R.; Meriwether, F.V.; and Yant, W.P. (1922). Physiological effects of exposure to low concentrations of carbon monoxide. *Pub. Health Rep.*, 37:1126-1142.

The combination of CO with Hb occurs slowly when the subject is exposed to low levels and remains at rest, with many hours needed to reach equilibrium. The rate of combination of CO with Hb occurs much faster during the first hour of exposure than during any succeeding hour. High temperature and humidity and strenuous exercise all cause much more rapid combination of CO with Hb than occurs during normal resting condition.

100. Schlipkoeter, H. (1972). Conclusions. *Staub, Reinhaltung Luft*, 32(4): 193-194. Presented at the VDI (Verein Deutscher Ingenievre) Clean Air Maintenance Committee, Carbon Monoxide Symposium, Düsseldorf, West Germany, October 28-29, 1971. (German).

Carbon monoxide effects are not due just to O_2 deficiency; inhibition of tissue enzyme activity is probable. Effects of CO are best evaluated from COHb content which is dependent on concentration, exposure time, tidal volume, and barometric pressure. Maximum allowable concentrations, based on the results in this study and applying a safety factor of five, are 6 ppm (8-hour mean) and 30 ppm (1-hour mean).

101. Stewart, R.D.; Newton, P.E.; Hosko, M.J.: and Peterson, J.E. (1973). Effect of carbon monoxide on time perception. *Arch. Environ. Health*, 27:155-160.

Volunteers were exposed to varying levels of CO for periods up to 5 hours in length to determine the effect on time perception. These exposures, which gave COHb saturations up to 20%, produced no impairment in the ability to perform a time discrimination test, to estimate 10- to 30-second intervals or to perform a time estimation test.

102. Von Post-Lingen, M.L. (1964). The significance of exposure to small concentrations of carbon monoxide. Results of an experimental study on healthy persons. *Proc. Royal Soc. Med.*, 57 (Part II): 1021-1029.

The results of tests showed that: daily inhalation of CO for 4 weeks producing 10-11% COHb gave rise to a cumulative effect which was manifested as latent impairment of the ability to distinguish between light flashes in rapid succession; daily inhalation of CO producing 6-7% or 10% COHb caused increases of sensitivity in some persons and reduction in others, the increased sensitivity subsiding during the following months. These changes in sensitivity were more pronounced when the daily tests gave 6-7% COHb for 8 weeks than when 10-11% was given for 4 weeks.

103. Winneke, G.; Groll-Knapp, E.; and Kastka, J. (1973). Experiences with psychomotor and sensory effect criteria within the framework of

air hygiene research. *Proc. Int. Clean Air Congr., 3rd,* Düsseldorf, West Germany, 1973, p. A31-A35. (German).

A COHb level of up to 10% didn't cause any major changes in the results of the flicker fusion test and aaoustic vigilance test, while a linear statistically secured dose-effect relationship between the CO concentration and the expectation potential was observed. Substances with hypoxic action, such as CO, seem to affect mainly information processing.

104. Wright, G.; Randell, P.; and Shephard, R.J. (1973). Carbon monoxide and driving skills. *Arch. Environ. Health,* 27:349-354.

Carboxyhemoglobin was increased by 3.4% in persons receiving CO. Brake reaction time, night vision, glare vision, glare recovery, hand-steadiness, and depth perception all showed a small amount of deterioration, while during operation of a driving simulator this group showed a significant deficit in "careful driving" skills. Thus there is a need to revise the permitted 8-hour industrial CO level of 50 ppm.

Cardiac Impairment (105-112)

105. Anderson, E., *et al.* (1973). Effect of low-level carbon monoxide exposure on onset and duration of angina pectoris. A study in the patients with ischemic heart disease. *Ann. Internal Med.,* 79(1):46-50.

After exposures of patients with stable angine pectoris to CO, tests were run at COHb levels of 1.3% (control), 2.9% (50 ppm CO), and 4.5% (100 ppm CO). Mean duration of exercise before onset of pain was shortened at both 2.9 and 4.5%, while the duration of pain was prolonged at 4.5%, but not at 2.9% COHb. The electrocardiograms showed worsening of ST-segment changes, with earlier onset and longer duration of ST-segment depresssion.

106. Aronow, W.S., and Isbell H.W. (1973). Carbon monoxide effect on exercise-induced angina pectoris. *Ann. Internal Med.*, 79(3):392-395.

Patients with angina pectoris exercised until they developed angina before and after breathing 50 ppm CO or purified air. Two-hour exposures to 50 ppm CO induced angina sooner, and significant decreases at angina onset were noted for systolic blood pressure and heart rate.

107. Aronow W.S., *et al.* (1972). Effect of freeway travel on angina pectoris. *Ann. Internal Med.*, 77:669-676.

Patients with angina were tested after being driven for 90 minutes during heavy freeway traffic. These patients were also tested after breathing purified air during freeway traffic. There was a decrease in the amount of exercise performed before onset of angina, in systolic blood pressure at angina, in heart rate at angina, and in the forced expiratory volume in one-second/forced vital capacity after breathing freeway air.

108. Astrup, P. (1972). Some physiological and pathological effects of moderate carbon monoxide exposure. *Brit. Med. J.* 4:447-452.

Carbon monoxide hastens the development of arteriosclerosis and has a damaging effect on the myocardium. Low levels of COHb in pregnant rabbits have a profound influence on fetal development and studies of pregnancy in smokers indicates a similar effect for humans. These effects should be acknowledged when discussing air pollution and threshold limit values for CO.

109. Ayres, S.M., *et al.* (1969). Systemic and myocardial hemodynamic responses to relatively small concentrations of carboxyhemoglobin (COHb). *Arch. Environ. Health*, 18:699-709.

Measurements were made before and after elevation of COHb to 8.96%. Venous oxygen tension decreased and significant increases in minute ventilation, cardiac output peripheral oxygen extraction, oxygen

consumption, and the alveolar-arterial oxygen difference were observed. Coronary blood flow increased and extraction ratios for oxygen, lactate, and pyruvate decreased.

110. Ayres, S.M., *et al.* (1970). Myocardial and systematic responses to carboxyhemoglobin. *Ann. N.Y. Acad. Sci.*, 174:268-293.

Five or 0.1% CO were administered to humans. Arterial and mixed venous oxygen tensions were decreased by both levels with changes identifiable at COHb levels below 5%. Cardiac output and minute ventilation increased when COHb was elevated by breathing 5% CO, and the coronary arteriovenous oxygen difference was uniformly decreased and coronary blood flow increased when COHb was raised to 5-10% saturation. Significant changes were seen in heart patients with COHb above 6%.

111. Cohen, S.I.; Deane, M.; and Goldsmith, J.R. (1969). Carbon monoxide and survival from myocardial infarction. *Arch. Environ. Health*, 19:510-517.

This report studied case fatality rates for patients admitted with myocardial infarction (MI) to 35 Los Angeles hospitals during 1958. The results indicate that there is an increased MI case fatality in "high" CO pollution areas; this difference is only evident during periods of relatively increased CO pollution.

112. Gokina, N.S. (1971). Myocardial contractile function in workers exposed to prolonged action of small carbon monoxide concentration. *Vrachebnoe Delo (Kiev)*, 8:130-132. (Russian).

Two groups, one exposed to CO levels of 11 to 78 mg/m^3 (9.6 to 68.2 ppm), and the other subjected to no CO, were tested. An increase in the isometric contraction 15 minutes after nitroglycerine intake in those exposed for less than 5 years to CO, indicates a decrease in the contractile capacity of the myocardium. Alterations of the left ventricle systolic phases in those exposed for more than 11 years show the noxious effect of CO upon myocardial contractile capacity.

Etiological and Epidemiological Studies (113-121)

113. Ayres, S.M., *et al.* (1973). Health effects of exposure to high concentrations of automobile emissions. *Arch. Environ. Health*, 27:168-178.

Tests were performed on bridge and tunnel personnel. Carbon monoxide in the working environment averaged 63 ppm with a maximum hourly concentration of 217 ppm. A high percentage had symptoms suggestive of chronic bronchitis; airway resistance was elevated in one-third; and almost all workers had an increase in closing volume, suggesting small airway disease.

114. Fiandaca, S., and Vercellotti. E. (1964). Effects on the sick and accident rates in subjects exposed to the risk of chronic carbon monoxide poisoning. *Rass. Med. Indust.*, 33:360-379.

A survey was made of the sickness and accident rate in workers exposed to chronic CO poisoning. The increased accident rate found was probably due to the high COHb level. A direct relationship may be found in the sickness increases and in the short indispositions identified in subjective symptomatology, these being due to sudden increased environmental CO levels, along with cigarette smoke.

115. Ford, B. (1971). Poisons in the air: What they can do to you. *Sci. Digest*, 70(3):73-78, 85.

The type of studies on which the CO standards are based are examined. More heart patients admitted to Los Angeles hospitals in more polluted areas during a high CO pollution period died from myocardial infarction than patients admitted during a lower CO period.

116. Goldsmith, J.R., and Cohen, S.I. (1969). Epidemiological bases for possible air quality criteria for carbon monoxide. *J. Air Poll. Control Admin.*, 19:704-713.

Epidemiological studies have looked at 3 possible effects: a persistent
toxic reaction (evidence insufficient), the contribution of CO to
mortality of persons hospitalized with myocardial infarction (good
correlation with daily CO levels above 10 ppm), and the possibility
of drivers involved in accidents having high COHb levels (good evidence).
As little as 2% COHb can impair driving performance.

117. Hexter, A.C., and Goldsmith, J.R. (1971). Carbon monoxide: association
       of community air pollution with mortality. *Science*, 172:265-267.

Regression analysis of daily mortality in Los Angeles County shows a
significant association between community CO levels and mortality.
Cyclic variation and maximum temperature were the main contributors.

118. Katz, M. (1958). Carbon monoxide asphyxia, a common clinical entity.
       Canadian Med. Assoc. J., 78:182-185.

Forty-one cases of chronic CO poisoning are reviewed, with symptoms of
headache, anorexia, dyspepsia, weakness, and dizziness, singly or in
combination. The finding of a COHb level of 10% or more plus relief
of symptoms when the patient is removed from exposure confirms the
diagnosis.

119. Nagaoka, S. (1971). Environmental polluton vs. health. *Tokyo - to
       Kogai Kenkyusho Nenpo. (Ann. Dept. Tokyo Met. Res. Inst. Environ.
       Prot.)*, 2:301-307. (Japanese).

An epidemiological study was conducted to investigate the health
effects of CO. The CO in the subjects' breath and ambient CO levels
were measured. Relationships between CO in breath and number of years
employed, the mileage driven the preceding day, or the mileage driven
during the day of examination were analyzed.

120. Savicevic, M.; Millijic, B.; and Stankovic, M. (1959). Contribution
       to the study of chronic intoxication with carbon monoxide. *Acta
       Med. Iugosl. (Belgrade)*, 13:129-137. (Yugoslavian).

Symptoms of chronic CO intoxication are: above 0.75% CO in the blood
along with at least 50 ppm in the air, not yet fully developed encep-
phalitic signs, and the presence of the cephalic triad asthenia, vertigo
and syndrome of neurovegetative dystonia. People sporadically exposed
to CO are much more sensitive to further exposure than were the normal,
healthy individuals.

121. Stevens, A.M. (1926). Carbon monoxide poisoning. Gradual, cumulative
effects in young children with report of a fatal case. *J.A.M.A.*,
86:1201-1204.

There is a cumulative poisonous effect of repeated or continuous expo-
sure to low CO levels, with young children and infants particularly
susceptible. In serious cases there is usually more than 10% COHb in
the blood; this level is detectable by a simple and rapid qualitative
test.

Nervous System Effects (122-127)

122. Beard, R.R., and Grandstaff, N. (1970A). Carbon monoxide exposure
and cerebral function. *Ann. N.Y. Acad. Sci.*, 174:385-395.

The observed effects of CO on cerebral function have been variable, so
no conclusions can be drawn about an absolute CO threshold for these
effects. Different environments can modify behavioral patterns just
as do sizable amounts of CO, and attention must be given to details
of tests in order to obtain reproducable results.

123. Gilinskiy, V.A., *et al.* (1963). The effect of low concentrations of
carbon monoxide on man in pressurized cabins of passenger planes.
IN: Parin, V.V., (ed.) *Aviation and Space Medicine*, Moscow NASA
Technical Translation TT-F-228.

Pressure chamber tests and in-flight observations both showed that 3
hours' exposure (0.01 mg/liter or more) had adverse effects on several

organs and systems, namely: higher nervous activity, functions of the visual and vestibular analyzers, metabolic processes, cardiovascular system, muscular strength, tissue respiration, and leukopoiesis. It is suggested that the maximum permissible level of CO in presssurized passenger airplane cabins be 0.01 mg/liter.

124. Goldsmith, J.R. (1970A). Carbon monoxide research - recent and remote. *Arch. Environ. Health*, 21:118-120.

This is an editorial comment on recent meetings and research   There is a need to reevaluate the role of CO exposures on heart and central nervous system functions.

125. Grudzinska, B. (1963). Electroencephalographic patterns in cases of chronic exposure to CO in air. *Folia Medica Cracoviensia*, 3:493-515.

It was found that chronic exposure to low CO levels doesn't cause distinct changes in the nervous system, but may have a certain inhibitory effect on the bioelectric activity of the brain, manifested clinically as neurasthenia and in the EEG as scanty low-voltage alpha rhythm and tracings of the first sleep phases.

126. Kovnatskyy, M.A. (1961). Clinical study of chronic intoxication with carbon monoxide. *Gigiena Truda Professional Zabolevaniia (Moscow)*, 5:25-30. (Russian).

Experimental data and clinical observations prove that prolonged CO exposure may lead to chronic intoxication. Symptomatology of chronic intoxication, early manifestations of the poisoning, and curative-preventive measures are listed, with special attention to the changes in the nervous and the cardiovascular systems.

127. Schulte, J.H. (1963). Effects of mild carbon monoxide intoxication. *Arch. Environ. Health*, 7:524-537.

The exposure to 100 ppm CO for varying periods of time produced impairment of function earliest in the higher centers of the central nervous system which control some of the cognitive and psychomotor abilities. Impairment is detectable below 5% COHb, and the degree of impairment increases as the COHb level increases.

Occupational and Community Exposures (128-152)

128. Canella, D.J. (1973). Pb and CO effects on office personnel of narrow streets with intensive traffic. *Proc. Int. Clean Air Congr., 3rd., Düsseldorf, West Germany, pp. A56-A58.*

Results of analysis of lead, CO, and COHb from indoor environments and personnel in offices on narrow streets with heavy traffic differed greatly, with the exception of values found for one location. The concentration decreased as collecting time increased, and no reasonable explanation was found for this fact.

129. Cohen, S.I.; Dorion, G.; Goldsmith, J.R.; and Permutt, S. (1971). Carbon monoxide uptake by inspectors at a United States - Mexico border station. *Arch. Environ. Health, 22:47-54.*

After work shifts during which high ambient CO levels persisted, increases in COHb were noted in both smokers and nonsmokers among the border inspectors tested. The hazards of such COHb elevations are discussed in light of recent evidence of a lack of a threshold for cardiovascular and central nervous system effects.

130. Connolly, J.I.; Martinek, M.J.; and Aeberly, J.J. (1928). The carbon monoxide hazard in city streets. *Amer J. Pub. Health, 18:1375-1383*

The CO level in the air of city streets other than automobile boulevards is not a serious health hazard, but it can be one near the boulevards if

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exposure time is several hours. Idling of motors should be kept to a minimum as the tall buildings of the downtown areas concentrate CO in the areas of highest population density.

131. deBruin, A. (1967). Carboxyhemoglobin levels due to traffic exhaust. *Arch. Environ. Health*, 15:384-389.

In Rotterdam the COHb levels of policemen and traffic participants exposed to car exhaust increased from 0.93% to 1.11% (nonsmokers) as a result of traffic duty for 1-4 hours. Similar increases were noted in Amsterdam for various groups.

132. Emara, A.M.; Waquity, I.; El-Gendi, S.; and El-Samra, G.H. (1971). Carbon monoxide hazard in Cairo traffic. *J. Egypt Med. Assoc.*, 54(10):714-722.

Carbon monoxide was estimated in the air of 5 different zones of Cairo and its concentration was related to the nature of the traffic with regard to the streets, surroundings, and traffic load. Carboxyhemoglobin levels of traffic policemen were related to CO levels in the air, with the mode of exposure to exhaust also influencing COHb levels.

133. Gibbs, G.W.; Allard, D.; Gray, R.; and Corsillo, A. (1973). Carbon monoxide and nitrogen dioxide exposure of Montreal longshoremen. *Can. J. Public Health (Toronto)*, 64(2):147-153.

The COHb level of nonsmoking longshoremen working in the holds of ships rose from 0.6% to 2.0% (maximum - 5%) after two hours in the hold while smokers showed no demonstratable increase. Carbon monoxide levels occasionally exceeded 50 ppm and on one ship reached 300 ppm. On the basis of % COHb found and the present work routine, no serious hazard seemed to exist.

134. Goldsmith, J.R. (1970B). Contribution of motor vehicle exhaust, industry, and cigarette smoking to community carbon monoxide exposures. *Ann N.Y. Acad. Sci.*, 174:122-134.

This article contrasts the various forms of exposure, such as occupational, household, and community exposures to motor vehicle exhausts, with respect to the proportions of people affected, the magnitude of short- and long-term exposure in relation to the possibility of illness, and the time-course of exposure in relation to the possible hazards.

135. Gothe, C., *et al.* (1969). Carbon monoxide hazard in city traffic. *Arch. Environ. Health*, 19:310-314.

Carbon monoxide exposure in dense traffic was examined in policemen by analysis of the COHb in blood. Smokers' COHb decreased when their hours of traffic duty increased, due to decreased smoking. The increase of COHb levels in nonsmokers wasn't much higher than 1%.

136. Grut, A. (1949). *Chronic Carbon Monoxide Poisoning, A Study of Occupational Medicine*, Ejnar Munksgaard, Copenhagen, 229 pp. (Danish).

The following topics are discussed: CO exposure, chronic and acute CO poisoning, hyperthyroidism due to CO exposure, occupational exposures, susceptibility to CO, pathogenesis and pathological anatomy, and prophylaxis.

137. Jeeh, J. (1972). Carbon monoxide and its importance in the urban atmosphere. *Cesk, Hyg. (Prague)*, 17(2-3):93-99. (Czech).

The effect of CO on the human organism is governed by concentration, length of exposure, and volume of ventilated air. Most affected by CO are cardiacs, anemics, persons with metabolic defects and pulmonary diseases, and fetuses.

138. Kitamura, S.; Tsukamoto, T.; Sumino, K.; and Hirano, I. (1971). Carbon monoxide and lead contents in blood of clerks for collecting charges at toll road. *Nippon Koshu Eisei Zasshi (Japan. J. Public Health)*, 18(10):414. (Japanese).

The concentration of CO in the air was determined for toll facilities and COHb in the blood of nonsmoking clerks was analyzed. The CO was the same as that of a comparatively highly polluted city and the blood COHb did not indicate it to be a health hazard.

139. Luderitz, P. (1971). Experimental studies concerning the effect of carbon monoxide from the exhaust gas of vehicles on the physical condition of traffic policemen. *Z. Ges. Hyg. Ihre Grenzgebiete (Berlin)*, 17(9):645 646. (German).

Carbon monoxide exposed traffic policemen complained significantly more about headache, fatigue, sick feeling, and vomiting. Some damage of the central nervous system was found which was worse than that of smokers but reaction times showed no difference. Carbon monoxide is probably not the sole cause for the bad physical condition of traffic policemen.

140. Murayama, N. (1971). The effects of low-level exposure of carbon monoxide upon the health of traffic policemen. *Nippon Eiseigaku Zasshi (Japan. J. Hyg.)*, 26(1):145. Presented at the Japanese Society for Hygiene, annual meeting, 41st, Tokyo, Japan, April 3-4, 1971. (Japanese).

Carboxyhemoglobin, CO, and oxygen levels in expired air, pulmonary function, and subjective symptoms were tested in policemen. After work COHb levels were higher in policemen working outdoors with very high levels in traffic policemen and those working in police boxes.

141. Kuroya, H., *et al*. (1971). Some health survey results of underground garage workers. *Nippon Eiseigaku Zasshi (Japan. J. Hyg.)*, 26(1): 144. Presented at the Japanese Society for Hygiene, annual meeting, 41st, Tokyo, Japan, April 3-4, 1971. (Japanese).

Underground parking workers were examined with respect to pulmonary ventilation and COHb. The average CO in the parking area was 25-30 ppm. Some workers showed a reduction of vital capacity and the non-smokers averaged around 4.0% COHb.

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142. Prerovska, I., and Drdkova, S. (1971). Influence of chronic effects of carbon monoxide on clinical state and biological changes in the serum of exposed persons in view of precocious development of atherosclerosis. *Int. Arch. Arbeit med.*, 28:175-188. (German).

Workers exposed to CO levels producing COHb ranging from 2-26% were examined and did not show any deviations suggesting early development of atherosclerosis. A check 6 years later gave the same result. But in persons with sclerotic vessels the increase of anoxia due to exposure to CO might lead to more serious changes of the organs.

143. Ramsey, J.M. (1967). Carboxyhemoglobinemia in parking garage employes. *Arch. Environ. Health*, 15:580-583.

Carboxyhemoglobin increased dramatically in exposed parking garage workers (2.4 to 8.4% COHb) due to an average CO level of 58.9 ppm in the garage. Carbon monoxide was eliminated from the blood each night.

144. Ricci, C.; Capellaro F.; and Gaido, P.C. (1964). Electrophoretic and immuno-electrophoretic examinations in workers exposed to chronic carbon monoxide intoxication. *Rass. Med. Indust.*, 33:414-416.

The behavior of transferrin was examined with immunochemical methods in subjects exposed occupationally to CO. In all subjects an increase was noted in the globulin fraction (transferrin or siderophillin) of the serum regardless of the time of exposure.

145. Salas, F.N. (1971). Occurrence of carbon monoxide in the occupational environment: Medical aspect: Experiences of the author. *Ion. (Madrid)*, 31(355):66-72. (Spanish).

The present United States occupational standard is 50 ppm for an eight-hour average, while England and the Soviet Union have set limits at 58 and 20 mg/m^3 (51 and 17.5 ppm), respectively. The longer the CO exposure, the more enduring and irreversible the symptoms become.

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145. Sievers, R.F.; Edwards, T.I.; Murray, A.L.; and Schrenk, H.H. (1942). Effect of exposure to known concentrations of carbon monoxide. *J. Amer. Med. Assoc.*, 118:586-588.

Examination of a group of Holland Tunnel traffic officers exposed to an occupational CO level of 70 ppm for 13 years didn't reveal any evidence of injury to health attributable to CO exposure.

147. Szoelloesi, E.; Medve, F.; and Jeney, E. (1971). The effect of low carbon monoxide concentrations in the air on humans. Part II: Physical examination of workers in car repair and construction workshops. *Zentr. Arbeitsmed. Arbeitsschutz*, 21(3):69-74.

Blood pressure was 29% higher in smoking and nonsmoking auto mechanics exposed to CO. The COHb content in smokers increased 2.3% after exposure, while nonsmokers COHb increased 1.26%. Polycythemia and hyperchromia were very frequent.

148. Takemoto, Y., *et al.* (1973). Evaluation of the concentration of CO in the expired air: A case of groups of housewives in a city. *Nippon Koshu Eisei Zasshi (Japan. J. Public Health)*, 20(10), 1 pg. Presented at the Japan Society of Public Health, annual meeting, 32nd, October, 1973, paper 568. (Japanese).

Expired CO, vital capacity, peak flow, and hemoglobin were determined in a group of subjects. The CO showed no increase with age, hemoglobin, nor decreased respiratory function. The CO level in the room where the study was carried out correlated well with the expired air CO content.

149. Tomita, K.; Kawaraya, T.; and Haruki, K. (1972). Studies on carbon monoxide exposure by an analysis of expired air. *Osaka Shiritsu Daigaku Igaku Zasshi (The Journal of the Osaka City Medical Center)*, 21(4 6):173-186. (Japanese).

The CO in the expired air of inhabitants in polluted areas was 50 percent higher than that in non-polluted areas. The CO in expired air of

the following workers decreased in this order: underground parking workers, highway charge collectors, underground tunnel workers, loading and unloading workers, with traffic policemen having the lowest CO.

150. Tomita, K.; Kawaraya, T.; and Haruli, K. (1973). Studies on CO exposure among neighbors of urban traffic (Report 3). Effect of automobile exhaust upon the workers. *Nippon Koshu Eisei Zasshi (Japan. J. Public Health)*, 19(8):412-417. (Japanese).

Mean CO values in expired air of workmen were compared with those of school children (2.5 ppm). The values were four times higher in traffic policemen, five times in unloading workers six times in underground road workers, nine times in elevator operators at underground tunnels and highway toll collectors, and twelve times in underground parking workers.

151. Wilson, E.D.; Gates, I.; Owen H.R.; and Dawson, W.T. (1926). Street risk of carbon monoxide poisoning. *J. Amer. Med. Assoc.*, 87:319-320.

Policemen complained of headache, slight nausea and muscular weakness. Values from 0-30% COHb were found in 14 foot-traffic patrolmen, with 6 of them between 20 and 30%. There is a definite street risk of repeated or chronic slight CO anoxemia.

152. Zorn, H. (1964). On the diagnosis of chronic carbon monoxide poisoning. *Rass. Med. Indust.*, 33:325-329. (German).

Workmen exposed to low levels of CO over a long period showed an increase in the excitability and irritability to noises while the electro-encephalogram revealed a picture of extremely unstable frequency. The tests returned to normal when the CO exposure was stopped.

Tissue and Blood Chemistry (153-193)

153. Anonymous (1959). Chronic carbon monoxide poisoning. *New England J. Med.*, 261:1248-1249.

It is possible that some people are more susceptible to chronic CO intoxication than are others, but the timing of attacks, their nature, the mental changes and the intermitten symptoms should lead to a diagnosis in all persons exposed to CO.

154. Astrup, P. (1970A). Intraerythrocytic 2,3-diphosphoglycerate and carbon monoxide exposure. *Ann. N.Y. Acad. Sci.*, 174:252-254.

Individuals who had their COHb raised to 20% had an average drop of 8% in 2,3-diphosphoglycerate concentrations. This leads to a higher affinity of hemoglobin for oxygen and a displacement of the oxyhemoglobin dissociation curve to the left.

155. Ayres, S.M.; Giannelli, S., Jr.; and Armstrong, R.C. (1965). Carboxyhemoglobin: Hemodynamic and respiratory responses to small concentrations. *Science*, 149:193-194.

Inhalation of sufficient CO to raise the COHb to between 5 and 10% decreased arterial and mixed-venous oxygen tensions on an average of 7.3% and 13.3%, respectively. One of five subjects developed evidence of mild left-ventricular dysfunction.

156. Bartlett, D., Jr. (1968). Pathophysiology of exposure to low concentrations of carbon monoxide. *Arch. Environ. Health*, 16:719-727.

The effects of CO stem mainly from its reactions with hemoproteins such as hemoglobin and myoglobin. Both the uptake and elimination of CO in the blood are most rapid early in their course and then taper off. Persons particularly sensitive to the effects of CO are those already subject to a degree of hypoxia from altitude, anemia, or reduced cardiac output, or those with above normal oxygen needs due to pregnancy, hyper-

thyroidism, or fever. Carbon monoxide exposure during pregnancy may result in the birth of smaller babies, and may have other effects on fetal development.

157. Behrman, R.E.; Fisher, D.E.; and Paton, J. (1971). Air pollution in nurseries: Correlation with a decrease in oxygen-carrying capacity in hemoglobin. *J. Pediat.*, 78(6):1050-1054.

When the ambient CO level is greater than 20 ppm, the decrease in the oxygen-carrying capacity of newborn infants is greater than when the CO level of air is 5-20 ppm. The older infants, who had been breathing nursery air for the longest time, had a greater decrease in oxygen-carrying capacity.

158. Bender, W.; Goethert, M.; Malorny, G.; and Sebbesse, P. (1971). Effects of low carbon monoxide concentrations in man. *Arch. Toxikol. (Berlin)*, 27(2):142-158.

After 8 hours of breathing 100 ppm CO, diffusion equilibrium had not yet been reached. Exposure to 100 ppm CO for 2-1/2 hours caused a significant decrease in visual perception, manual dexterity, and ability to learn and perform certain intellectual tasks.

159. Brody, J.S., and Coburn, R.F. (1970) Effects of elevated carboxyhemoglobin on gas exchange in the lung. *Ann. N.Y. Acad. Sci.*, 174:255-260.

Carbon monoxide produces tissue hypoxia by combining with hemoglobin (Hb) to decrease the amount of Hb that is available for carrying oxygen and by increasing the affinity of the remaining unbound Hb for oxygen so that Hb gives up oxygen less readily to the tissues. This hypoxia may be accentuated by rather marked degrees of arterial hypoxemia in patients with heart or lung diseases.

160. Chance, B.; Erecinska, M.; and Wagner, M. (1970). Mitochondrial responses to carbon monoxide toxicity. *Ann. N.Y. Acad. Sci.*, 174:193-204.

This is a study of the dynamic response of the CO-inhibited respiratory component of isolated mitochondria. The extreme sensitivity of mitochondria to small concentrations of CO in transient changes from anoxia to normoxia is emphasized.

161. Chevalier, R.B.; Krumholz, R.A.; and Ross, J.C. (1966). Reaction of nonsmokers to carbon monoxide inhalation. *J. Amer. Med. Assoc.*, 198.1061-1064.

Nonsmokers raised their COHb level to the range seen in smokers which caused the development of an increased oxygen debt with exercise and a reduced pulmonary diffusing capacity at rest. The changes after CO inhalation were similar to those found when comparing smokers to non-smokers.

162. Coburn, R.F. (1970). The carbon monoxide body stores. *Ann. N.Y. Acad. Sci.*, 174:11-22.

Most of the body CO stores are bound to hemoglobin, but 10-15% may be located elsewhere, bound to hemoproteins, cytochromes a_3 and P_{450} catalase, peroxidases, and others. The body CO stores are increased by endogenous CO production and respiratory uptake of CO, while excretion via the lungs and metabolism of CO tend to decrease the body stores.

163. Collier, C.R., *et al.* (1972). *Physiological Adaptations to Carbon Monoxide Levels and Exercise in Normal Men*, University of Southern California, Los Angeles, Dept. of Medicine Environmental Protection Agency Contract 68-02-0334, Program 1A1007 EPA-RI-72-002, 20 pp.

An increase of COHb from 1% to 8-9% increased the minute volume and breathing frequency during exercise but not at rest; it did not affect cardiac output, heart rate, lactate, lactate/pyruvate ratio, tidal volume, carbon dioxide output, or 2.3-diphosphoglycerate during rest or exercise; and it decreased oxygen consumption, arterial-venous oxygen content difference, and venous oxygen and pulmonary content during exercise and, in the latter two, at rest.

164. Curphey, T.J.; Hood, L.P.L.; and Perkins, N.N. (1965). Carboxyhemoglo-
     bin in relation to air pollution and smoking. *Arch. Environ. Health*,
     10.179-185.

     A total of 1,075 cadavers were examined to ascertain what, if any,
     association existed between the CO content in the ambient air, smoking
     history, and COHb levels found in cadaver blood. There was a signifi-
     cant association between COHb levels and ambient air CO content.

165. Drouvin, M. (1971). Operation carbon monoxide in the blood. IN:
     Etudes de Pollution Atmosphere Atmospherique a Paris et les
     Departements Peripheriques en 1970. Prefecture de police, Paris
     (France). Lab. Central, pp. v-3 to v-17. (French).

     In one study the CO content in the blood was below 0.4 ml/100 ml in
     189 cases, between 1.2 and 2.0 ml/100 ml in 19, and above 3.6 ml/100
     in 7 cases, the maximum being 8.25 ml/100 ml. In another study 326
     nonsmokers and 142 smokers had values below 0.4 ml/100 ml, 71 smokers
     had between 1.2 and 1.6 ml/100 ml, and 57 smokers had between 2.0 and
     3.6 ml/100 ml.

166. Estabrook, R.W., *et al*. (1970) Factors influencing the inhibitory
     effect of carbon monoxide on cytochrome P_{450}-catalyzed mixed
     function oxidation reactions. *Ann. N.Y. Acad. Sci.*, 174:218-232.

     This paper describes the differences observed when examining the inhi-
     bitory effect of CO on mixed function oxidation reactions catalyzed by
     cytochrome P_{450} in liver microsomes. The steady-state concentration
     of ferrous cytochrome P_{450} is the critical determinant in establishing
     the degree of CO inhibition.

167. Fenn W.O. (1970). The burning of CO in tissues. *Ann. N.Y. Acad. Sci.*,
     174:64-71.

     The amount of CO burned in the human body would be too small to have
     any practical importance but on a world scale could be of importance.

A world population of 3 billion persons could raise the earth's CO concentration by one ppm in 270 years, plus automobiles and industry would make a much bigger contribution.

168. Forbes, W.H. (1970). Carbon monoxide uptake via the lungs. *Ann. N.Y. Acad. Sci.*, 174:72-75.

A carboxyhemoglobin level of 0.2 to 1.0% is produced exogenously in the human blood. A graph is presented showing per cent CO in the air versus per cent COHb in the blood for different periods of time.

169. Forster, R.E. (1970). Carbon monoxide and the partial pressure of oxygen in tissue. *Ann. N.Y. Acad. Sci.*, 174:233-241

The major effect of COHb in the blood is a lowering of tissue venous oxygen pressure produced by changes in the oxy-hemoglobin equilibrium, although we should look for other sites of action. The precise effects of the decreases in tissue oxygen pressure are difficult to predict because of our lack of knowledge of tissue oxygen pressure itself.

170. Goldsmith, J.R.; Terazgh, J.; and Hackney, J.D. (1963). Evaluation of fluctuating carbon monoxide exposures. *Arch. Environ. Health*, 7:647-663.

The patterns of population exposure must include the exposure of cigarette smokers, of those subjected to community air pollution, those with exposures to motor vehicles exhaust during commuting, those with occupational exposure to CO, and those unusually sensitive to impaired oxygen transport because of age or medical problems.

171. Haddon, W. Jr.; Nesbitt, R.E.L.; and Garcia, R. (1961) Smoking and pregnancy: Carbon monoxide in blood during gestation and at term. *Obstet. Gynec.*, 18:262-267.

Blood CO levels in pregnant women were higher in smokers than in non-smokers. Carbon monoxide levels in paired cord and maternal blood

specimens obtained at term were approximately equal. The reductions
found in maternal and fetal oxygen-carrying capacity and the action
of CO as an enzyme inhibitor are discussed from the standpoint of their
possible effects on fetal development.

172. Hansen, O.; Wilke, H.; Maloney, G.; and Goethert, M. (1972). Absorption
and release of carbon monoxide in smokers and nonsmokers during
the inhalation of low CO concentrations. *Staub Reinhaltung Luft*,
32(4):167-169 Presented at the VDI (Verein Deutscher Ingenieure)
Clean Air Maintenance Committee, Carbon Monoxide Symposium,
Düsseldorf, West Germany, October 28-29, 1971. (German).

Equilibrium is reached at the same time by smokers and nonsmokers alike
exposed to 200 ppm, while smokers reach equilibrium earlier than non-
smokers when exposed to 50 ppm. The higher the volume of CO absorbed
prior to the tests, the lower the volume absorbed during the test.

173. Killick, E.M. (1948). The nature of the acclimatization occurring
during repeated exposure of the human subject to atmospheres
containing low concentrations of carbon monoxide. *J. Physiol.*
(London), 107:27-44.

Acclimatization was indicated by the diminution in severity of the
symptoms during successive exposures to the same level of CO and by
the discrepancy between the observed % COHb at the end of an exposure
and the % COHb obtained in vitro when the subject's blood was equili-
brated with a mixture of O_2 and CO at the same partial pressure as in
the alveolar air.

174. Knelson, J.H. (1972). Discussion of the carbon monoxide standards for
the Federal German Republic, proposed by the VDI-Kommission
Reinhaltung Der Luft. *Staub, Reinhaltung Luft*, 32(4):191-192.

The most pertinent parameter of measurement is COHb, not ambient CO.
The two most pertinent questions are: what level of COHb results from
a given exposure to CO; and what emission levels are necessary to
achieve the required ambient level?

175. Lindquist, J.A.Y. (1972). Carbon monoxide: its relationship to air pollution and cigarette smoke. *Public Health (London)*, 86(1): 20-26.

Carbon monoxide impairs oxygen transport by combining with hemoglobin and by increasing the affinity of the remaining hemoglobin for oxygen, which causes the arterial oxygen tension to drop. Elevation of the COHb to 12.5% over an eight-day period lowered tissue oxygenation at rest by 15 to 20%.

176. Longo, L.D. (1970). Carbon monoxide in the pregnant mother and fetus and its exchange across the placenta. *Ann. N.Y. Acad. Sci.*, 174:312-341.

During pregnancy $COHb_m$ and $COHb_f$ are a function of the endogenous CO production of the mother, the level of CO in inspired air, the alveolar ventilation and the pulmonary CO-diffusing capacity, the endogenous CO production of the fetus, and the rate of CO exchange across the placenta. The resulting decreased availability of oxygen is probably injurious to fetal tissues.

177. McIlvaine, P.M.; Nelson, V.C.; and Bartlett, D. Jr. (1969). Temporal variation of carboxyhemoglobin concentrations. *Arch. Environ. Health*, 19:83-91.

Long-term average COHb can be estimated reliably from two or more instantaneous samples for each subject. This may be useful in estimating chronic CO exposures for epidemiologic studies. Overall COHb values averaged 3.8% for five smokers and 1.64% for ten nonsmokers.

178. Medaglini, E. (1962). Studies on the urinary elimination of 17-keto-steriods and 17-hydroxycorticosteroids in persons affected with chronic intoxication from carbon monoxide. *Rass. Neuropsichiat (Salerno)*, 16:55-58. (Italian).

Studies of the 17-ketosteroids and the 17-hydroxycorticosteroids in the
urine of chronically CO-exposed persons showed a diminshed elimination
of these substances during intoxication with a gradual return to normal
of adrenal functioning as the patient improves.

179. Mitsui, K., and Yanagisawa, M. (1972). The effects of air pollution and
     smoking on arterial blood hemoglobin. *Nippon Kyobu Shikkan Gakkai
     Zasshi (Japan J. Thoracic Dis.)*, No. 11:73. Presented at the meeting
     on air pollution, April 5, 1972. (Japanese).

Levels of COHb of smoking and nonsmoking patients were compared. Those
chronically exposed to CO showed a tendency to prolong the retention of
CO in the blood.

180. Nagaoka, S. (1972). Report of the investigation on the effects of
     carbon monoxide in the air on human bodies. *Tokyo-to Kogai
     Kenkyusho Nenpo (Annual Rept. Tokyo Met. Res. Inst. Environ. Prot.)*

The effects of CO concentrations in the open air of 5-10 ppm were studied
in bus drivers and conductors. The mean value of CO levels in expired
air of the subjects was 15 ppm, even among nonsmokers; this value being
higher than that in nonsmokers (5-10 ppm) engaged in other employment.
Both bus drivers and conductors showed an increase in CO at the end
of the work day.

181. Nielsen, B. (1971). Thermoregulation during work in carbon monoxide
     poisoning. *Acta. Physiol. Scand.*, 82:98-106.

Subjects showed increases in the plateau level of body temperature of
0.3-0.5°C during CO poisoning. The CO-poisoning may act 1) directly
on the hypothalamic temperature centre, the low tissue O_2 tensions
changing the activity of its neurons, 2) through the low venous O_2 ten-
sions on peripheral chemoreceptors in the working muscles of the venous
side of the circulation, or 3) the changes in temperature may be a
passive reaction to a shift in blood towards the periphery in the CO-
poisoned state.

182. Otis, A.B. (1970). The physiology of carbon monoxide poisoning and evidence for acclimatization. *Ann. N.Y. Acad. Sci.*, 174:242-245.

This is a summary of some of the articles on the possibility of acclimatization to CO. While acclimatization in humans is discussed, most of the research that has been done on this subject concerns animals. Most of the experiments on human acclimatization have been conducted only once and remain unverified.

183. Paulson, O.B.; Parving, H.H.; Olesen, J.; and Skinhoj, E. (1973). Influence of carbon monoxide and of hemodilution on cerebral blood flow and blood gases in man. *J. Appl. Physiol.*, 35(1): 111-116.

Cerebral blood flow increased both after CO exposure and after hemodilution using a solution of human albumin, this increase being more pronounced after CO exposure due to the leftward shift of the oxyhemoglobin dissociation curve. Jugular PO_2 decreased slightly during exposure but remained constant during hemodilution, probably due to changes in blood viscosity.

184. Peterson, J.E. (1970A). Postexposure relationships of carbon monoxide in blood and expired air. *Arch. Environ. Health*, 21:172-173.

The postexposure relationship between venous blood COHb saturation and the CO level in breath is described by an equation derived from data obtained from experimental human exposures to CO. Alveolar breath analysis can be used to estimate accurately the postexposure COHb saturation in adult white males.

185. Peterson, J.E., and Stewart R.D. (1970B). Absorption and elimination of carbon monoxide by inactive young men. *Arch Environ. Health*, 21:165-171.

Carboxyhemoglobin blood samples were obtained during exposures to varying CO levels for various periods of time. One equation accurately predicted

COHb levels resulting from continuous and discontinuous exposures to unvarying concentrations and from continuous exposure to a steadily rising concentration.

186. Pirnay, F.; Dujardin, J.; Deroanne, R.; and Petit, J.M. (1971). Muscular exercise during intoxication by carbon monoxide. *J. Appl. Physiol.*

During moderate exercise in which CO intoxication immobilized 15% of the hemoglobin, O_2 consumption wasn't modified, but the heart rate increased in an attempt to increase cardiac output. During maximal exercise, the maximal O_2 consumption parallels the reduction of the O_2 transport possibilities of the blood, which shows a circulatory limitation upon the maximal O_2 consumption.

187. Ramsey, J.M. (1969). The time course of hematological response to experimental exposures of carbon monoxide. *Arch. Environ. Health*, 18:323-329.

Hemoglobin and hematocrit values show significant postexposure increases which subside in two days but don't return to pre-exposure levels. These are gradual increases in these values that continue for 2-3 weeks after exposures have ceased and for 2 months maintain levels significantly higher than original values.

188. Roberts, W.C. (1952). Correlation of blood carbon monoxide level with symptoms. *Indust. Med. & Surg.*, 21:323-325.

No close correlation was found between symptoms and physical findings and CO blood saturation levels. Physiological reactions to CO vary with the state of health of the individual or the presence of fatigue. Frequent small exposures to CO may develop a considerable degree of acclimatization and thus alter the physiological reactions to CO.

189. Roughton, F.J. (1970). The equilibrium of carbon monoxide with human hemoglobin in whole blood. *Ann. N.Y. Acad. Sci.*, 174:177-188.

The equilibrium between oxygen, CO, and Hb is represented by the equation: $(PO_2 \times COHb)/(P_{CO} \times O_2Hb) = M$, where $\log M = 2.02 + 0.00254$ (% COHb). The dissociation curves of both COHb and O_2Hb are presented, along with determinations of O_2Hb in the 0-2% saturation range, of COHb and P_{CO} in the 0-2% and 98-99.5% range, and at 99.0-99.7% saturation with CO.

190. Scheidemandel, V., and Daum, S. (1973). Carboxyhemoglobin concentrations in the population of Munich. *Muench. Med. Wochschr. (Munich)*, 115(4):109-112.

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Recovery of visual function lags behind elimination of CO from the blood,
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LITERATURE LISTED

The entries in this list were not abstracted for one of three reasons:

1. the authors were unable to obtain the reference;

2. the reference was in a foreign language with no translation available;

3. the reference was not thought by the authors to be directly applicable to the subject reviewed but may be useful to other researchers.

Also, the large volume of articles on exposure of animals to carbon monoxide concentrations was not included in this review which deals only with human exposure.

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