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# POLICE SCIENCE

## PHYSIOLOGICAL PRINCIPLES OF CARBON MONOXIDE POISONING

FRANK R. DUTRA

Frank R. Dutra, M.D., is Pathologist, Eden Hospital, Castro Valley, California, and Associate Clinical Professor of Pathology, University of California Medical School, San Francisco. Dr. Dutra is a Diplomate of the American Board of Pathology in Anatomical Pathology and Forensic Pathology, and was formerly Associate Professor of Forensic Pathology, University of Cincinnati Medical School, and Pathologist for the Coroner of Hamilton County, Ohio. Dr. Dutra has served as an Associate Editor of this Journal for a number of years and is the author of more than sixty publications on pathology and legal medicine.—*EDITOR*

“But the carbon monoxide, in displacing the oxygen that it had expelled from the blood, remained chemically combined in the blood . . . so that death came through death of the molecules of blood, or in other words by stopping their exercise of a physiological property essential to life”. Claude Bernard (1813-1878)

This statement, first printed a century ago, indicates the earliest understanding of the fact that the primary toxic effect of carbon monoxide depends upon the ability of the gas to combine with hemoglobin and to interfere with the transport of oxygen by hemoglobin throughout the body. All other results of carbon monoxide poisoning are secondary to the reduction in the supply of oxygen to the tissues during the period of intoxication.

The combination of hemoglobin and carbon monoxide is entirely reversible, and neither the hemoglobin nor the erythrocytes are damaged by an interlude of carbon monoxide transport.

### ABSORPTION OF CARBON MONOXIDE

During the early part of a period of exposure to carbon monoxide, about half of the total quantity of the gas which enters the lungs passes across the alveolar walls into the blood. It enters the erythrocytes and combines with hemoglobin to form carboxyhemoglobin, a compound structurally analogous to oxyhemoglobin (1).

As more and more of the hemoglobin combines with carbon monoxide, the rate of retention of the inhaled carbon monoxide diminishes considerably. After a time, for any given sublethal concentration of carbon monoxide in the atmosphere, the concentration of the gas in the blood will reach an equilibrium with that of the atmosphere, so that the flow of the gas from the blood into the alveolar

air is as rapid as the flow from the alveoli into the blood. The time required for the blood to reach this state of equilibrium is essentially identical at different concentrations of carbon monoxide in the atmosphere when the rate and depth of respiration are constant.

When a person inhales air containing carbon monoxide, the quantity of this gas passing into the blood and combining with hemoglobin before equilibrium is established depends upon the partial pressures of carbon monoxide and oxygen and on the relative affinity of hemoglobin for each of the two gases. With the relative affinity of human hemoglobin for carbon monoxide and oxygen established as 210:1, if the concentration of carbon monoxide in the air is known, it is possible to predict by the formula of Sayers and Yant (2) the proportion of hemoglobin that will be combined with this gas when equilibrium is attained:

$$\begin{aligned} & \% \text{ Hb combined with CO} \\ &= \frac{a_{\text{CO}} \times t_{\text{CO}}}{(a_{\text{CO}} \times t_{\text{CO}}) + (a_{\text{O}_2} \times t_{\text{O}_2})} \times 100 \end{aligned}$$

a = relative affinity of Hb for the gas

t = percentage of the gas in the alveolar air

Thus, a concentration of 0.05 percent (500 p.p.m.) of carbon monoxide in the pulmonary air (which contains approximately 15 percent of oxygen), would result in an equilibrium at which about 41 percent of the hemoglobin would be in combination with carbon monoxide:

$$\begin{aligned} & \% \text{ Hb combined with CO} \\ &= \frac{210 \times 0.05}{(210 \times 0.05) + (1 \times 15)} \times 100 \\ &= 41.2\% \end{aligned}$$

The blood of a resting human being who is exposed to a low, constant concentration of carbon monoxide will reach half the final saturation in approximately 47 minutes, and will be maximally saturated for this atmospheric concentration at approximately 5 hours after the start of the exposure (3). Experiments indicate that when the concentration exceeds 0.07 percent (700 p.p.m.) of carbon monoxide in the atmosphere the rate of rise of blood concentration toward saturation may be somewhat more rapid (4). Equilibrium will be reached more rapidly in the blood of small mammals which have a high rate of respiratory exchange per unit of body weight (5).

The rate of absorption is greatly increased by physical activity, the resting rate being approximately doubled during moderate exercise such as walking, and tripled during heavy exercise (4). Even though the final equilibrium is the same, regardless of the rate with which it is achieved, the person who is engaged in some physical activity is more likely to suffer injury from carbon monoxide than is one exposed to the same atmosphere at rest. The reasons for this are that the former will attain maximal saturation more rapidly, thereby suffering a longer period of oxygen deficiency to his tissues, and that the oxygen requirement of his tissues is greater because of his activity.

An equation that has proved to be of practical value for calculating the rate of absorption of carbon monoxide has been presented by Pace, Consolazio, White, and Behnke (6). Its validity is said to be high until the concentration in the blood has reached one-third of the predicted equilibrium for the concentration under consideration; as the concentration in the blood increases beyond this, the rate of uptake of carbon monoxide diminishes considerably so that the formula is not applicable. Assuming that the blood contains no carbon monoxide when the exposure begins, the calculation is as follows:

% Hb combined with CO

$$= \frac{\% \text{ CO in Air} \times \text{Minute Volume} \times \text{Exposure Time}}{46.5 \times \text{Blood Volume}} \times 10,000$$

(The minute volume is the volume of respiration in liters per minute, corrected to S.T.P.; exposure time is the duration of exposure in minutes; blood volume is expressed in liters, and for the purposes of this calculation it may be

obtained by multiplying the square meters of body surface by 3; the body surface area can be obtained by conversion charts from height and weight or may be calculated by the DuBois method.)

A nomogram developed from human experimental data by Forbes, Sargent, and Roughton (1) graphically depicts the rate of absorption of carbon monoxide from air containing various concentrations of the gas, and this permits easy estimation of the concentration of carbon monoxide in the blood at any time during a period of exposure when the atmospheric concentration of carbon monoxide is known (Fig. 1).

#### COMBINING WITH HEMOGLOBIN

Each molecule of hemoglobin can combine with from one to four molecules of either oxygen or carbon monoxide. However, hemoglobin has a much greater affinity for carbon monoxide than for oxygen, accounting for the harmful effects of carbon monoxide when the ratio of carbon monoxide to air is relatively low. In 1929, Sendroy, Liu, and Van Slyke (7) observed a constant relationship between the affinity of human hemoglobin for carbon monoxide and for oxygen, this relationship being 210:1. In none of their determinations was the variation from the average greater than  $\pm 2.5$  per cent. A number of samples of ox blood were also examined, and a relationship of 179:1 was constant with bloods from 10 different oxen.

The differential affinity of hemoglobin for two gases is the ratio between the partial pressures of the gases that will saturate the hemoglobin to the same degree with each. This ratio can be ascertained empirically by mixing the two gases (each at a known partial pressure) with a solution of hemoglobin, after which the concentrations of oxyhemoglobin and carboxyhemoglobin are determined.

$$\text{Relative affinity of hemoglobin: } \frac{a_{\text{CO}}}{a_{\text{O}_2}} = \frac{\text{HbCO} \times p_{\text{O}_2}}{\text{HbO}_2 \times p_{\text{CO}}}$$

As an example, consider that after a mixture of oxygen at a partial pressure of 28 mm. Hg and carbon monoxide at a partial pressure of 0.133 mm. Hg attains equilibrium with a solution of human hemoglobin, exactly 50 percent of the hemoglobin is combined with oxygen and 50 percent with carbon monoxide. Then, applying

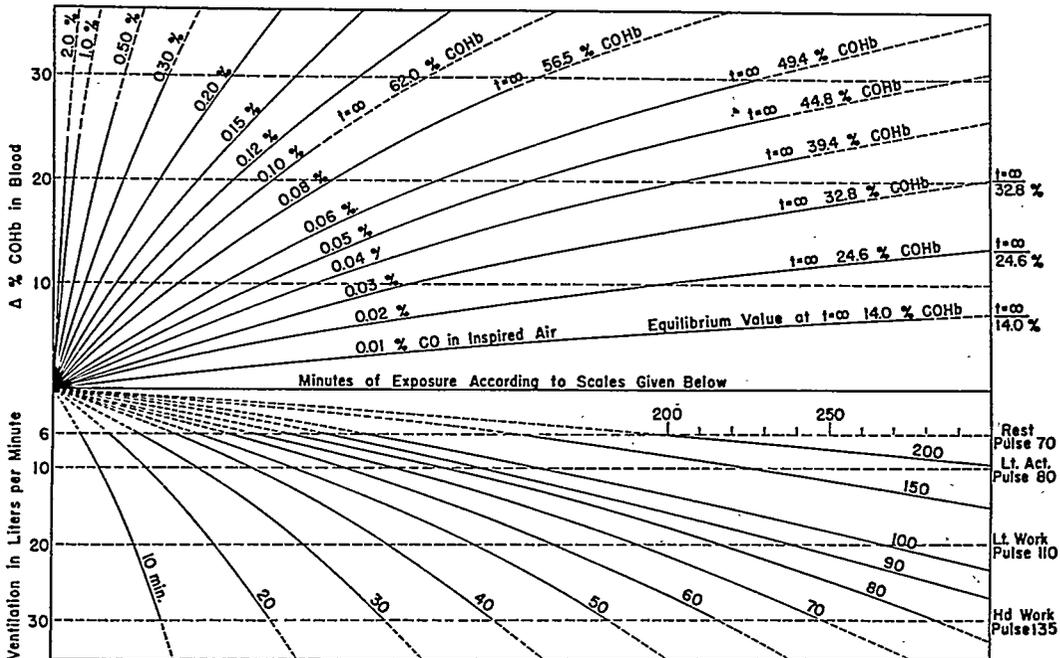


FIGURE 1

Nomogram for estimating human rate of absorption and final blood concentration of carbon monoxide from various atmospheric concentrations of the gas and at different rates of ventilation. This was constructed from experimental data in the ranges represented by solid lines, the dotted lines being extrapolations. The upper and lower quadrants give the relationships of four variables: (1) absorption of carbon monoxide, (2) concentration of carbon monoxide in atmosphere, (3) period of exposure, and (4) rate of ventilation in liters per minute.

To use, first determine the approximate rate of ventilation and fix this point upon the vertical (ordinate) scale of ventilation; then draw a horizontal line to the right intercepting the time curves (marked 10, 20, 30, etc.). The points of interception define the time scale for the rate of ventilation under consideration, and a vertical line raised from the point of intersection of these two lines to the curve which reflects the air concentration of CO in the upper quadrant will give on the ordinate scale the increase in the per cent of carboxyhemoglobin resulting from this degree of exposure over this period of time. The curved lines in the lower quadrant indicate time, i.e., all points on

the 20 minute line are 20 minutes. The equilibrium values which each curve approaches and which would be reached at infinite time are indicated after the symbol "t = ∞".

With this nomogram it is possible to determine the increase in carboxyhemoglobin that will occur over a given period of time when an average normal adult is exposed to any air concentration of carbon monoxide between 0.01 per cent and 2.0 per cent at sea level and at any ventilation rate between 6 and 30 liters per minute.

Example: What would be the concentration of carboxyhemoglobin in the blood of a previously unexposed man whose ventilation rate is 25 liters per minute after 85 minutes' exposure to air containing 0.05 per cent carbon monoxide? First, draw a horizontal line from 25 liters on the lower left hand scale to a point half way between the 80 and 90 minute lines. Then raise another line vertically to the 0.05 per cent curve in the upper half of the figure, and thence horizontally to the left to the ΔCOHb scale. The answer is 28.5 per cent carboxyhemoglobin. (This nomogram is reproduced with permission of the authors, Forbes, Sargent, and Roughton, (1), and the Editor of the American Journal of Physiology.)

the formula:

$$\frac{aCO}{aO_2} = \frac{50 \times 28}{50 \times 0.133}$$

$$\frac{aCO}{aO_2} = \frac{210}{1}$$

Thus, the relative affinity of human hemoglobin for carbon monoxide and oxygen is 210:1.

The fact that the relative degrees of affinity of

human hemoglobin for carbon monoxide and oxygen are correctly expressed as 210:1 appears to have been proved by the recent work of Sjöstrand (8); this constant is an essential part of his theory for determining the concentration of carbon monoxide in the blood by analyzing samples of alveolar air, and the success of the method attests to the constancy and validity of this ratio.

The most reasonable explanation for the difference in the affinity of hemoglobin for the two

gases is that while oxygen and carbon monoxide both combine rapidly with hemoglobin, the time required for the dissociation of carboxyhemoglobin is much greater than for oxyhemoglobin (9, 10, 11, 12).

Carbon monoxide combines rapidly with hemoglobin and will displace oxygen from oxyhemoglobin until equilibrium is reached. Under experimental conditions with carbon monoxide at a partial pressure of 75 mm. Hg, the gas combines with hemoglobin from an adult sheep over the following periods of time (13):

*Average Time for Half Reaction*

Hemoglobin in Erythrocyte	Hemoglobin in Solution
0.15 second	0.06 second

The difference in rate of reaction depends on the greater accessibility of the molecules of hemoglobin in the solution as compared with those in the erythrocytes.

In the circulating blood, carbon monoxide combines with hemoglobin in proportion to its partial pressure, while the concentration of the gas which remains dissolved in the plasma depends upon its solubility and partial pressure. The same rules apply to oxygen; thus, blood leaving the lungs during exposure to carbon monoxide carries an almost normal concentration of oxygen dissolved in the plasma, but because of the greater affinity of hemoglobin for carbon monoxide disproportionately less oxygen is carried by the hemoglobin. Blood entering the arterial capillaries has an almost normal partial pressure of dissolved plasma oxygen, but as that gas diffuses into the tissues, the absence of the usual reserves of oxygen in the erythrocytes becomes apparent.

EXCRETION OF CARBON MONOXIDE

The only route for excretion of carbon monoxide is the respiratory tract, whence it is eliminated in the expired air. When a patient is moved from the contaminated atmosphere, elimination of the gas begins at once. The rate of elimination depends upon the composition of the atmosphere being breathed.

Sayers and Yant (2) studied the elimination of carbon monoxide by human subjects during the inhalation of air, of oxygen, and of a mixture of 8 to 10 percent carbon dioxide with pure oxygen.<sup>1</sup> As was anticipated on the basis of the work of Henderson and Haggard (14), elimination was

slowest when the victim inhaled only air, and was most rapid with the inhalation of the mixture of carbon dioxide and oxygen. At first, the gas is lost rapidly but the rate diminishes progressively until toward the end of the excretory period elimination proceeds very slowly. The curves of excretion are of the exponential type: the log of any percentage ( $S'$ ) of carboxyhemoglobin after a lapse of time ( $t$ ) from the termination of exposure is equal to the log of the initial saturation ( $S$ ), plus a constant ( $b \log e$ ), multiplied by the time ( $t$ ):

$$\log S' = \log S + (b \log e) t$$

The constant ( $b$ ) is a negative number and was determined from experimental curves of elimination made under varying respiratory conditions, and the following average values are given:

<i>Patient Breathing</i>	<i>b</i>
Air	-0.00178
Pure Oxygen	-0.00693
CO <sub>2</sub> in Pure Oxygen	-0.01169

The value for  $\log e$  is 0.4343. Sample calculation to determine the proportion of carboxyhemoglobin that would be present 100 minutes after start of therapy with mixture of oxygen and carbon dioxide, when the initial hemoglobin saturation with carbon monoxide was 35 per cent:

$$\begin{aligned} \log S' &= \log S + (b \log e) t \\ \log S' &= \log 35 + (-0.01169 \times 0.4343) \times 100 \\ \log S' &= 1.544 + (-0.0050770) \times 100 \\ \log S' &= 1.544 - 0.50770 \\ \log S' &= 1.0363 \\ \text{Saturation after 100 minutes treatment} &= 10.87\% \end{aligned}$$

The data from the experiments of Sayers and Yant (2) were expanded and presented in curves to illustrate the varying rates of carbon monoxide elimination, depending upon whether the subject was breathing air, oxygen, or carbogen. These demonstrate that the increase of the oxygen tension of the alveolar air enhances the elimination of carbon monoxide from the blood. The additional effect of carbon dioxide results from stimulation of the respiratory centers yielding increased pulmonary ventilation, and on lowering the pH of the blood causing the equilibrium of the equation  $\text{Hb} + \text{CO} \rightleftharpoons \text{HbCO}$  to shift to the left.

EFFECT OF CARBON MONOXIDE ON DISSOCIATION OF OXYHEMOGLOBIN

If certain peculiarities of carbon monoxide intoxication are to be understood, it is essential to

<sup>1</sup> This mixture is known as "carbogen."

appreciate that carbon monoxide in the blood enhances the combination of oxygen with hemoglobin (15, 16). Thus, when some of the hemoglobin is combined with carbon monoxide, the concentration of oxygen in the tissues must fall to lower than usual levels before oxygen will dissociate from oxyhemoglobin and move into the tissues. A person whose blood oxyhemoglobin is diminished because of the presence of carbon monoxide will have more severe symptoms than one whose oxyhemoglobin is diminished to an identical degree as a result of anemia.

In an example cited by Stadie and Martin (16), a contrast has been made between an individual who had only 40 percent of his total hemoglobin available for combination with oxygen due to carbon monoxide poisoning, and another individual whose hemoglobin was diminished to 40 percent of the normal amount because of pernicious anemia. In both cases, the maximum amount of oxygen available to the tissues was 8 ml. O<sub>2</sub> per 100 ml. of blood, and the tissues of both patients required about 4 ml. O<sub>2</sub> per 100 ml. of blood, or approximately one-half the maximum amount of oxygen that might be available. In the patient with pernicious anemia, the required quantity of oxygen would dissociate from the hemoglobin at a partial pressure in the blood greater than 28 mm. of oxygen, but the oxygen tension in the blood of the individual with carbon monoxide poisoning must drop to 12 mm. before half of the oxygen would be dissociated from the hemoglobin. Because of this increase in the affinity of hemoglobin for oxygen in the presence of carbon monoxide, profound deficiency of oxygen in the tissues can result during carbon monoxide poisoning even though the amount of oxygen actually present in the blood is two or three times that necessary to maintain tissue function.

The contrast of the effects of carbon monoxide poisoning with those of methemoglobinemia serves to emphasize the clinical importance of the altered dissociation curve of oxyhemoglobin in the presence of carboxyhemoglobin (17). Human beings who have concentrations of methemoglobin equivalent to 30 percent of their total circulating hemoglobin are cyanotic but have no other apparent symptoms; on the other hand, when 30 percent of the hemoglobin has been converted to carboxyhemoglobin, such symptoms as headache, weakness, nausea, and a considerable feeling of discomfort are invariably present.

In an effort to obtain information concerning the mechanism whereby the presence of carbon monoxide in the blood diminishes the ease of dissociation of oxyhemoglobin, an investigation has been made by Drabkin et al. (18) into the nature of the intimate relationship that exists between carbon monoxide and hemoglobin. After dogs had been exposed to an atmosphere containing carbon monoxide until the animals' hemoglobin was 75 percent saturated with the gas, the animals collapsed with evidence of cardiac and respiratory failure; in those that survived, extensive necrotic changes were later found in the brain and heart. In another group of dogs, the concentration of carbon monoxide in the blood was brought to 75 percent of saturation by partial replacement transfusion with washed erythrocytes that had been completely saturated with carbon monoxide. In the latter animals, there were no signs of deficiency of oxygen; they were later killed, and autopsies revealed no evidence of myocardial or cerebral damage. In addition, the rate of carbon monoxide elimination was reported to be twice as rapid as from dogs which had inhaled the gas. On the basis of the dissociation curve of oxyhemoglobin in the presence of 75 percent saturation with carbon monoxide, the dogs that had inhaled the carbon monoxide actually had available for the tissues not 25 percent of the normal amount of oxygen, but only 11 percent. On the other hand, the dogs that were transfused with erythrocytes saturated with carbon monoxide had available to their tissues 25 percent of the amount of oxygen normally carried by the blood in the absence of carbon monoxide. These observations indicated that there was no change in the ability of oxygen to dissociate from the oxyhemoglobin in the erythrocytes which were substantially free of carboxyhemoglobin.

Drabkin (19) then postulated that the left shift of the dissociation curve of oxyhemoglobin in carbon monoxide poisoning is due to the simultaneous combination of oxygen and carbon monoxide with the hemoglobin molecules. He illustrates this with a hypothetical patient who has 25 percent of the hemoglobin present as carboxyhemoglobin. Functional impairment is greater than from the simple loss of one quarter of the blood's capacity to carry oxygen. Assuming that none of the molecules of hemoglobin escaped combination with carbon monoxide, the blood then would contain "100 percent of *partially poisoned molecules* of the species, Hb<sub>1</sub>(O<sub>2</sub>)<sub>3</sub>(CO)." According to Drabkin's

hypothesis, further saturation of the blood with carbon monoxide produces "*progressive molecular poisoning*, consonant with the existence of intermediate molecular species of the type  $\text{Hb}_4(\text{O}_2)_3(\text{CO})$ ,  $\text{Hb}_4(\text{O}_2)_2(\text{CO})_2$ , and  $\text{Hb}_4(\text{O}_2)(\text{CO})_3$ , in between completely oxygenated  $\text{Hb}_4(\text{O}_2)_4$  and completely poisoned  $\text{Hb}_4(\text{CO})_4$ ." The greater the saturation of the molecules with carbon monoxide, the more firm become the bonds between the hemoglobin and the remaining oxygen molecules. In other words, the partial pressure of oxygen in the plasma must fall to a lower level before hemoglobin will give up oxygen when carbon monoxide is also attached to the hemoglobin molecule than when only molecules of oxygen are bound to it.

On the other hand, the possibility that the explanation of Drabkin represents an over-simplification is suggested by the report of Allen, Guthe, and Wyman (20) which supports the concept that the four oxygen-combining centers of a molecule of hemoglobin are all inherently identical. Their work indicates that the curve of dissociation of oxygen from each combining-center is the same, and is unaffected by the presence or absence of oxygen in combination with any of the other three.

#### EFFECTS OF OXYGEN DEFICIENCY

Oxygen deficiency of the arterial blood in carbon monoxide poisoning is, in one respect, even more pure than that in hypoxemia from decrease of atmospheric oxygen as at high altitudes. In the latter, the diminished partial pressure of oxygen in the plasma of the arteries results in hyperpnea which becomes complicated by respiratory alkalosis.

Differences in deaths from carbon monoxide poisoning and from hypoxemia due to diminished oxygen pressure in the atmosphere have been described by Haldane and Priestley (21). When death results purely from insufficiency of oxygen, the immediate cause is failure of the respiratory centers. This is in part predisposed by hyperpnea associated with diminishing partial pressure of oxygen in the plasma. On the other hand, in carbon monoxide poisoning the partial pressure of oxygen in the circulating plasma is normal as the blood reaches the chemoreceptor bodies<sup>2</sup>, so that hyperpnea does not occur. However, the carbon monoxide present has greatly reduced the oxygen-

carrying capacity of the hemoglobin so that depletion into the tissues of the small amount of oxygen dissolved in the plasma leaves little oxygen reserve in the erythrocytes. Thus, the supply of oxygen to important organs may be greatly impaired, resulting in irreversible damage, even though the respiratory rate and depth are not altered during the episode of poisoning.

J. S. Haldane (5) demonstrated that the physiological effects of carbon monoxide could be mitigated considerably by increasing the partial pressure of oxygen in the blood. For example, a mouse exposed to air contaminated with 0.022 percent of carbon monoxide died in 2 hours and 25 minutes, but in an atmosphere comprised of 97 percent oxygen, 2.84 percent nitrogen, and 0.25 percent carbon dioxide, about 0.08 percent of carbon monoxide was required to "distinctly affect a mouse, and very much more to produce death."

In discussing the results of these experiments, Haldane wrote (5), "In the case of pure oxygen the tension of oxygen is nearly five times as great as in air, so that to produce equal saturation of the haemoglobin of the corpuscles with carbonic oxide (carbon monoxide) in oxygen and in air, the tension of carbonic oxide would presumably require to be five times as great in the oxygen as in the air. Hence on the hypothesis on which the investigation started one might expect that carbonic oxide would turn out to be about five times as poisonous in air as in oxygen—that is to say, that five times as high a percentage of carbonic oxide would be required in oxygen to produce the effect of a given percentage in air.

"Now the experiments . . . clearly showed that carbonic oxide is much more than five times as poisonous in air as in oxygen. In the latter gas the poisonous action is reduced to about a tenth or less. Evidently then some other factor has to be taken into account besides the relative tensions of oxygen and carbonic oxide."

In order to account for this discrepancy between the original hypothesis and the subsequent experimental data, "the hypothesis suggested itself that the higher the oxygen tension the less dependent an animal is on its red corpuscles as oxygen carriers, since the oxygen supply simply dissolved in the blood becomes considerable when the oxygen tension is high."

Accordingly, Haldane contrived an experiment to assess this possibility. He found that mice in a chamber containing only oxygen at a pressure of

<sup>2</sup> The organs that initiate reflex hyperpnea when there is a fall in the oxygen tension of their afferent blood.

two atmospheres would suffer but slight distress as carbon monoxide was added up to a pressure of one atmosphere of the latter gas. Thus, the introduction of enough carbon monoxide to saturate the hemoglobin completely, had little deleterious effect because the oxygen dissolved in the plasma was able to meet the resting metabolic requirement, although Haldane recognized that the amount of oxygen that could dissolve in the plasma at this pressure would not support great physical activity.

Some years later J. B. S. Haldane (22) performed a similar experiment with rats as subjects and found that when the animals were under a pressure of three atmospheres of oxygen and one of carbon monoxide, their activities were essentially normal, but that the addition of a second atmosphere of carbon monoxide caused hyperventilation and, within a few minutes, convulsions and death. Such effects were not observed when the experiment was repeated using nitrogen in place of carbon monoxide. The elder Haldane (5) had concluded on the basis of his experiment that carbon monoxide is not toxic except for its capacity to diminish the oxygen-carrying capacity of the hemoglobin, but the experiment of J. B. S. Haldane indicated that at higher pressures of carbon monoxide the gas does affect the metabolic activities of the body. J. B. S. Haldane believed this effect of carbon monoxide to be the result of its combination with one or more enzymes that are concerned with intracellular oxidation-reduction reactions, and that this effect is fundamentally similar to the effects of carbon monoxide on yeasts, germinating seeds, and on insects (moths) that he used in other studies.

#### COMBINATION OF CARBON MONOXIDE WITH MYOGLOBIN

Not all of the carbon monoxide that is absorbed remains within the blood. Myoglobin has a much greater affinity for oxygen than does hemoglobin, so that oxygen passes with great facility from the blood to combine with the myoglobin. The affinity of myoglobin for carbon monoxide is also high. Therefore, in the presence of carboxyhemoglobin in the blood, carbon monoxide will be transferred to the myoglobin of the skeletal muscles and heart and will remain there until the carbon monoxide is eliminated from the blood (23). This combination of carbon monoxide with myoglobin does not result in direct damage to the muscle but does tend to disrupt the flow of oxygen to the intracellular

oxidases, and thereby probably results in functional disturbance. It is possible that the extreme muscular weakness which accompanies significant absorption of carbon monoxide is, in part, the result of the carboxymyoglobin in the skeletal muscles.

The presence of carboxymyoglobin is indicated at the postmortem examination of persons who have died during exposure to carbon monoxide by the bright red appearance of the skeletal muscles.

#### TISSUE OXYGEN REQUIREMENTS

The rate at which any tissue utilizes oxygen in order to maintain the life of its cells may be considered as the "survival oxygen requirement" of that tissue. This survival requirement differs greatly in different kinds of tissue, and even with different cells within the same tissue. For example, the requirement for nerve cells of the cerebral cortex is considerably greater than that for the nerve cells of the various nuclei of the medulla oblongata.

Recognition of the differences in the survival oxygen requirements of different tissues and cells is the key to an understanding of some of the peculiarities of the pathology of carbon monoxide poisoning. The cells that have the greatest requirement are the first to die during the development of carbon monoxide poisoning, while other tissues adjacent to them may be affected little or not at all during the poisoning episode.

In this connection it is also proper to indicate that organs receiving less than optimal blood supply are more susceptible during carbon monoxide poisoning. Thus, the heart in which severe sclerosis of the coronary arteries exists is much more likely to sustain anoxic damage than one in which the vessels are widely patent.

#### DURATION OF DEFICIENCY OF OXYGEN

A considerable clinical difference will exist between two patients each of whom has 40 percent of his hemoglobin combined with carbon monoxide, and who are similar in all respects except that one has attained this degree of saturation by exposure to a relatively high atmospheric concentration of carbon monoxide for a short time, while the other was exposed to a relatively low concentration for a number of hours. Assuming that the first person had been exposed to air containing 0.5 percent carbon monoxide for 20 minutes, he would tend to respond quickly to treatment with carbogen, and virtually complete recovery would probably occur

within an hour or so. The second person may be assumed to have been exposed to the concentration of 0.05 percent carbon monoxide for 6 to 8 hours; carbogen therapy would also lead to prompt elimination of carbon monoxide, but it is unlikely that this would be accompanied by quick recovery of consciousness, while damage which had occurred in the brain, heart, and other organs during the period of oxygen deficiency might be permanent.

When the absorption of carbon monoxide occurs quickly, and resuscitative efforts are prompt, the blood vessels are injured only slightly or not at all, and transudation of edema fluid and extravasation of erythrocytes are minimal or absent. When the period of hypoxia is prolonged, the cells lining the blood vessels may be damaged greatly, and vascular dilatation throughout the body is usually marked. Fluid escapes from the damaged vessels, resulting in the development of hemoconcentration and a tendency toward stagnation of the blood flow, thus further diminishing the supply of oxygen to the tissues. The injured vessels also permit diapedesis of cellular elements, and perivascular hemorrhages are common.

It is possible for an oxygen debt to exist in the tissues for a relatively short period without damage. However, if oxygen is not supplied promptly, irreversible degenerative phenomena become established in the central nervous system, heart, kidney, and other organs. Such lesions are well known as residua of carbon monoxide poisoning (24). Although elimination of carbon monoxide from the blood occurs rapidly with the inhalation of carbogen, the coma may linger for days or even weeks as a result of the damage to the central nervous system caused by oxygen deficiency during the episode of poisoning.

#### SUMMARY

The signs and symptoms of carbon monoxide poisoning are manifold, but the physiological principles can be stated in a few brief paragraphs:

1. Carbon monoxide and oxygen each combine in the same manner with hemoglobin. However, hemoglobin has a much greater affinity for carbon monoxide than for oxygen so that relatively little carbon monoxide in the air can displace much of the oxygen from the blood.

2. Carbon monoxide has no significant intrinsic toxicity for tissues. Injuries sustained during

poisoning result only from deficiency in the supply of oxygen to the tissues.

3. The presence of carbon monoxide in the blood appears to increase the strength of the chemical bonds between hemoglobin and oxygen, so that whatever oxygen the hemoglobin may still be transporting is given up to the tissues only when there has been unusual depletion of the tissue oxygen reserves.

4. Brief periods of oxygen deficiency can be relatively harmless, but deficiency of corresponding intensity for several hours can cause extensive and perhaps fatal injuries.

5. Cells that require the largest amounts of oxygen for survival are the first to die during poisoning.

6. Diminution of the supply of blood to an organ is more likely to be harmful when the blood contains carbon monoxide than when it is free of this gas.

An understanding of these physiological principles of carbon monoxide poisoning is necessary if one is to comprehend the symptoms and injuries that are produced during poisoning. Alleviation of symptoms and prevention of tissue damage are the aims of rational therapy. The disease is anoxia, and the treatment is oxygen.

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