PULMONARY AND CARDIOVASCULAR RESPONSE MECHANISMS 
IN DOGS DURING INHALATION OF LOW CONCENTRATIONS 
OF CARBON MONOXIDE

DISSERTATION

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By

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INTRODUCTION

A. Statement of the Problem

The voluminous literature on the mechanisms and manifestations of carbon monoxide poisoning has in many respects failed to clarify some basic physiological considerations. Many clinical papers have been published which reiterate the same histopathological observations(6,7,19,34,52,54). Many excellent physiological studies can be found in the literature which elucidate phenomena which occur during carbon monoxide inhalation. In particular, there has been much controversy in regard to cardiovascular and respiratory responses during administration of sub-lethal doses of carbon monoxide. Published papers describing changes in respiration, blood pressure, cardiac output, heart rate, and blood chemistry with various concentrations of CO indicate a minimum of general agreement among investigators(3,10,11,12,25,35,36,44,45,49,56,57,58,59,63). The direction and extent of these changes have not been fully verified to say nothing of the physiological mechanisms which produce the changes.

It was therefore decided to investigate fully the effects of inhalation of sub-lethal doses of CO on the respi-
ratory and cardiovascular systems with particular emphasis on physiological response factors. This study is essentially an attempt to measure the chemical parameters which influence respiratory and cardiovascular regulation and to ascertain whether changes in these parameters during inhalation of low concentrations of CO are sufficient to account for the observed responses.
B. Mechanics of CO and O₂ Combination with Hemoglobin

Human experience with carbon monoxide gas has always been considered a consequence of the evolution of civilized man. When man first discovered fire, he was destined not only to reap its many benefits but also to suffer its disadvantages. Great tragedies have resulted from the uncontrolled or careless use of combustible materials. In addition to the more obvious disastrous consequences of ill-fated uses of fire, there is a more subtle and equally menacing threat, namely, the formation of the odorless, colorless, and lethal gas, carbon monoxide, when organic materials are incompletely oxidized through combustion.

When a material burns freely in an atmosphere containing sufficient oxygen, carbon dioxide is given off. However, if the oxygen supply is limited and the amount of the substance is large, considerable quantities of CO are liberated. Even under the most favorable conditions for complete combustion, small amounts of CO can be formed due to incomplete conversion of carbon to carbon dioxide.

Carbon monoxide, CO, has a molecular weight of 28.01, a specific gravity of 0.9671 (air = 1), and a density of 1.2504 grams per liter under standard conditions (60). It is a colorless gas which at moderate concentrations has no odor,
however, at 75-100% concentration, it has a definite garlic-like odor.

CO is a toxic gas and exerts its toxic effects by combining with the hemoglobin of the blood and in this way preventing the absorption and transport of O$_2$ to the tissues of the organism. Carboxyhemoglobin is a reversible combination of CO with hemoglobin. In 1889, Hoppe-Seyler advanced the concept that in this reversible reaction, 1 atom of iron in the heme molecule reacts with 1 molecule of CO in the same fashion that a molecule of O$_2$ combines with the iron atom. Referring to Figure 5, we note that the dissociation curves of oxyhemoglobin and carboxyhemoglobin are almost identical. The effects of pH and temperature on the CO dissociation curve are approximately the same as on the O$_2$ dissociation curve.

In 1911, Douglas and Haldane performed a classic experiment in which they attempted to ascertain the validity of a theory advanced by Bohr and others that active secretion of O$_2$ and CO$_2$ by the alveolar membrane occurs under certain conditions. They employed the CO diffusion method and brought to light some very basic facts pertaining to the mechanics of O$_2$ and CO combination with hemoglobin. The most important contribution of this study was the construction of a CO dissociation curve. Figure 6 shows such a curve which has been
modified somewhat by Roughton(48). This curve was plotted using a constant percent of \( O_2 \) (21\%) and varying percentages of CO. Douglas and Haldane also used a constant percent of CO and constructed a second dissociation curve with various percentages of \( O_2 \) plotted against the percent \( HbCO \) saturation. This curve resembled the CO dissociation curve but possessed a negative slope. These two curves verified the assumption made by previous workers that the CO saturation of hemoglobin depends on the relative partial pressures of CO and \( O_2 \) multiplied by a constant.

A year later, Douglas, Haldane, and Haldane(18) extended their investigations on the combination of \( O_2 \) and CO with hemoglobin. Again using the CO method, they constructed CO dissociation curves using arterial and venous blood from humans and mice. They established the fact that the Bohr shift occurred in these curves by plotting a family of CO dissociation curves under conditions of varying partial pressures of \( CO_2 \). These workers also showed that the \( O_2 \) dissociation curve is progressively shifted to the left as the amount of \( HbCO \) increases when blood is exposed to CO.

The CO dissociation curve in Figure 6 shows that only a very small concentration of CO in air is required to saturate hemoglobin with CO to a considerable extent. Workers
such as Haldane(26), Douglas, Haldane, and Haldane(18), Barcroft(5), and others have established that the affinity of hemoglobin for CO is about three hundred times greater than its affinity for O₂. It is believed that this difference in affinities is due to a difference in the velocity of reaction, and that the combination of CO with hemoglobin occurs much more rapidly than with O₂. If blood is exposed to a mixture of the two gases, an equilibrium is eventually reached according to the following equation:

\[
\frac{[\text{HbCO}]}{[\text{HbO}_2]} = M \frac{P_{\text{CO}}}{P_{\text{O}_2}}
\]

The terms \([\text{HbCO}]\) and \([\text{HbO}_2]\) represent respectively the number of moles of CO and O₂ combined with the hemoglobin in one liter of blood. \(P_{\text{CO}}\) and \(P_{\text{O}_2}\) are the partial pressures of CO and O₂ respectively that are exposed to the blood. \(M\) is a constant which varies from 200 to 300 according to the species of animal considered and represents the relative affinity of CO for hemoglobin as compared to O₂. If four of the five terms of the equation are known, the fifth may be calculated provided the reaction, \(\text{HbO}_2 + \text{CO} \rightleftharpoons \text{HbCO} + \text{O}_2\), has reached equilibrium. Allen and Root(1) investigated the effects of pH and C\(_2\) on \(M\) values and on CO and O₂ partition in dog blood. Using tonometric procedures, they found that competition between O₂ and CO for hemoglobin is definitely influ-
enced by pH and Pco₂. With an increase in pH, the M value decreased, and with a rise in CO₂ tension, the M value increased. Peak M values were found in the normal pH range of the body.

Let us now consider in some detail the reaction, HbC₀₂ + CO ⇌ HbCO + O₂. This reversible reaction represents empirically the mechanism by which O₂ and CO interact as they combine with hemoglobin. The reaction to the right shows that HbCO is formed when CO is exposed to oxygenated blood with the resulting release of O₂ from in combination with hemoglobin. It follows the law of mass action since increasing the concentration of the reactants on the left drives the reaction to the right until it reaches an equilibrium point where the products of the concentrations on each side of the equation are again equal. If the resulting hemoglobin mixture is exposed to an atmosphere containing O₂, the reaction is, in this case, driven to the left since the concentration product has been increased on the right side of the equation.

Barcroft in his book Respiratory Functions of the Blood published in 1928(5) considers the interaction of O₂ and CO with hemoglobin a two-stage affair rather than the simple reversible displacement reaction given above. He envisions the reactions in two ways. If oxyhemoglobin is exposed to CO, the reaction would proceed as follows:
If carboxyhemoglobin is exposed to $O_2$, a two-stage reaction would occur in this fashion:

\[
\begin{align*}
(1) \quad & HbO_2 \rightleftharpoons Hb + O_2 \\
(2) \quad & Hb + CO \rightleftharpoons HbCO
\end{align*}
\]

Barcroft's is quite academic, however, these equations give a more accurate representation of what happens chemically during the interaction since both the reactive masses of $O_2$ and CO enter into the overall process making the classic double displacement expression quite oversimplified.

The speed and degree of saturation of hemoglobin with CO during CO inhalation by an intact organism depends primarily upon three factors: (1) CO concentration of the inspired air, (2) duration of exposure, and (3) pulmonary ventilation rate. The influence of the first two factors is clearly illustrated in Figure 7. For each concentration of CO, an equilibrium is reached which is not exceeded. With very low concentrations of CO, an equilibrium results after a considerable length of time, and this equilibrium exists at a relatively low HbCO saturation level. Higher CO concentrations produce much higher HbCO saturation levels after a short length of time. It is easy to see why severe anoxic symptoms are observed in mammals almost immediately following the adminis-
tation of high concentrations of CO. The third factor, ventilation rate, is closely related to the second factor in that a large ventilatory volume brings more CO in contact with the blood per unit time and thus accelerates the carboxyhemoglobin saturation process.

It has long been known that conversion of a considerable portion of the circulating hemoglobin to HbCO produces more serious hypoxic manifestations than the deficiency of a similar amount of hemoglobin in anemic states. Likewise, in hypoxic hypoxia, if the $O_2$ saturation falls to a level equal to the $O_2$ saturation found in a case of CO poisoning, the anoxic symptomology would be markedly less severe. These facts are readily explained by reference to Figure 8 in which are plotted the $O_2$ dissociation curves of human blood containing 0, 20, 40, and 60 percent HbCO, respectively, together with the $O_2$ dissociation curve of anemic blood containing only 40% of the normal amount of hemoglobin. With higher percentages of HbCO, the curve loses its sigmoid shape, and the steep portion of the curve is flattened considerably. At HbCO saturations of 40% and above, $O_2$ diffusion from the blood into the tissues is inhibited markedly due to the increased $O_2$-binding characteristics of the hemoglobin, and severe anoxic manifestations appear. The dotted curve in Fig-
Figure 8 shows an O$_2$ dissociation curve in an anemic state where the O$_2$ saturation of arterial blood leaving the lungs is 40% of normal due to a deficit of circulating hemoglobin. In contrast to the 60% HbCO curve, which is hyperbolic in shape, the anemia O$_2$ curve has a normal sigmoid shape, and, therefore, the blood unloads oxygen into the tissues without interference. The same situation applies when hypoxic hypoxia is considered. The O$_2$ dissociation curve originates further to the left on the abcissa since alveolar P$_{O_2}$ is diminished, but the normal slope prevails.

Roughton, in his report on the respiratory functions of blood\cite{48}, gives a possible explanation for the shifting of the O$_2$ dissociation curve to the left with its assumption of a hyperbolic shape when CO combines with hemoglobin. It is believed that when one or more of the four iron atoms on the Hb molecule has combined with CO, an interaction effect takes place which leads to an increased affinity of the remaining iron atoms for oxygen. In this manner, the unloading of O$_2$ in the tissues is inhibited since the remaining iron atoms that are still combined with O$_2$ possess an enhanced binding power for the oxygen and do not release it as easily as under normal physiological conditions.
C. Chemical Control of Respiration

Since this study is oriented primarily toward the chemical factors which may influence respiration during carbon monoxide poisoning, it is now advisable to consider briefly the mechanisms involved in normal chemical control of respiratory function.

There are three chemical factors which normally regulate respiration, namely, CO₂ tension, pH, and O₂ tension. O₂ tension, or Po₂, exerts an effect through the carotid and aortic arch receptors which monitor the level of dissolved oxygen in the arterial blood. CO₂ tension, or PCO₂, and pH act directly through the respiratory center to stimulate or inhibit pulmonary ventilation. Classically, these sites of action are accepted today; however, deviations from this dogma have been observed by various investigators so that strict acceptance is not possible.

Even though respiratory physiologists for the most part accept the fact that respiration is primarily governed by the three factors, PCO₂, pH, and Po₂, there is no general agreement on the respective roles that these factors play on an integrated basis. Although PCO₂ is considered by many physiologists to have the most powerful stimulatory effect of the three, and Po₂ is believed to influence respiration
only under abnormal conditions, it is unclear how these factors interact and produce a ventilation rate that serves the purposes of the organism most efficiently. Gray has taken a common-sense view of the matter and proposed a multiple factor theory which in equation form defines the relative roles of $P_{CO_2}$, pH, and $P_{O_2}$ in the regulation of pulmonary ventilation (24). By observing the ventilatory responses induced by changing each of the three factors independently, Gray was able to derive a mathematical formulation which described additive and differential effects of the factors on respiration. He believed that ventilation rate was determined by the algebraic sum of $P_{CO_2}$, pH, and $P_{O_2}$ during the steady state, and his multiple factor equation expressed this relationship. Figure 9 depicts the additive effects of pH and $P_{CO_2}$ during CO$_2$ inhalation. If the H-ion concentration was maintained at a normal physiological level, the rise in arterial $P_{CO_2}$ would elicit a ventilatory response shown by the dashed line. If the pH was allowed to decrease in addition, then the ventilatory rate increase would follow the solid line. On the other hand, pH and $P_{CO_2}$ have antagonistic effects as illustrated in Figure 10. It is seen that the actual ventilatory response to pH is much less extreme than would be expected if the pH were the sole factor producing the effect. This
graph shows the compensatory respiratory adjustment made in
metabolic disturbances of acid-base balance. To the left of
the normal point, acidosis is present, and ventilation rate
increases, blowing off CO₂ in order to diminish the carbonic
acid concentration of the plasma and thus raise the pH back
toward normal. However, if this ventilatory response were
permitted to occur to its fullest extent as represented by
the dashed line, Pco₂ would drop to extremely low levels,
interfering with normal physiological function. Therefore,
Pco₂ exerts an inhibitory effect through the respiratory
center and maintains arterial CO₂ at near physiological
levels. To the right of the normal point, alkalosis is present
and if total pH inhibition of respiration prevailed, CO₂
would rise to near narcotic levels. Therefore, Pco₂ has a
stimulatory effect on the respiratory center and antagonizes
the pH factor.

Ventilatory responses to hypoxia are strongly affected
by pH and Pco₂. Reference to Figure 11 shows that a pure
hypoxic ventilatory response to low Po₂ would produce vent-
ilation rate of considerable magnitude. Gray plotted this
particular curve by determining the actual ventilation rates
from his formal ventilation equation, \( VR = \frac{40}{Pco₂} \), and then
subtracting from these values ventilation rates which had
been computed from an equation derived from data observed
during metabolic disturbances of acid-base balance. Below an alveolar \( \text{P} \text{O}_2 \) of around 55 mm. Hg., the normal respiratory response is inhibited by pH and \( \text{P} \text{CO}_2 \). Obviously, this is necessary in order to maintain proper acid-base balance in the face of an increased need for oxygen. Above 55 mm. Hg. alveolar tension, the \( \text{PO}_2 \) stimulation is practically nil, and again acid-base balance would be disturbed unless a particular level of pulmonary ventilation was present to prevent a rise in \( \text{P} \text{CO}_2 \) and, therefore, a diminished pH.

It is clearly seen from this discussion that all chemical factors interact to produce a pulmonary ventilation rate compatible with the normal metabolic needs of the organism. It must be pointed out that Gray does not believe that arterial \( \text{PO}_2 \), pH, and \( \text{P} \text{CO}_2 \) necessarily regulate respiration. Older theories of chemical control of respiration hold that various chemical factors in the arterial blood do directly control ventilation; usually these theories specify a single factor which is responsible for respiratory regulation, and this factor is all-important in its action. Gray does not specify either the site or mode of action of the chemical factors, however, he does maintain that the arterial blood is the most accurate index of the tissue environment (i.e., the respiratory center environment) during the steady state. In
summary, then, Gray's theory states that ventilation rate is a function of independent action of the three chemical factors, $P_{CO_2}$, pH, and $P_{O_2}$, and is equal to the algebraic sum of the partial effects of the separate factors. By measuring these factors in the arterial blood during homeostatic conditions, Gray assumes that the chemical environment in the respiratory center and in the peripheral chemoreceptors is closely approximated.

It is imperative that the inter-relationships of the chemical factors be kept in mind when pulmonary responses to various agents are investigated. Undertaking a study that does not include accurate determinations of all three chemical factors will result only in an incomplete picture of respiratory response activity. In addition, the determination of venous $P_{CO_2}$, pH, and $P_{O_2}$ gives information as to the make-up of the chemical environment of the tissues since venous blood reflects the chemical state of the capillary bed. This may be an important factor in regulation of both respiration and circulation. Although it is universally accepted that the arterial blood composition is the basic controlling mechanism in regulation of respiration, some important investigations have been carried out in the past which indicate that ventilation rate may vary independently of the arterial factors (22, 43).
HISTORICAL REVIEW

The effects of carbon monoxide inhalation have been observed for centuries; in fact, descriptions of carbon monoxide poisoning are almost as old as civilization itself. Lewin in his report on the history of CO intoxication (140) mentions a historical note as far back as 200 B.C. where a statement in Livius describes the fate of allied commanders who were captured during the second Punic War. They were bound and suspended over glowing fires and apparently died as a result of "heat taking away their breath." Julian the Apostate (331-363 A.D.) describes an experience while in winter quarters in Paris. To combat the severe cold, he ordered a small fire brought to his room "to prevent so much moisture from exuding from the walls." However, there was "still a vapor coming from the walls" which put him to sleep, and he was carried from the room unconscious.

In the fifteenth century, Symphoranus Campeguis tells of two merchants traveling in the wintertime who stopped at an inn for the night. To warm the room, they built a fire in the fireplace and retired for the night. The next morning, the innkeeper found them dead. Attending physicians ascribed the cause of death to coal vapor.
Suicides and death sentences were carried out through use of carbon monoxide even in ancient times. In 68 A.D., Seneca ended his life by inhaling charcoal vapor. Plutarch, after having been sentenced to death by Marius, shut himself in a room and suffocated by breathing the vapor from a glowing fire which had been kindled to heat bath water. Lewin found many references to executions through the use of CO. At the time of Cicero (106-143 A.D.), numerous persons were put to death by administration of the gas, and in the period of history from 193-305 A.D., many martyrs died by this means.

Of interesting historical note are the many early attempts to explore the nature of carbon monoxide and how it exerts its lethal effects. Sayers and Davenport, in their Public Health Bulletin report, give a fine comprehensive survey of the early evolution of thought concerning the manifestations of CO poisoning. A brief summary of Sayers and Davenport's account will serve to show how obscure the details of CO intoxication remained right up to the middle of the nineteenth century. Cassius in Medical Questions published in 130 A.D. attributed the harmful effects of charcoal vapors to the action of dry heat and not to the vapor produced by glowing coals. He stated erroneously that since wood charcoal
contained a certain degree of moisture, it did not produce headache. In the fifteenth century, Marsilius Ficinus thought that all coals caused headache, but that more harmful effects could come about as a result of inhalation of vapor arising from extinguished coals. A contemporary author, Mercurialis, opined that bad coal was the source of the trouble. The nature of the gas itself remained unknown during the seventeenth century, and as late as the eighteenth century, death from the lethal substance was sometimes attributed to the work of the devil.

Baconis de Verlamio in 1648 was the first to mention the fact that this substance possessed no odor and therefore was doubly dangerous. He spoke of the gas as "vapor carbonum" instead of using the older designation, "fumus." Van Helmont's publication in 1667 first referred to carbon monoxide fumes as "carbon gas." In 1732, Boerhave made probably the first animal experiments with CO. He found that all red-hot organic matter gave off a vapor which would quickly kill an animal confined in a small closed space. In 1776, F. de Lassone first made CO experimentally by reducing zinc oxide with charcoal and prepared considerable quantities of the gas. Lavoisier attempted to fit CO in with his theory of oxidation, but even though he knew that this gas was oxidized to CO₂, he was unsuccessful. Then in 1800, Cruickshank estab-
lished the chemical nature of CO and showed it was simply a "gaseous oxide of carbon." As late as 1812, the *Dictionnaire des Science Medicales* of Paris stated:

> It has not been definitely determined to which of these gases carbon monoxide or hydrogen sulphide are due the pernicious effects of vapor from charcoal.

In the nineteenth century, mechanism of CO poisoning was studied within a more scientific frame of reference. Von Oettingen's review of carbon monoxide poisoning published in 1944(60) observes that toward the end of the century, two schools of thought evolved in regard to the mechanism of action of CO as a toxic substance. One school supported by Bernard(1857), Hoppe-Seyler(1858), and later by Dreser(1892), Haldane(1895), and Hoke(1906) held that the toxic effects of CO are due to its great affinity for hemoglobin, and that its action is mediated through progressive inhibition of O₂ transport of the blood by direct combination with the hemoglobin ultimately causing asphyxia. They considered this the sole effect exerted by CO on the body. On the other hand, such investigators as Geppert(1892), Marcacci(1893), and Treves, Benedicenti, Herlitzka, and Giacosa(1897) concluded that since the respiratory response of animals to O₂-lack differs from the response to CO inhalation, CO must have a direct effect on the central nervous system. Other workers
such as Wacholtz (1905), Herlitzka (1900), and Sibelius (1903) felt that the toxicity of CO manifested itself through direct effects on blood vessels and certain nerve elements of the central nervous system and of the brain (60).

Warburg's classic experiment in 1926 (62) in which he observed diminished respiratory function in yeast cells exposed to CO atmospheres gave further impetus to the theory of direct toxic action of CO. Warburg incubated yeast cells sealed in flasks at 37.5°C with a gas mixture of 80% CO and 20% O₂ and found a 35% decrease in metabolic rate. With higher concentrations of CO, he noted even greater inhibition of metabolism. Furthermore, he observed that upon exposure to light, the cells increased their O₂ uptake when compared to their consumption in the dark. He postulated from these findings that CO combines with a respiratory enzyme present in the yeast cells, and the compound dissociates upon exposure to light. Since other substances present in various tissues had exhibited this same dissociation phenomenon, he believed that the enzyme resembled iron-containing myoglobin and circulating hemoglobin in respect to its structure and called it "Atmungsferment." This compound was later isolated and given the name cytochrome oxidase. It must be kept in mind that Warburg's investigation involved tremendously high
concentrations of CO and also that yeast cells and not intact organisms high on the phylogenetic scale were employed.

In 1927, Haldane performed an experiment using moths, rats, and watercress seeds in a similar attempt to prove CO acted as a tissue poison(29). We will consider only his rat data. Using three atmospheres pressure of O₂ and one atmosphere of CO, he observed no untoward effects on the rats and maintained that the hemoglobin was essentially 100% saturated with CO, and, therefore, the plasma remained the only O₂ carrier. The rats continued to show little distress until another atmosphere of CO was added, and then convulsive seizures and finally death resulted. Haldane reasoned that since the rat normally has a low O₂ consumption, it could maintain normal metabolism by use of the O₂ dissolved in the plasma, and that since addition of the second CO atmosphere produced ill effects, these effects must be localized at the tissue level. This author feels that justifiable criticism can be made of these interpretations. First of all, Haldane assumed but did not actually measure HbCO saturation in his rats. Possibly the extremely high pressure of O₂ at three atmospheres would inhibit the reaction, HbO₂ + CO → HbCO + O₂, from going to the right in spite of the CO under one atmosphere. This fact would result in a much lower HbCO saturation than Haldane
assumed thus producing little hypoxic effect. Addition of the second CO atmosphere might then drive the reaction to the right decreasing the HbO₂ saturation to fatal levels.

In contrast to Warburg's findings with yeast cells, Fenn and Cobb in 1932(20,21) and Schmidt and Scott in 1934 (53) observed that various frog tissues showed increases in metabolic rate when incubated with 79% CO and 21% O₂ mixtures. This phenomenon was explained by a postulation that the conversion of CO to CO₂ occurred in the tissues and required large quantities of O₂ to accomplish the oxidation. These authors felt that the direct inhibitory effects of CO on the tissues were masked by the CO CO₂ conversion.

In addition to these early studies, more recent isolated and scattered botanical and zoological observations have been made on the effects of CO on tissue metabolism(51). These studies showed largely that depressant effects were experienced by the experimental organisms or cells. However, it must be borne in mind that these observations were on non-mammalian forms and may have little relevance to an understanding of the mechanisms involved in CO intoxication in man. The tremendously high concentrations of CO used in isolated tissue studies would produce a rapid and overwhelming anoxia in mammals that would eliminate any opportunity for systematic observation of possible non-hemoglobin effects of
Present evidence seems to indicate that although discrete and direct effects of CO may be present at the cellular level, tissue O₂-lack in mammals due to low arterial blood O₂ saturation and altered O₂ dissociation characteristics is by and far the most important consideration in assessing the effects of CO poisoning.

A historical review of the literature will now be presented covering the work on respiratory and cardiovascular effects of carbon monoxide inhalation. We will first consider studies dealing with respiratory function and blood chemistry only. Many of these experiments also include circulatory observations, however, these will be considered separately and included in a later part of this section where a review of the cardiovascular CO literature will be given.

The first classic experiments on the effects of CO on mammals were done by Haldane in 1895(27,28). The first of these studies (27) was performed on mice. The animals were placed in sealed containers and exposed to various percentages of CO in air and in O₂. He found that a .22% CO-air mixture would kill the animals after two hours and twenty-five minutes and observed an initial hyperpnea which declined steadily until death occurred. Higher CO concentrations in air produced an earlier death with hypoxic convulsions.
With an 0.8% CO-O₂ mixture, he observed a moderate loss of power with hyperpnea, and upon increasing the CO-O₂ concentration to 2.3% and 7.2% for shorter periods of time, he noted no ill effects. Using two atmospheres of O₂ with extremely high concentrations of CO, Haldane observed no effects. He concluded that the poisonous action of CO diminishes as O₂ tension increases up to the point where two atmospheres of O₂ abolishes toxic symptoms. He also maintained that at high O₂ tensions, the oxygen-carrying function of hemoglobin is unnecessary, and that no toxic action of CO occurs except through the decreased O₂-carrying capacity of the red blood cells. A second experiment (28) was done by Haldane using himself as an experimental subject in which he breathed varying percentages of CO up to 0.41% CO in air for varying periods of time. His observations included subjective visual and auditory impairment with feelings of giddiness. CO saturation levels of the arterial blood were measured, and in one procedure, Haldane reached a CO saturation of 56% which caused him to fall whenever he attempted to walk. He noted the hyperpnea he had observed in his previous experiment with mice. Haldane's astute observations and interpretation of data made him the first to recognize the basic physio-chemical events which occur during CO inhalation. He believed that the symptoms of CO intoxication
on the extent of CO saturation of hemoglobin, and that the maximum amount of CO absorbed is determined by the relative affinities of O₂ and CO for hemoglobin. Furthermore, he pointed out that the disappearance of CO from the blood when air breathing is again instituted is chiefly due to the mass influence of O₂ in the pulmonary capillaries.

In 1921, Haggard and Henderson(25) administered concentrations of from 0.15% to 0.45% CO in air to unanesthetized dogs with the purpose in mind to establish that CO poisoning produced alkalosis and not acidosis. They observed an increase in O₂ consumption, R.Q., and in minute respiratory volume. Arterial blood was analyzed, and it was found that with saturations of approximately 50% HbCO, CO₂ content and alkaline reserve were diminished, and they concluded that the blood alkali decrease was due to the acapnic condition and not brought about by anerobic metabolism resulting in an accumulation of lactic acid in the blood. Implicit in this postulation is the assumption that the hyperventilation was due to the anoxemic state. Later work has shown that the hypoxia alone caused by CO poisoning is a relatively weak stimulus to increased ventilation. Moreover, the determination of alkaline reserve does not give any information as to the extent of respiratory disturbances of acid-base balance since this
this measurement can be used only to estimate metabolic disturbances. Consequently, Haggard and Henderson's assumption that a respiratory alkalosis was present on the basis of a diminished alkaline reserve was not valid. H-ion concentration and total CO₂ content must both be measured in order to describe respiratory changes in acid-base balance. Indeed, it is surprising to note that these authors did not measure blood pH since the Kerridge glass electrode had been well established by 1921.

In 1922, Sayers, Meriweather, and Yant did a study for the New York and New Jersey Tunnel Commission. They placed human subjects in a chamber and observed effects of long exposures to various concentrations of CO under conditions of rest and strenuous exercise. Some hyperpneic response was noted at rest.

Mikami in 1926 carried out an investigation similar to Haggard and Henderson's work. They studied primarily the respective roles that alkalosis and acidosis play in CO intoxication. In one section of the experiment, pH was measured simultaneously with determination of blood gases and respiratory rate after 250-500 cc. of CO had been injected subcutaneously into each of eighteen rabbits. Results showed that tachypnea invariably occurred with the higher concen-
trations and continued for one or two hours. O₂ content and CO₂ content in arterial blood decreased together with pH, the larger the injection dose, the more prolonged and extensive was the decline. Inhalation experiments with rabbits placed in a chamber were also carried out. Arterial blood O₂ and CO₂ content and O₂ saturation were determined along with respiratory rate. Gas contents were found diminished, and tachypneic responses were observed at CO saturation levels from 40% to 70% HbCO. Mikami states that the CO₂ content decline and the pH increase did not always coincide with the extent of hyperpnea, and that the CO₂ content continued to drop one or two hours after cessation of CO administration. Thus, Mikami contended that CO inhalation produces an acidotic state which is responsible for the decrease in alkaline reserve. This experiment is notably well-designed in that a considerable number of animals were utilized in the experimental groups, and also because of the existence of a control group numbering twelve rabbits. Its limitations are apparent when an attempt is made to compare it to our experiment since Mikami's study was designed primarily as a blood sugar and blood gas investigation. Furthermore, only respiratory rates were measured in lieu of ventilation volumes, and pH determinations are admittedly crude when measured by
the Cullen and Billman method which Mikami utilized in this study.

In 1929, Sayers, Yant, Levy, and Fulton (50) conducted a study in which six medical students were placed in a chamber and exposed to CO-air mixtures of 0.02%, 0.03%, and 0.04% CO for two to three hours until venous blood samples showed a saturation of from 25% to 35% HbCO. These workers observed no change in respiration, blood pressure, pulse rate, and body temperature. Increases in red blood cells and hemoglobin concentration were noted. Mild symptoms such as headache, dizziness, blurred vision, etc. were also observed.

Kamei in 1931 (36) observed gas content and alkalinity changes in arterial blood during CO administration to small unanesthetized dogs. Five dogs were injected subcutaneously, and six dogs inhaled CO-air mixtures ranging from 0.05% to 3% CO. The lower concentrations (0.05-0.08%) produced only a slight increase in respiration although in some cases, no response occurred. Higher concentrations elicited pronounced hyperventilation in all cases. Diminution in CO2 capacity, CO2 content, and pH was noted which led Kamei to suggest that an increased \( \frac{H_2CO_3}{HCO_3^-} \) ratio had resulted. However, since \( P_{CO_2} \) was not measured directly, this observation was speculative. Kamei's conclusions were similar to those of
Mikami's since he felt that CO₂ content declined independently of the ventilatory increases and therefore acidosis was the immediate result of progressive CO anoxemia. However, no control groups were employed in Kamei's experiment, and only the pre-CO measurements served as normal control values. Kamei also produced double vagotomies in some of his dogs as did Mikami and similarly observed that respiration changed in the same direction and to the same extent as in intact dogs when CO was administered. Inhalation and injection techniques appeared to show the same overall changes.

In 1933, Thiel published data from a study done on anesthetized dogs inhaling 0.5% and 1% CO in air(58). Arterial blood was analyzed and indicated that a decrease in CO₂ content occurred, and a decline in pH from 7.60 to 7.35 on the average. Minute volume, arterial blood sugar, and lactic acid showed definite increases. As was the case in most of the previously heretofore described experiments, no control group of animals was employed. pH's were determined with use of a Michaelis electrode in conjunction with a calomel electrode. This technique was far superior to the method employed by Mikami, and the pH values were accordingly more quantitatively free from error. Thiel's results are difficult to compare with other work on CO since his data do not include deter-
mination of HbCO saturation levels.

Also in 1933, Chartschenko(11) reported that in dogs exposed to concentrations of 0.15% to 0.45% CO in air, a steady increase of respiratory volume paralleled by a progressive decrease of the CO$_2$ content and CO$_2$ combining power of blood. Depression of the respiratory center caused a subsequent ventilatory decrease after prolonged exposure.

Yant, Chornyak, Schrenk, Patty, and Sayers in 1934 (63) did an extensive blood chemistry study using venous blood obtained at the point of death from anesthetized dogs breathing 0.6% CO in air. A decline in pH, CO$_2$ capacity, CO$_2$ content, and O$_2$ saturation was noted as well as increase in blood sugar, uric acid, non-protein N$_2$, urea, hemoglobin, and red and white blood cells. They stated that the blood chemistry findings were similar to those found with the same degree of hypoxic hypoxia.

Di Prisco in 1939 noted in animals exposed to CO concentrations of 0.2% to 0.3% in air that an initial tachypnea resulted which gradually slowed as the animal became more comatose(60).

In 1941, Asmussen and Chiodi(3) administered CO in air to three human subjects for thirty to forty-five minutes until blood CO saturation reached 20-30%. Venous blood
was analyzed for CO₂ content and O₂ content, and both were found to be diminished. Alveolar CO₂ and O₂ were measured and found to be essentially unchanged. These observations were compared to a second set of results from an experiment in which a 10% O₂ mixture was inspired producing a 70% to 80% HbO₂ saturation. In contrast to the considerable increase in respiration in this experiment, very slight ventilatory responses were noted in the CO experiments. It is felt by this author that Asmussen and Chiodi's experiment is rather inconclusive since only three subjects were employed, and a 20-30% HbCO saturation level is not severe enough to produce a marked hypoxic state. Even at this relatively mild hypoxic level, two of the three subjects did show some increase in ventilation.

Chiodi again in 1941 and in collaboration with Dill, Consolazio, and Horvath(12) published data from a CO experiment which was done on human subjects and on trained unanesthetized dogs in an attempt to investigate the effect of higher blood CO saturations on respiration and circulation. Four human subjects inspired 0.15% to 0.35% CO in air for seventy minutes which produced carboxyhemoglobin saturations of 19.6% to 53%. Increases were found in arterial Pco₂ while ventilation and arterial pH were diminished. Results on the
two dogs showed no change in respiration, an increase in $O_2$ consumption, and decreases in A-V $O_2$ difference and arterial pH although in one of the dogs, no change in pH was noted. As was the case in Asmussen and Chiodi's work, an inadequate sampling of experimental subjects was utilized which did not warrant the conclusions that were made. This fact is particularly evident in the dog experiments with the pH determinations. Even though fifteen experiments with various HbCO saturations were done on one dog and eight experiments were done on the other, only one of the dogs showed any significant change in arterial pH as higher carboxyhemoglobin levels were reached. These workers concluded that in general, pH was toward the acid side although even the human pH results showed much variation.

Also in 1941, Von Oettingen investigated CO poisoning in anesthetized dogs exposed to 0.25% and up to 1% CO in air(59). Changes with the various concentrations were approximately equal. Respiratory effects included increases in minute volume up to 170%, decreases in tidal volume, and marked increases in respiratory rate. Venous blood was analyzed, and it was found that $CO_2$ content increased in six dogs and decreased in two. The HbCO saturation was approximately 82% at death in the dogs inhaling lethal doses of CO.
Two CO experiments were done in 1943, one by Klimmer on guinea pigs (39), and the other by Müller on anesthetized dogs (46). Klimmer used concentrations of 0.1%, 0.2%, and 0.4% CO in air and noted that moderate dyspnea resulted with all concentrations. Müller exposed his dogs to concentrations of 0.22%, 0.25%, and 0.29% CO in air and in general noted a greater increase in ventilation with greater CO concentrations in the inspired air.

An investigation was made by Dahlström, Obreschkow, and Sjöstrand in 1947 (16) in which ventilation and cardiovascular functions were studied under conditions of low O2 inhalation and inspiration of low concentrations of CO in air. Respiratory changes with CO-air breathing were quite small, ranging from -9.7% to 33.3% of normal with HbCO saturations of 30-45%. Alkaline reserve showed no appreciable change. The discussion of these results proved to be a reiteration of the classically observed responses of the respiratory system during CO hypoxemia as contrasted to those observed during inspiration of low O2 mixtures, namely, that ventilatory responses during hypoxic hypoxia are of much greater magnitude than during CO inhalation. This is assumed to be primarily due to the fact that a normal arterial Po2 level is present in the latter case which prevents carotid and aortic body
stimulation. Breathing low O₂-air mixtures produces a diminished arterial Po₂, and consequently, the carotid glomus are stimulated. As was the case with almost all previous physiological studies of CO poisoning, no attempt was made in this experiment to explain why hyperventilation, even though small in amplitude, does occur during CO inhalation.

Swann and Brucer published results in 1949 from an investigation on the effects of lethal concentrations of CO on dogs(56). Trained unanesthetized dogs were used in this experiment and observed during the course of inhalation of 1% CO in air. Pulmonary ventilation volumes were double the normal value until O₂ saturations of 10-12% were reached where a sharp decline occurred. CO₂ content and Pco₂ decreased to the point where breathing began to fail, and then Pco₂ rose sharply. pH fell slowly until at death where it dropped precipitously, however, the pH did not change significantly until HbCO saturations above 50-60% were evident.

The most recent work done on the physiological responses of the cardiopulmonary system to CO poisoning was in 1957 by Terzioglu and Emiroglue(57). These investigators felt that possibly the chemoreceptors played a role in the variability found by other workers in carrying out respiratory experiments involving CO inhalation. Since they considered
the possibility that chemoreceptor and respiratory center depression might occur as a result of anesthesia administration, they used unanesthetized rabbits, denervated the chemoreceptor areas, and then administered 0.3% to 0.65% CO in air in various experiments. They found in eight rabbits that respiratory rate and minute volume did not increase as in the eleven control animals that were also employed in the experiment. Acid-base measurements were also made on the arterial blood of rabbits exposed to 0.3% CO in air. In twelve intact animals, pH, CO₂ content, alkaline reserve, and Pco₂ all declined. Po₂ remained essentially unchanged. Blood CO saturation levels averaged around 62%. In twelve denervated animals also given the 0.3% CO-air mixture, changes of the same degree of magnitude and in the same direction resulted. The design of this experiment appeared adequate since a control group of rabbits was utilized in the investigation, however, certain interpretations of data do not seem valid, and these merit some comment later in the Discussion section.

A brief review of the literature covering cardiovascular effects during CO poisoning will now be given. Only work done in the 1920's and in subsequent years up to the present time will be considered.

Sayers et al. in 1929(50) observed in six human sub-
jects that with a 25-35% HbCO saturation, no change in blood pressure or pulse rate resulted when CO-air mixtures of 0.02%, 0.03%, and 0.04% were administered.

In 1936, Miura (45) observed the effects of CO on cardiac output and blood volumes. Cardiac output was determined using the direct Fick method. A CO-air concentration of 0.2% was administered to anesthetized rabbits for sixty minutes. In seven experiments on seven animals, cardiac output increased 37.4% on the average, stroke volume increased 28%, and heart rate rose 20 beats per minute. HbCO saturations averaged 55-60% at the end of the experiment. In control rabbits, average values indicated a 15% decrease in both cardiac output and stroke volume with only a very slight increase in heart rate.

Brewer in 1937 (10) showed that in anesthetized dogs, a CO-air mixture produced varying blood pressure changes. His results indicated that blood pressure on the average rose much more markedly in response to inhalation of mixtures of CO + N₂, CO alone, and N₂ alone than with the CO + air mixture. These differences were ascribed to differential carotid sinus responses to the varying O₂ tensions of the plasma resulting from the inspiration of the various mixtures.

Kayser in 1939 (35) attempted to demonstrate the direct
hypoxic effects of CO on the central nervous system by measuring blood pressure changes during administration of various O₂, CO₂, and CO mixtures to anesthetized cats. He found that with HbCO saturations of approximately 60% or 70%, inhalation of a 10% + 90% CO₂-O₂ mixture or 100% N₂ produced an immediate transitory rise in blood pressure which was even greater in magnitude than under normal conditions where no HbCO was present. In every case where 10% CO + 90% O₂ (or 10% CO + 90% N₂) mixtures were given, an initial sharp drop in blood pressure occurred followed by subsequent recovery to normal levels in a few minutes. From these data, Kayser made the interesting conclusion that since blood pressure responses to anoxia or high CO₂ concentrations were normal even with high HbCO saturations, carboxyhemoglobin accumulation is not the stimulus for blood pressure changes during CO inhalation, but rather it is the Pco of the plasma. Therefore, he believed that the effects of CO on the central nervous system are direct toxic effects and are not mediated through the ensuing asphyxia.

Chiodi et al., in 1941(12) in their previously described experiment found that with 0.15% to 0.35% CO in air, four human subjects showed an increase in cardiac output accompanied by a rise in heart rate with HbCO saturations of from 16% to 52%. Repeated observations of two trained dogs also
gave evidence of increased cardiac output and pulse rate with carboxyhemoglobin levels corresponding to those in the humans. Earlier in 1941, Asmussen and Chiodi(3) had observed respiratory and circulatory changes with lower HbCO saturations(20%-30%), and found that little or no effect on cardiac output was evident. Since a high pulse rate with an unchanged cardiac output was observed, they concluded that the stroke volume must have decreased.

Also in 1941, Von Oettingen(59) found that in his dogs, an initial rise in blood pressure(7%) occurred with a steeper fall after twenty-five minutes of breathing a 1% CO-air mixture. Heart rate in two cases showed a slight primary reduction followed by an increase. In four other cases, however, the primary reduction prevailed until death.

In 1943, Loeper, Cottet, and Varay(l42) studied the effects of CO on vasomotor and kidney function. Using ten chorolosed dogs, they showed by using onconometric measures of kidney volume that inhalation of low concentrations of CO-air mixtures produced kidney constrictions which corresponded in time to a rise in blood pressure. They considered this the normal expected visceral vasoconstriction which occurs during hypoxic states.

In their experiment on respiratory and circulatory
changes during CO inhalation previously referred to, Dühlstrom et al. (16) demonstrated that no consistent changes in blood pressure occurred with carboxyhemoglobin saturations up to 45%. Heart rate showed generally an increase while cardiac output, computed from the Liljestrand-Zander product of pulse rate, pulse pressure, and arterial blood pressure, also was augmented.

Swann and Brucer in 1949(56) in their experiment found that during the course of inhalation of 1% CO in air, unanesthetized dogs showed an initial increase in heart rate with subsequent decline when O2 saturation levels reached 10-15%. Blood pressure showed a gradual rise until just prior to death.
A. Preliminary Procedures

Male and female dogs ranging in weight from nine to thirteen kilograms were used in this study. The dogs were divided into two groups; one was composed of ten experimental animals, and the other included six control dogs.

Prior to the surgical procedures, all dogs were anesthetized intravenously with 30 mg. sodium pentobarbital (Nembutal) per kilogram of body weight. An endotracheal tube equipped with an inflatable cuff was inserted into the trachea, and the cuff inflated so that air flow in and out of the lungs was directed through the tube alone.

The right jugular vein was exposed, incised, and a catheter introduced. With the use of a fluoroscope, the catheter was passed caudally toward the heart and finally positioned in the right ventricle where it served as a source of mixed venous blood. The left femoral artery was then cannulated with a blunted number 13 hypodermic needle to provide a means for obtaining arterial blood and also for arterial blood pressure recordings.

A special valve constructed as a respiratory valve
containing only 17 cc. of dead space was connected to the tracheal tube with the expiratory side leading to a Tissot gasometer equipped with a kymograph drum and pen-writer attachment. The inspiratory side of the valve was connected to Douglas bags arranged in series and containing a CO-air mixture. Figure 12 is a schematic diagram of the experimental set-up.

Previous to all surgical procedures carried out on the dogs, a 0.15% CO-air mixture was prepared by introducing 187 cc. of 100% commercial grade carbon monoxide into a Douglas bag and then adding 124.9 liters of room air. The CO concentration was always checked prior to the experimental procedures with the use of a hoolamite CO detector manufactured by the Mine Safety Appliance Company. Hoolamite is a compound which is formed when iodine pentoxide reacts with fuming sulfuric acid. This compound when exposed to relatively minute concentrations of CO turns green; the higher the concentration of the CO, the darker green is the color. This detector will accurately measure concentrations of CO in air as low as 0.07%. Enough bags were prepared so that the carboxyhemoglobin saturation of the blood approached approximately 40% after the dog had inspired the mixture for about ninety minutes and was in a steady state in regard to
respiration, blood pressure, and heart rate. These criteria were established after several pilot studies were carried out with various CO-air concentrations.

Following completion of the surgery, the blood pressure recording system was assembled. One end of a short length of polyethylene tubing was attached to a three-way valve which was connected to the cannula in the femoral artery. The other end of the tubing was attached to a Statham pressure transducer which in turn led to a Sanborn oscillograph pen writer.

B. Measurements

Arterial blood pressure and pulse rate were recorded at frequent intervals throughout the course of the experiment. These factors are easily and accurately monitored by use of the Statham strain gauge and oscillograph arrangement. The blood pressure and pulse pressure distort a pressure-sensitive diaphragm located in the fluid-filled transducer, and deflections of the diaphragm produce electrical signals which are transmitted to the recorder amplifier.

Mixed expired air collected in the spirometer was analyzed for $O_2$, $CO_2$, and $N_2$ concentrations using a Schlo-lander gas analyzer apparatus. Minute volumes, tidal volumes, and respiratory rates were obtained from the kymograph
drum on the gasometer. Alveolar ventilation rate was calculated using the recorded minute volume and respiratory rate and the calculated physiological dead space. Metabolic rates, CO₂ elimination, and R.Q. were calculated using the Tissot-Haldane method.

Blood analyses included the determination of pH with a Cambridge pH meter, O₂ and CO₂ tensions by the direct bubble method of Riley(47), O₂ and CO₂ content with a Van Slyke manometric apparatus. O₂ capacity was measured only on blood obtained before administration of CO. A comparison of the arterial O₂ content after CO with the original O₂ capacity gives an estimate of how much hemoglobin has combined with CO. All measurements were made on arterial blood obtained from the femoral artery and on venous blood drawn from the right heart.

Cardiac output was determined using the direct Fick method which utilizes in equation form the arterio-venous O₂ content difference and the O₂ consumption.

C. Experimental Procedure

Upon completion of the preliminary procedures, the dog was allowed to reach a steady state in regard to respiration, blood pressure, and heart rate. This steady state
was presumed to be present when the slope of the ventilation tracing became constant, and the arterial blood pressure and pulse rate no longer showed persistent changes. Simultaneous monitoring of these events was achieved at periodic intervals. Following stabilization of cardiovascular and respiratory function, the first blood samples were taken simultaneously with the collection of mixed expired air, and a recording of respiration, blood pressure, and heart rate. Fifteen cc. each of arterial and venous blood were drawn over a period of two minutes. At the end of the two minute collection period, the 0.15% CO mixture from the Douglas bags was administered to the experimental group. A period of time ensued during which cardiorespiratory changes again occurred in the experimental animals. A steady state, as previously defined, appeared approximately ninety minutes on the average from the time of CO administration. As during the pre-CO phase, measurements of blood pressure, heart rate, and respiratory tracings were made intermittently. The second blood samples were then drawn over a period of two minutes simultaneously with the cardiovascular and respiratory recordings and with the collection of mixed expired air. A third phase was then entered during which the dog inspired either room air or 100% O₂ and was allowed to recover from
the CO inhalation. No further blood samples were drawn, however, blood pressure, heart rate, minute volume, tidal volume, and respiratory rate were recorded at frequent intervals during the recovery phase.

The control group of six dogs was handled in exactly the same manner as the experimental group except that the Douglas bags were filled with room air only, and this was administered to the dogs in lieu of the CO-air mixture. The same measurements were obtained, and the experimental procedure followed was identical to that carried out on the experimental dogs.

A second series of experiments were performed in order to investigate certain discrepancies in the data obtained from the previously described study. A detailed explanation and discussion of this will be found later under the discussion section (p. 60); however, the experimental procedures will be described here.

Five male and female dogs ranging in weight from nine and one-half to twenty-one kilograms were used. The right femoral artery of all the dogs was cannulated, and a catheter was inserted into the right femoral vein and introduced into the inferior vena cava so that the tip of the catheter was positioned two or three inches below the entrance to the
right heart. A 0.15% CO-air mixture was prepared in the same manner as in the first experiment and placed in Douglas bags.

Measurements of arterial and venous pH were made together with arterial and venous $O_2$ and $CO_2$ contents. Using the method of Van Slyke and Sendroy (61), arterial and venous $PCO_2$ was calculated. Venous blood was obtained from the inferior vena cava, and arterial blood was drawn from the femoral artery. Arterial blood pressure was recorded in the same manner as before, and venous pressure in the inferior vena cava was simultaneously recorded with the arterial pressure. Hematocrits were determined both before and after CO administration for use in the $CO_2$ tension computation.

In general, the experimental procedure used in the first experiment was followed. The dog was allowed to reach a respiratory and cardiovascular steady state, fifteen cc. each of arterial and venous blood were drawn, and the animal was then administered the CO-air mixture. When respiration and circulation again stabilized, arterial and venous samples were taken for the second time. Intermittent recordings of ventilation, venous and arterial blood pressure, and heart rate were made during the course of the experiment.
D. Calculations

Alveolar ventilation was calculated from the relationship:

\[ V_A = MV - (DS \times RR) \]

Where:
- \( V_A \) = alveolar ventilation - cc./min.
- \( MV \) = minute volume or total ventilation - cc./min.
- \( DS \) = dead space volume - cc.
- \( RR \) = respiratory rate/min.

Minute volume and respiratory rate were measured on the spirogram, and dead space was calculated using the Bohr equation:

\[ DS = TV \left( \frac{F_A CO_2 - F_e CO_2}{F_A CO_2} \right) \]

Where:
- \( TV \) = tidal volume - cc.
- \( F_A CO_2 \) = alveolar CO\(_2\) fraction
- \( F_e CO_2 \) = expired CO\(_2\) fraction

The dead space of the respiratory valve was measured and found to be seventeen cc. This volume was subtracted from each calculated physiological dead space volume. The dead space of the Tissot spirometer could be eliminated from the calculations since the apparatus was thoroughly washed out with expired air from the dog prior to the extraction of each mixed expired air sample. Alveolar CO\(_2\) fraction was determined by assuming that the alveolar Pco\(_2\) is nearly equal to the arterial Pco\(_2\) since the blood comes into near equilibrium
with the alveoli in regard to CO₂ partial pressures. The relationship:

\[ F_{ACO_2} = \frac{Pco_2 - B-47}{Pco_2} \]

\( Pco_2 \) = arterial CO₂ tension - mm. Hg.
\( B-47 \) = barometric pressure minus H₂O vapor pressure at 38° C.

This relationship gives the value for the alveolar CO₂ fraction which can then be inserted into the Bohr equation.

Cardiac output was calculated from the Fick equation:

\[ C.O. = \frac{O_2 \text{ consumption}}{A-V O_2 \text{ cont. diff.}} \]

where \( A-V O_2 \) content difference represents the difference between arterial and venous O₂ content of simultaneously collected mixed venous blood and arterial blood samples, and the O₂ consumption is the total uptake of oxygen by the dog in cc./minute during the drawing of the blood samples.

O₂ consumption (metabolic rate) was computed using the Tissot-Haldane open-circuit method with the equation:

\[ MR = (F_{iO_2} \times V_i) - (F_{eO_2} \times V_e) \]

\( F_{iO_2} \) = fraction of O₂ in inspired air
\( F_{eO_2} \) = " " " " expired "
\( V_i \) = minute volume, inspired air
\( V_e \) = " " " " expired "
The inspired volume of air can be determined from the relationship:

\[ V_i = \frac{V_e \times F_eN_2}{F_iN_2} \]

- \( V_e \times F_eN_2 \): expired \( N_2 \) fraction
- \( F_iN_2 \): inspired \( N_2 \) fraction

In Experiment 2, arterial and venous CO\(_2\) tensions were calculated using a three-scale nomogram and pH table from Van Slyke and Sendroy(61). A factor, \( f_0 \), can be read from one scale on the nomogram if pH and hematocrit are known on the other two scales. To calculate the Pco\(_2\), \( f_0 \) is multiplied by total whole blood CO\(_2\) determined by the Van Slyke manometric method, and this product represents serum CO\(_2\). A factor, \( f \), is read from the pH table according to the pH value of the whole blood as measured by the Cambridge pH meter, and this factor is multiplied by the serum CO\(_2\) to give Pco\(_2\) directly.

All gas exchange volumes were corrected to STPD conditions.
RESULTS

Respiration

Table I summarizes the respiratory changes. Individual and average values of the experimental and control groups are listed together with the percent change in each. The experimental group showed a significant average increase in minute volume of 67.5%, and a smaller increase in alveolar ventilation of 45.7%. Respiratory rates exhibited marked augmentation whereas tidal volumes measurements showed a decline in most cases. Control dogs remained essentially unchanged.

Blood Chemistry

The blood chemistry data are tabulated in Table II. This chart includes individual values for all dogs as well as means for both groups. Upon consideration of the experimental dogs, we note that the arterial blood showed no significant changes in pH and P02 during the CO inhalation period as compared with the pre-CO period. Statistical analysis of all data was achieved through use of the method of paired comparisons(2). The arterial Pco2 showed a slight reduction. More-
over, the $O_2$ content displayed marked diminution, and the $CO_2$ content declined slightly. On the venous side, the picture was quite different. The data showed that an average reduction in pH from 7.28 to 7.23 occurred which represented a statistically significant decrease. However, arterial pH did not show this decline, and all attempts to explain this difference logically were unsuccessful. Therefore, it was decided to reinvestigate pH and $O_2$ and $CO_2$ content changes by performing another series of experiments. In addition to these measurements, it was deemed advisable to record venous pressure in order to determine whether and discernible change in this variable could have any direct application to respiratory and cardiac function. The results of this experiment are given at the end of this section (p. 54).

Average figures for the $O_2$ tensions and contents showed a considerable decrease. $CO_2$ tensions and contents, however, showed a reduction of approximately the same magnitude as the arterial values, however, these changes were not statistically significant. The control dogs exhibited no significant changes in arterial and venous pH, $O_2$ content, or $O_2$ tension. The control arterial and venous $CO_2$ determinations indicated no significant changes according to statistically insignificant figures for the confidence limits.
Circulation and R.Q.

Table III includes all cardiovascular data and Table IV lists all gas exchange data. Blood pressure and heart rate did not change significantly during the course of CO inhalation, however, cardiac output increased 34% on the average. Statistical analysis of cardiac output data indicated a probability of greater than 5% that this represents random change. However, dog #13 showed a considerable decrease in cardiac output after CO inhalation, and it was believed that the analyses of O₂ contents were in error giving a falsely high A-V O₂ difference. Statistical treatment of the data excluding this dog produced a highly significant probability figure testing this increase in cardiac output. Stroke volume showed a statistically significant increase of 27% on the average. Metabolic rates showed a slight decline while CO₂ elimination values increased somewhat. These factors resulted in a statistically significant increase in R.Q. The control dogs showed no appreciable changes in regard to circulatory or cardiac function. Control O₂ consumptions, CO₂ outputs, and R.Q.'s were altered little; all changes being statistically insignificant.

Figure 3 is a composite graph of all experimental
dogs showing minute volume changes prior to CO administration, during CO, and during the recovery phase. Figures 1a to 1j are individual experimental dogs depicting arterial blood pressure and a comparison of minutes volumes and alveolar ventilation volumes during the three phases. Figures 2a to 2f represent individual control animals showing the course of blood pressure, minute volume, and alveolar ventilation during the course of the experiment. Figure 4 is a composite plot of minute volume measurements of all control dogs during the experiment. A comparison of this graph with Figure 3 gives at a glance the respiratory trend under experimental and control conditions.

It should be noted that in all figures showing the recovery course of ventilation in the experimental dogs, ventilation rates, both total and alveolar, show a distinct tendency to return to pre-CO levels. Dogs #26 and #28 were given 100% O₂ to breathe during recovery, and it will be noted that the return to normal respiration is greatly accelerated probably due to the mass activity of the high O₂ pressure in the alveoli. This observation during the recovery period is further evidence that the ventilatory response is due to some variable associated with CO breathing and not a result of anesthesia administration or other parameters.
unrelated to CO administration.

Results of Experiment 2.

The results of the second series of experiments are tabulated in Table V. These data show that both arterial and venous pH are increased after CO when compared to the pre-CO values, however, the post-CO arterio-venous pH difference show no appreciable change over the pre-CO difference. Minute volume increases averaged 113.4%. Heart rate and arterial blood pressure showed no essential changes; this was in general agreement with the first series of experiments. Both arterial and venous O₂ and CO₂ contents were decreased markedly after CO inhalation, and calculated Pco₂ was diminished. Venous blood pressure showed some decline in all dogs, however, it was most evident in dogs #31 and #32. None of the dogs displayed any rise in inferior vena caval pressure.
DISCUSSION

In our opinion, this investigation has settled any controversy over whether hyperventilation occurs to any extent whatsoever in anesthetized dogs inhaling relatively low concentrations of carbon monoxide over a period of time during which the CO saturation of the blood reaches approximately 40%. In the past, few experiments have utilized a reasonably large number of experimental animals, and still fewer studies have included control groups. In this study, we feel that we have utilized enough experimental animals to warrant valid interpretation of data. In respect to criticism leveled at investigations using anesthetized animals, it is felt by this author that anesthesia, even though exerting certain depressant effects upon various higher central nervous reflex centers, can be employed effectively in many studies on cardiopulmonary mechanisms if the experiment is adequately controlled. Fear, anxiety, and other emotional states experienced by trained unanesthetized dogs undergoing either rapid or slow onset of hypoxic states may interfere with or, indeed, even prevent accurate observation, and thus the disadvantages inherent in this technique are clearly comparable to those encountered in procedures using barbi-
tuates.

The data show conclusively that a rise in pulmonary ventilation does occur during CO administration, and, moreover, that upon cessation of CO inhalation, respiration again returns toward the pre-CO levels as the dog eliminates the gas from the blood. These findings agree well with similar work done by Von Oettingen(59), Swann and Brucer(56), Henderson and Haggard(25), Thiel(58), Haldane(27,28), Kamel(36), Chaftschenko(11), Klimmer(39), Müller(46), and Terzioğlu and Emiroğlu(57). On the other hand, Sayers et al.(50), Hayhurst(34), Chiodi et al.(12), and Asmussen and Chiodi(3) all report that either no hyperventilation occurred, or that respiration was actually depressed. These latter workers appear to depend heavily upon the concept that since arterial $Po_2$ is normal in CO poisoning(actually unmeasured, however), no hyperpneic response should be elicited. Von Oettingen, in a very comprehensive review article(60), appears to accept the evidence in favor of a hyperventilatory response to CO, however, he summarized his interpretations by concluding that due to the complicating factors of CO-induced lung hyperemia and edema, oxygenation of the blood is impaired during its passage through the lungs. Therefore, arterial $Po_2$ decreases resulting in hyperventilation. Von
Oettingen conceded that determination of $O_2$ tensions would be required to bear out this contention. Our experiment contraindicates the possibility of hypoxic stimulation through a diminished arterial $Po_2$. Lilienthal\(^{(41)}\) stressed the fact that, although many investigators observed a heightened respiratory state, this response was found only in anesthetized animals and, therefore, must be due to complicating factors of the barbiturate directly or as a result of "the shock of overwhelming anoxia". However, Swann and Brucer\(^{(56)}\) published data in 1949 previous to Lilienthal's review in which trained unanesthetized dogs were used as experimental animals. Increases in ventilation rate were observed with arterial saturations of 15% and above.

The increase in ventilation is for the most part accomplished through tachypneic breathing, that is, a considerable increase in respiratory rate occurs with diminished tidal volume. When we consider the chemical factors of the blood, we find that analysis of the arterial blood drawn during the re-established steady state, which occurs after approximately ninety minutes of CO breathing, yields values which are not at levels normally sufficient to cause respiratory stimulation. In the first series of experiments on ten dogs, arterial $Po_2$ remained unchanged, arterial $Pco_2$ was
slightly diminished, and arterial pH was unchanged. The second series of five dogs showed a marked decrease in arterial CO₂ content with a corresponding rise in pH presumably due to the strong hyperventilatory response which occurred in these dogs. Since the arterial Po₂ remains unaltered, and the arterial Pco₂ and pH are either unchanged or diminished during the hyperventilatory state, we must look elsewhere other than the arterial blood for an explanation.

We do know that respiration is influenced by metabolic rate. Experimental data obtained during moderate exercise have been compiled from the literature by Gray(24), and ventilation rate was plotted against O₂ consumption. The two factors were found to vary directly so that as the metabolic rate went up, ventilation rate increased proportionally. This particular response depends upon yet unknown mechanisms since the three chemical factors in the arterial blood remain unaltered so long as exercise remains moderate. In our experiment, O₂ consumption changes are for the most part random in both experimental and control dogs with perhaps a slight trend toward a decreasing consumption as the experiment progresses. Obviously, this factor can be eliminated as a possible stimulus to the increased respiration.

Other physiological factors have been found to in-
fluence respiration. One variable which has been found to augment respiratory function is diminished arterial blood pressure (8, 24). Dog #11 in Figure 1f shows this phenomenon very clearly. However, in all other experimental dogs, the arterial blood pressure varied in a random manner showing no significant overall changes. Venous pressure may also have an influence on respiration. Harrison (32) has advanced the interesting possibility that pressoreceptors are present in the great veins which operate to increase ventilation when venous blood pressure rises. This theory, however, fails to explain the presence of hyperventilation in this experiment. Results of venous pressure measurements made on the second series of five dogs show that a decrease in vena caval pressure occurs after ninety minutes of CO breathing.

An interesting characteristic of the venous blood of post-CO dogs is the low O₂ tension. The explanation for this must certainly be that arterial blood flowing into the tissues contains a much diminished O₂ content with a normal Po₂. Since metabolic rate is not altered significantly before and after CO, the tissues tend to remove the same amount of oxygen per unit volume of blood coming to them. Consequently, the Po₂ of the blood falls precipitously as it traverses the tissues. The venous Po₂ must reflect approximately the
tissue $P_{O_2}$ since the two come into near equilibrium during blood flow through the capillary bed. A rise in cardiac output would decrease the arterio-venous $P_{O_2}$ difference, but, in our studies, the rise in cardiac output was not enough to obscure the augmented decline in blood $P_{O_2}$ associated with decreased $HbO_2$ capacity. The increase in cardiac output with constant arterial blood pressure indicates that a decreased peripheral resistance has taken place. Local tissue $O_2$-lack probably causes arteriolar and capillary vasodilation and induces an increase in blood flow through the capillary bed as a compensatory measure against tissue hypoxia. Haldane (30) originally believed that moderate hypoxia of the respiratory center could cause stimulation of respiration. He later (9) modified his theory, and with the revolutionary discovery of the carotid and aortic bodies (15), $O_2$ regulation of respiration was then believed to be mediated entirely through these glomi. Today, the common conception in regard to $O_2$ effects upon the respiratory center seems to be that severe hypoxia of the center depresses respiration. However, some physiological responses to low $O_2$ are active, excitatory processes. For example, $O_2$-lack has direct stimulatory effects on the heart and also has an effect on the arterioles and capillaries of active tissue; namely, a gen-
eralized pressor response mediated through the vasomotor center. Such examples indicate that the respiratory center cells too may be sensitive to a lowered $O_2$ tension.

McGinty and Gesell in 1925(43) proposed a theory which states that lactic acid accumulation in the brain tissues played a major role in regulation of respiration under anaerobic conditions. This study was carried out before Heymanns isolated the carotid bodies and was an obvious attempt to explain how hyperventilation occurred under conditions of low $O_2$. These workers induced CO hypoxemia in unanesthetized dogs and determined the rate of lactic acid build-up in brain tissue during the anoxemic state and found that a considerable amount of the acid did accumulate. They proposed that this condition induced lowering of the pH of the medullary respiratory center which in turn produced the hyperpneic state. Furthermore, they claimed that this condition explained why hyperventilation occurred even when the arterial blood was alkaline or showed a normal pH. Gesell extended this theory in later work(22) when he observed that ventilatory responses did not always vary in a predictable fashion when compared with blood pH and $P_{CO_2}$. This so-called dissociation theory holds that the arterial chemical factors ($P_{O_2}$, $P_{CO_2}$, pH) are not always an index of the tissue factors.
Modified buffering characteristics, unsteady states, etc., might easily cause a variation between intracellular and vascular chemical properties. In our experiment, a modified buffering capacity appears to prevail. A deficit of reduced hemoglobin which is basic in reaction develops during the course of CO inhalation in addition to the increasing amounts of carboxyhemoglobin. According to a study done by Hastings, Sendroy, Murray, and Heidelberger(33), the base-binding curves of HbCO and HbO₂ are identical, that is, HbCO has the same acid properties as HbO₂. As the blood flows through the tissues, the acid carboxyhemoglobin prevails, and a diminished amount of reduced hemoglobin is progressively produced. Thus, a moderate increase in H-ion concentration of the tissues could conceivably occur, since the buffering capacity of the hemoglobin is markedly diminished. The blood chemistry data in Table II from the first ten experimental dogs show that after CO, arterial pH remains unaltered while venous pH appears to be decreased. Using these data, an unsuccessful attempt was made to explain this phenomenon on the basis of alterations in the CO₂ dissociation curves. It was finally concluded that technical errors in pH measurements were at fault, and, therefore, another series of experiments were undertaken to establish definitely whether arterial and ven-
ous pH changed independently of one another during CO breathing. Table V shows the data from this experiment. It is to be noted that the five dogs hyperventilated to a greater degree than the previous ten animals, and, thus, the CO₂ contents were diminished quite markedly. However, pH values, although showing pronounced increases which were not evident in the first experiment following CO administration, exhibited essentially an unchanged arterio-venous pH difference. These results indicate that even with the presence of a diminished capacity of the circulating hemoglobin for buffering hydrogen ion concentrations in excess of normal, elimination of dissolved CO₂ from the plasma through hyperventilation maintained the pH at near normal levels; in fact, a moderate alkalosis actually prevailed. This fact, however, does not obviate an application of Gesell's concept that the respiratory center hydrogen ion concentration may differ considerably from that of the plasma even during steady states.

This discussion has dwelt primarily on chemical factors of the tissues and blood which exert their effects upon the medullary regions. However, since all tissues experience the effects of CO anoxemia, we may also consider the possibility of specific receptors in the tissues or on the venous side of the circulation. Low tissue and venous PO₂ could
conceivably stimulate receptors in active tissue such as the heart or skeletal muscle. Receptors in the great veins or entrance to the right heart sensitive to low O₂ tension could exist, such structures being analogous to the chemoreceptors located in the lungs or the carotid sinus and aortic arch areas. Perfusion experiments oriented toward establishment of the presence of specific receptors in these suspected areas would be of great value.

It is of interest now to discuss some of the respiratory investigations that were mentioned in the Historical Review section, and to compare results from these studies with the findings in this experiment.

Kamei's study(36) provides us with a specific experiment quite similar to those which were carried out in this investigation. Listed below are data from an individual experiment done on a female dog weighing nine kilograms. 0.1% CO in air was administered for two hours and forty-five minutes.

<table>
<thead>
<tr>
<th></th>
<th>Before CO</th>
<th>After CO</th>
</tr>
</thead>
<tbody>
<tr>
<td>arterial CO₂ content</td>
<td>46.2 v.%</td>
<td>43.2 v.%</td>
</tr>
<tr>
<td>arterial O₂ content</td>
<td>14.3 &quot;</td>
<td>7.7 &quot;</td>
</tr>
<tr>
<td>arterial pH</td>
<td>7.32</td>
<td>7.17</td>
</tr>
<tr>
<td>respiratory rate</td>
<td>18/min.</td>
<td>18/min.</td>
</tr>
<tr>
<td>ventilation rate</td>
<td>2.9 L./min.</td>
<td>3.9 L./min.</td>
</tr>
<tr>
<td>heart rate</td>
<td>144/min.</td>
<td>240/min.</td>
</tr>
</tbody>
</table>

It can be seen from the O₂ contents that following CO breath-
ing, the HbCO saturation was about 50% which compares with the levels found in our dogs. Discrepancies between Kamei's results and ours are immediately evident. pH is diminished markedly after CO in this dog even with some decline in CO2 content. In our dogs, we find either no change in arterial pH or a rise (Experiment 2) due to pronounced hyperventilation. Respiratory rate showed no change in Kamei's experiment in direct contrast to the consistent changes observed in our animals. In addition, Kamei's ventilation rate increase obviously came about as a result of an increase in tidal volume whereas, in general, our tidal volumes showed a diminution. Heart rate in Kamei's experiment increased considerably also in direct contrast to our findings. Two other dogs inhaling CO-air mixtures of 0.08% showed variable results. The data from these dogs show respiratory rate increases in two dogs, heart rate up in two dogs and down in two, and an arterial pH drop in two dogs with a rise in the other. These experiments have been singled out to exemplify the extreme variability found in most CO studies. Although the pH results were variable even with the higher CO-air concentrations used in Kamei's experiment, he interpreted CO anoxemia as basically an acidotic state. Mikami(44) supported Kamei in his contention that CO inhalation produces acidosis as a
result of lactic acid accumulation in the blood and tissues, and both workers regarded the alkaline reserve decline as a consequence of the acidosis. Haggard and Henderson (25) opposed this view and believed that CO poisoning produced an alkalosis due to the excessive elimination of CO₂ through the hyperventilation response. Our results contribute evidence to support these latter worker's contention. Data from the first series of experiments show no consistent variation in arterial pH. The second experiment shows a rise in pH in all five dogs presumably due to the greater ventilatory response. None of the fifteen experimental dogs showed a fall in pH; a fact which fails to substantiate observations of acidosis occurring during moderate CO poisoning.

Only one observation was found in the literature in which venous O₂ tension was measured before and after CO inhalation; a study done by Asmussen and Chiodi (3). Interestingly enough, their data indicated that venous Po₂ was diminished significantly when compared to normal values. The significance of a low venous Po₂ level in regard to possible ventilatory effects has already been discussed.

Chiodi's experiment (12) provides somewhat of a puzzle in that the moderate HbCO saturation levels (16-53%) present in their experimental subjects produced either di-
minished respiration or, as in the case of their dog experiments, no change in ventilation. It is difficult to understand why both dogs exposed to various CO concentrations showed no respiratory response since overwhelming evidence exists in the literature in favor of a definite hyperpneic response in both anesthetized and unanesthetized dogs during CO administration. These authors state that the respiratory center must be depressed by the CO-induced hypoxemia, however, it is difficult to believe that HbCO saturations as low as 16-30% could produce medullary center depression severe enough to affect the highly resistant respiratory area.

Terzioglu and Emiroglue's work in 1957(57) merits some discussion in relation to our results. These workers noted that a delayed respiratory response to CO occurred in chemoreceptorless dogs, and that an immediate response resulted in normal dogs. Their hypothesis was that in dogs deprived of their chemoreceptors, metabolic accumulation in the respiratory center was responsible for the delayed hyperpnea. On the other hand, dogs with carotid and aortic glomi intact experienced a hypoxic state in the chemoreceptive zone which elicited a reflexogenic ventilatory response mediated through the respiratory center. Terzioglu and Emir-
oglue believed that since the chemoreceptors are tissues, they experience the same overall hypoxemic effects as do the rest of the body tissues when the arterial O$_2$ content is diminished. This postulation is opposed by Comroe and Schmidt's view that the carotid body remains unstimulated so long as the arterial plasma Po$_2$ is normal. These latter workers perfused the carotid region in dogs with blood which had been 100% saturated with CO but still possessed a normal Po$_2$ of 100 mm. Hg. No changes in respiration were noted which led them to postulate that the metabolic requirements of the glomi can be met with the dissolved O$_2$ in the arterial plasma alone. Therefore, it is felt by this author that Terzioglu and Emiroglue's explanation for the hyperventilatory response in normal dogs is wholly unsatisfactory since we have shown in this experiment that arterial Po$_2$ remains unchanged during CO hypoxemia.

It is interesting to note that this experiment produced changes in arterial and venous pH values which were in direct contrast to data from the majority of other sub-lethal studies on CO. Our pH values showed either a rise over initial values, or else no significant changes at all were noted. As can be seen from a comparison of the data from the first group of ten experimental dogs and from the second
group of five dogs, the rise in pH appears to be directly related to the extent of the hyperpnea. A relatively vigorous hyperventilation could mask a moderate acidosis and actually raise the pH above normal levels. A second explanation for the contrasting results might be the fact that blood pH seems to be directly related to the rapidity of onset of CO hypoxemia and also the HbCO level existing at the time of the pH determinations. An examination of Swann and Brucer's data(56) shows that even with the high concentration of CO they utilized(1%), no excessive lactic acid accumulation and no decrease in pH was evident even up to HbCO saturations of 50%. After this somewhat critical point, blood lactic acid began to rise sharply, and consequently blood pH fell even though some hyperventilation was present. The concentration of CO in air used in our study was lower than the concentrations used in the great majority of investigations, and, therefore, any physiological compensatory measures would have more opportunity to exert their effects if the onset of hypoxemia were less rapid as in our experiment.

Let us now consider the cardiovascular effects of CO inhalation. Here again the literature points up a controversy over whether cardiac output, blood pressure, and heart rate exhibit changes during CO administration.
If we consider the question of cardiac output changes, we find no definite agreement among different investigators. Asmussen and Chiodi (3) failed to show any change in output with blood saturation levels up to 30% CO hemoglobin. However, Chiodi et al. (12) showed that cardiac output increased with saturations from 30% to 50% HbCO. Likewise, Miura (45) found an increase in cardiac output.

Arterial blood pressure changes appear variable. Brewer (10) reported that dogs exposed to an O₂ and CO mixture show no pressor response. Kayser (35) also showed that arterial blood pressure exhibited little change during CO inhalation. On the other hand, Von Oettingen, et al. (59), Loepper (42), and Swann and Brucer (56) found an initial rise followed by a progressive decline as CO inhalation continued.

Heart rate changes appear to show more general agreement among investigators than cardiac output and blood pressure. Swann and Brucer (56), Asmussen and Chiodi (3), Miura (45), Ciampolini (13), Killick (37) showed moderate increases in pulse rate during the course of CO breathing up to the point of circulatory failure. Kayser (35), however, found no apparent reflex activity with regard to both blood pressure and heart rate.

Our data show that definite increases in cardiac out-
put do occur. Moreover, arterial blood pressure and heart rate
do not change significantly. These dogs range from about 25% to
55% carboxyhemoglobin saturation and, therefore, fall in
the same range as the saturations reported in the literature
with sub-lethal studies. Since heart rate remains essentially
unchanged while cardiac output increases, it is clear that
the rise in cardiac output must have resulted from an in-
creased stroke volume. An explanation of this cardiac re-
sponse can be advanced on the basis of the altered chemical
factors of the blood and tissues. Low \( O_2 \) levels in the tis-
sues caused arteriolar and capillary vasodilation which re-
sulted in an increased venous pressure initially. The dia-
stolic filling pressure was augmented, hence, an increase in
stroke volume. The venous pressure again fell to normal lev-
els as the increased stroke volume pumped blood from the venous
side through the lungs and into the arterial system. How-
ever, capillary bed dilatation progressively increased be-
cause of the increasing tissue hypoxia, and a new volume
flow level toward the heart was established. Our data show
definite evidences of low tissue \( P_{O_2} \) which could activate
this response mechanism.

A general conclusion can be drawn with regard to the
question of when respiration and cardiovascular function
actually show increases during CO inhalation. On the basis of analysis of data found in the literature and also upon consideration of pilot studies done on anesthetized dogs in our laboratory using concentrations of CO somewhat higher than 0.15%, it would seem that the extent of hyperventilation depends primarily upon the concentration of the CO-air mixture used for a particular experiment, and the rapidity with which the hemoglobin is saturated with CO. According to Von Oettingen's review(60), an exposure to a very low concentration(0.01%) of CO in air would produce a CO saturation of 10% in five hours, whereas it would take only about ten minutes to produce the equivalent CO saturation with 1% CO.

The two ventilatory responses at this saturation level will tend to differ, the greater response occurring with the higher concentration which saturates the blood more quickly.

Cardiovascular changes seem to follow the same scheme as the respiratory responses, namely, that duration of exposure and concentration of the CO mixture play a vital part in determining the extent and direction of the response. Slow onset of CO anoxemia with low concentrations of CO appear to have much less of an effect than a more rapid onset with higher CO concentrations. These two factors must be carefully weighed when attempting to compare and interpret
results of various investigations.

We have seen that cardiovascular and pulmonary responses during CO poisoning are varied and somewhat unpredictable. We have made an attempt here, however, to carry out a thorough and comprehensive study of these responses with particular emphasis on the three main chemical factors of the blood and body fluids. It is realized that other factors certainly enter into the overall picture of compensatory physiological regulation during CO anoxemia, however, logical explanations may be found in the blood chemistry alterations described in these studies.
SUMMARY AND CONCLUSIONS

Data have been presented from which definite conclusions can be drawn about physiological responses of the respiratory and cardiovascular systems to inhalation of low, sub-lethal concentrations of carbon monoxide yielding carboxyhemoglobin saturations of about 40%. Conclusions may be summarized as follows:

1) In the first experiment, an average increase in total ventilation of 68% and in alveolar ventilation of 46% occurred. The alveolar ventilation tended to increase to a lesser extent because, in most cases, a tachypneic-type hyperventilation with diminished tidal volume ensued in post-CO dogs allowing a more significant contribution of the respiratory dead space to occur. In the second experiment, minute volume showed an overall mean increase of 113% in five dogs.

2) Cardiac output showed an average rise of 34%, and stroke volume exhibited an increase of 27%. Heart rate and arterial blood pressure showed no essential changes. Inferior vena cava blood pressure tended to decrease probably because the hyperpneic effort caused a diminution in mean intra-
thoracic pressure. This factor together with a progressive, generalized capillary bed dilatation, which caused an increase in venous return to the heart, was responsible for the increase in stroke volume and, therefore, cardiac output.

3) Arterial $\text{Po}_2$ showed no significant change while arterial $O_2$ content was diminished markedly. Arterial $\text{Pco}_2$, $CO_2$ content, and $pH$ were either unaltered or the $\text{Pco}_2$ level markedly diminished causing a rise in $pH$. Venous $\text{Pco}_2$, $CO_2$ content, $\text{Po}_2$, and $O_2$ content all showed a diminution over pre-CO values. Venous $pH$ showed either no change or a rise over initial values. The buffering characteristics of the blood presumably were altered, and this situation may have created a modified chemical environment in the respiratory center and in active tissues in general. Low $O_2$ tension in these areas also contributed to this modified state. It may be that this altered environment was responsible for the increased respiratory and cardiovascular function.
APPENDIX
Figure 1a. - Course of minute volume, alveolar ventilation, arterial blood pressure during the pre-CO period, CO period, and post-CO period. - Dog #12.
Figure 16. - Org #15.
Figure lc' - Dog No. 21

Mean Blood Pressure - mm Hg

Minute Volume - cc/min.

Alveolar Ventilation - cc/min.

Time in Minutes
Figure 1d - Dog No. 23
Figure 16: MEAN BLOOD PRESSURE - mmHg

- MEAN BLOOD PRESSURE
- TIME IN MINUTES
- MINUTE VOLUME - cc/Min
- ALVEOLAR VENTILATION - cc/Min
Figure 1h - Dog No. 19
Figure 1j - Dog No. 28
Figure 2a - Course of minute volume, alveolar ventilation, and arterial blood pressure during three time periods without CO corresponding to the three periods with experimental dogs - Dog No. 22.
Figure 2b - Dog No. 25

Mean Blood Pressure - mmHg

Minute Volume - cc/Min

Alveolar Ventilation - cc/Min
MEAN BLOOD PRESSURE - mm Hg

TIME IN MINUTES

MINUTE VOLUME - cc/MIN.

ALVEOLAR VENTILATION - cc/MIN.
Figure 2d - Dog No. 18
Figure 3 - Composite graph of all experimental dogs showing the time course of minute volume during the pre-CO period, CO period, and post-CO period. The dashed vertical line at zero represents the time point of CO administration to all dogs. The dashed lines clustered around the 90 minute point on the abscissa represent the individual time points when CO administration was halted and air or O2 was given.
Figure 4.- Composite graph of all control dogs showing the time course of minute volume during three periods of time corresponding to the three periods in experimental dogs. The dashed vertical line at zero represents the time point of the beginning of bag air administration to all dogs while the dashed lines clustered around the 90 minute point represent the individual time points when ambient room air was again given.
Figure 5 - Comparison of carboxyhemoglobin dissociation curve (points marked X) with oxyhemoglobin dissociation curve (points marked O) for human blood at 38°C, $pCO_2 = 40$ mm Hg. (after Roughton, 1954).
Figure 6 - Carboxyhemoglobin dissociation curve of human blood in presence of air and varying percentage of CO at 38°C (after Roughton, 1954).
Figure 7 - Speed of saturation of hemoglobin with different concentrations of CO until equilibrium between the concentration of CO in air and blood is produced (after Von Oettingen, 1944).
Figure 8 - Oxygen dissociation curve of (1) human blood, at pH 7.40 and 38°C containing various percentages of carboxyhemoglobin, and of (2) anemic human blood containing only 40% of the normal hemoglobin content (after Roughton, 1954).
Figure 9 - Analysis of partial stimulating effects on alveolar ventilation of increased $pCO_2$ and increased H ion concentration in experiments in which CO$_2$ was inhaled (after Gray, 1949).
Figure 10 - Analysis of resultant alveolar ventilation under conditions of metabolic acidosis and alkalosis. Partial stimulating effect of increased H ion concentration and partial inhibiting effect of decreased H ion concentration are incompletely balanced by opposite partial effects of changes in pCO₂ (after Gray, 1949).
Figure 11 - Analysis of resultant alveolar ventilation under conditions of anoxia in which a partial stimulating effect of low pO₂ is incompletely balanced by a partial inhibiting effect of low PCO₂ (after Gray, 1949).
Figure 12 - Diagram of Experimental Set-up
## TABLE I

**Respiratory Data**

<table>
<thead>
<tr>
<th>Experimental Dog No.</th>
<th>Wt. Kg.</th>
<th>Sex</th>
<th>Min. Vol. cc./min</th>
<th>% Change</th>
<th>Alv. Vent. cc./min</th>
<th>% Change</th>
<th>Tidal v. cc.</th>
<th>% Change</th>
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Mean:

- 2127 ± 67.5 1119 ± 45.7 173 ± 19

s(1) = 240.3 397 14.9

**Control Dog. No.**

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Mean:

- 2614 ± 4.8 1443 ± 4.8 164 ± 5.2

s(1) = 91.5 55.0 0.9

*Statistically significant, P < 5%

**Mean difference**

I = Before CO

II = After CO

#Standard deviation of mean differences
### TABLE II

**Blood Chemistry Data**

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*Statistically significant, P < 5%

**Mean difference**

I = Before CO

II = After CO

*Standard deviation of mean differences
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Cardio-vascular Data

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<th>Heart Rate</th>
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<th>Stroke Vol. cc.</th>
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Control

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* Mean difference
** Standard deviation of mean differences
I = Before CO
II = After CO
TABLE IV
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Control Dog No.

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*Statistically significant, \(P < 5\%\)
**Mean difference
\#Standard deviation of mean differences

I = Before CO
II = After CO
### TABLE V

Data from Experiment 2

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BIBLIOGRAPHY


I, Frederick Clayton Thiede, was born in Grand Rapids, Michigan, on September 17, 1929. Following graduation from Jackson High School in Jackson, Michigan, I entered Western Michigan College in the fall of 1947 and completed the requirements for the Bachelor of Arts degree in June, 1951.

I entered the Army in the fall of 1951, and after completing basic training, I was assigned to the Neuropsychiatry Division at the Walter Reed Army Institute of Research in Washington, D.C. where I participated in retinal sensitivity studies. Upon being discharged from the service in October, 1953, I accepted employment at the Institute in the same capacity as when in service. I began graduate work in physiology at the George Washington University School of Medicine in February, 1954, on a part-time basis while working full time at Walter Reed. I was granted a Master of Science degree in June, 1956, and then entered The Ohio State University the following fall to begin study toward a doctoral degree in physiology.

While at Ohio State, I have held several teaching and research assistantships. A research contract from the Army Chemical Center provided the opportunity to carry out an investigation on the toxicity of carbon monoxide which
is presented here in dissertation form in partial fulfillment for the degree Doctor of Philosophy.