

# THE ELIMINATION OF CARBON MONOXIDE FROM THE BLOOD

## A THEORETICAL AND EXPERIMENTAL STUDY

By WILLIAM C. STADIE AND KIRBY A. MARTIN

*(From the Department of Internal Medicine, Yale University School of Medicine and the Medical Service of the New Haven Hospital)*

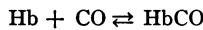
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The symptoms attending the partial or complete saturation of the hemoglobin of the blood with carbon monoxide are too well known to require detailed comment. With as little as 40 per cent of the hemoglobin combined with carbon monoxide there may ensue deep coma, marked central nervous system symptoms with ankle clonus, positive Babinski and Kernig signs and often death. Occasionally the blood becomes free of carbon monoxide, the coma terminates, but the patient subsequently sinks into coma again and dies, probably as a result of central nervous system damage.

The exact explanation of this train of symptoms is not entirely clear. Presumably the effects of carbon monoxide asphyxia are those of anoxemia. For, as is well known, anoxemia long continued results in irremedial damage to nervous tissue. This anoxemia is not due primarily to a reduction of the total oxygen of the blood as is commonly supposed, but rather to a marked lowering of the partial pressure at which oxygen is available for tissue metabolism. As will be shown subsequently this effect is the result of a marked alteration in the form of oxygen dissociation curve of blood by carbon monoxide. In the light of this alteration the desperate condition of a subject whose blood is half saturated with CO as contrasted with the comparatively comfortable condition of one who as in anemia cases, has merely lost half his hemoglobin is understandable.

That the effects of carbon monoxide are entirely those of anoxemia is at present an assumption based upon the fact that its toxic effects are supposedly nil. This will be discussed below.

Carbon monoxide, as contrasted with oxygen, has a peculiarly great affinity for hemoglobin. A very small concentration of carbon monoxide in the alveolar air will keep the blood highly saturated with CO. CO at a few millimeters of partial pressure has the same combining capacity as oxygen at a partial pressure of several hundred millimeters. This peculiarity of CO is as yet unexplained, but it enables a small concentration of carbon monoxide in the alveolar air to keep the blood highly saturated with CO and so lead to dangerous asphyxiation. Conversely the recovery of asphyxiated subjects is slow. The elimination of CO from the blood depends upon the reversal of the reaction.



Under the ordinary circumstances of recovery the conditions favor the establishment of an equilibrium toward the right. The blood gives up a small amount of CO to the alveolar air. But this small amount is sufficient to reestablish equilibrium at a point close to the original saturation. Part of the CO is removed from the alveolar air at each respiration it is true but as a rule the respirations are depressed. A kind of vicious cycle is set up. The two factors, great affinity of CO for hemoglobin and subnormal respiration, lengthen the time of recovery to hours. Unless the CO be rapidly eliminated in a subject with over 60 per cent of saturation, death usually occurs.<sup>1</sup>

The inhalation of CO<sub>2</sub> with pure oxygen effects this rapid elimination. First used by Henderson (1921) its use in many hospitals and particularly in mine rescue stations has demonstrated its value.

Henderson and subsequently Yant and Sayre (1922) showed in experimental animals and subjects that the addition of CO<sub>2</sub> to the air or oxygen inhaled shortened the time of elimination of CO frequently to as brief a time as one-half hour. But these investigators attributed the action of CO<sub>2</sub> to the increased pulmonary ventilation which it

<sup>1</sup> It has been erroneously supposed by some that the velocity of reaction of CO with Hb is a factor; i.e., reaction (1) goes with great speed toward the right and slowly toward the left. Hartridge (1922) has shown that the reaction is practically instantaneous in either direction. If the conditions are properly selected the reaction *in vivo* can be made to go with great rapidity in either direction as the subsequent protocols will show.

caused. This increased ventilation washed out the CO from the alveolar air rapidly, hastening the elimination from the blood by lowering the alveolar CO pressure to a minimum. But increased ventilation may not be the sole or even the important factor operating when  $\text{CO}_2$  was inhaled by asphyxiated animals. The increased hydrogen ion concentration of the blood during  $\text{CO}_2$  inhalation must be taken into account and this was not considered by either Henderson or Yant and Sayre.

Theoretical considerations of the equilibrium relations of oxyhemoglobin reduced hemoglobin, carbon monoxide hemoglobin, oxygen carbon monoxide and hydrogen ion concentration, supported by experimental evidence, have enabled us to predict that an increase of the acidity of the blood by any agent, ventilatory rate remaining constant, would result in an increased rate of elimination of CO from the blood. Experimental rates of elimination under these conditions were found to be quite in accord with the prediction.

In addition, the relations developed showed that the primary effect of carbon monoxide was a profound alteration of the oxygen dissociation curve, which, rather than the mere loss of functioning hemoglobin, was the cause of the anoxemia.

#### EQUILIBRIUM BETWEEN $\text{Hb}$ , $\text{HbO}_2$ , $\text{HbCO}$ , $\text{O}_2$ , $\text{CO}$ AND $\text{H}^+$ . THEORY

Two assumptions are made to develop an expression for the effect of CO on the combination of oxygen with hemoglobin.

1. Hemoglobin combines with a mixture of  $\text{O}_2$  and CO as if they were one substance due regard being paid to the relative affinity of the two gases. I.e., a partial pressure  $P_{\text{CO}}$  of CO is equivalent to a partial pressure  $(K'_{\text{CO/O}} \cdot P_{\text{CO}})$  of oxygen,  $K'_{\text{CO/O}}$  being a constant unaltered for a given blood by any condition save temperature. It expresses the relative affinity or saturating capacity of CO for hemoglobin as compared to oxygen. At 38°C. in human blood it has a value of  $300 \pm 50$  as experimentally determined by Barcroft, Douglass and many others. In other words, a gas mixture containing  $P_{\text{O}_2}$  mm. of  $\text{O}_2$  and  $P_{\text{CO}}$  mm. of CO would be equivalent to  $[\text{Gas}] = (P_{\text{O}_2} + K'_{\text{CO/O}} P_{\text{CO}})$  mm. of  $\text{O}_2$  in its combining value toward hemoglobin.

Hence for the reaction.



we have by mass action

$$\frac{[\text{Hb Gas}]_n}{[1 - [\text{Hb}]_n [P_{\text{O}_2} + K'_{\text{CO/O}} P_{\text{CO}}]^n]} = K_g \quad (1)$$

Here  $[HbGas]$  represents the fraction of total hemoglobin combined with  $O_2$  and  $CO$ .

2. The ratio of  $HbO_2$  to  $HbCO$  in any mixture of hemoglobin is proportional to the partial pressure of the two gases in equilibrium with it. I.e.,

$$\frac{[HbO_2]}{[HbCO]} = \frac{P_{O_2}}{K_{co/o} P_{co}} \quad (2)$$

These assumptions were likewise employed by Hill (1921) in the development of an hypothesis which postulated the dissociation of hemoglobin into a non-protein fraction combining with oxygen or carbon monoxide and a protein fraction not capable of combination with either.

Equation 2 is known to be true for the case where the hemoglobin is completely saturated with gas. But it is as yet undetermined whether this relation holds true when the hemoglobin is *not* completely saturated, i.e., when there is still some reduced hemoglobin present. However, the validity of this relation for partially saturated hemoglobin is here assumed. The identity of  $K_{CO/O}$  and  $K'_{CO/O}$  remains to be proved.

Since  $[Gas] = P_{O_2} + K'_{co/o} P_{co}$  and  $[HbGas] = [HbO_2] + [HbCO]$ , we have

$$K_g = \frac{[HbO_2] + [HbCO]}{[1 - ([HbO_2] + [HbCO])] [P_{O_2} + K'_{co/o} P_{co}]^n} \quad (3)$$

If  $P_{co} = 0$

$$\begin{aligned} K_g &= \frac{[HbO_2]}{(1 - [HbO_2]) P_{O_2}^n} \\ &= K_o \end{aligned}$$

i.e., Hill's oxygen dissociation constant.

Further if  $P_{CO} = 0$

$$K_g = K_o = \frac{[HbCO]}{K_{co/o}^n (1 - [HbCO]) P_{CO}^n}$$

but since

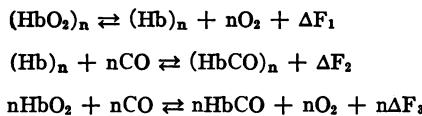
$$K_{co} = \frac{[HbCO]}{(1 - [HbCO]) P_{CO}^n}$$

we have by division

$$\frac{K_{co}}{K_o} = K_{co/o}^n \quad (4)$$

A similar relation involving  $K_{CO/O}$  may be derived thermodynamically and independently of any considerations of the kinetics of the reactions concerned.

Consider the following equilibrium states:



where  $\Delta F_1$ ,  $\Delta F_2$  and  $n \Delta F_3$  are the free energy changes of the respective reactions.  
From the known equilibrium constants we have

$$-\log K_o = \Delta F_1$$

$$\log K_{\infty} = \Delta F_2$$

$$n \log K_{co/o} = n \Delta F_3$$

Since  $\Delta F_1 + \Delta F_2 = n\Delta F_3$ , we have

$$-\log K_o + \log K_{\infty} = n \log K_{co/o}$$

or

$$\frac{K_{co}}{K_o} = K_{co/o}^n \quad (4')$$

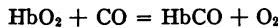
It follows from 4 and 4' that  $K'_{co/o} = K_{co/o}$

Experimental proof of (4) is offered by the data on the blood of C. A. Douglass (1912). Figures 1, 3 and 4 of their paper give the following data.  $n$  is taken as 2.5.

Hemoglobin constants of Douglass blood at 40 mm.  $\text{CO}_2$  and  $38^\circ\text{C}$ .

$K_{co}$ .....	Obs	25000
$K_o$ .....	Obs	0.031
$K_{co/o}$ .....	Obs	250
$K_{co/o}$ Calculated by equation 4'.	.....	230

The experimental and theoretical proof of the identity of the constant  $K'_{co/o}$  by which the partial pressure of CO is multiplied to give its combining capacity in oxygen terms with the equilibrium constant  $K_{co/o}$  of the reaction.



of which equation 2 is the mass action expression permits the introduction of equation 2 into (3).

Eliminating  $P_{co}$  we obtain, remembering that  $K_g = K_o$ .

$$K_o = \frac{[\text{HbO}_2]^n}{([\text{HbO}_2] + [\text{HbCO}])^{n-1} (1 - ([\text{HbO}_2] + [\text{HbCO}])) P_{\text{O}_2}^n} \quad (5)$$

This equation was tested experimentally on the blood of W. C. S. The blood was equilibrated at  $38^\circ$  with amounts of CO and  $\text{O}_2$  necessary to give partial

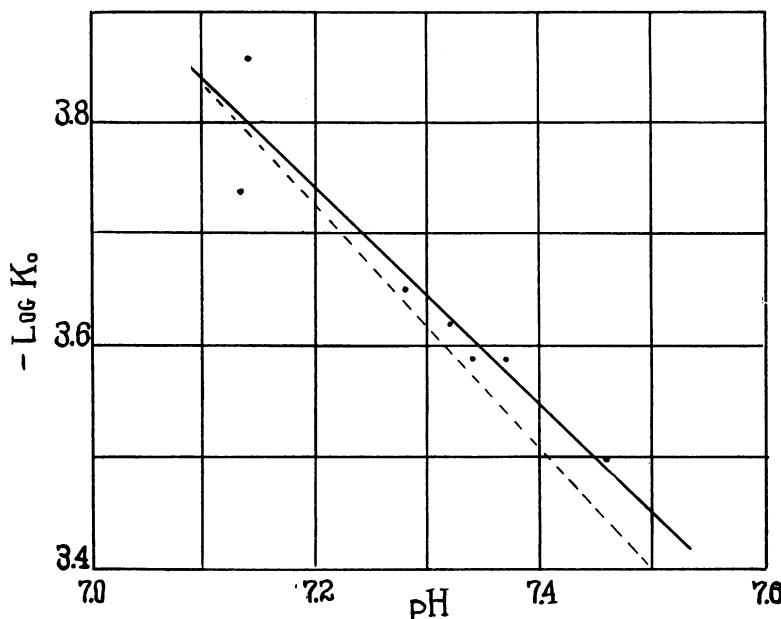


FIG. 1. SOLID LINE =  $\log K_o$  AT VARYING pH CALCULATED BY EQUATION 5 IN BLOOD PARTIALLY SATURATED WITH CO AND  $O_2$   
 DASHED LINE =  $\log K_o$  determined at varying pH in the presence of  $O_2$  only

TABLE 1

Date	Oxygen Tension	HbO <sub>2</sub>	Satn. O <sub>2</sub>	HbCO	Satn. CO	pH calculated	-log K <sub>o</sub> calculated by equation 5
1922-23	mm.	volumes per cent	per cent	volumes per cent	per cent		
December 7.....	20.3	7.3	36.5	6.9	35.0	7.28	3.65
December 13.....	18.6	6.9	32.0	8.3	38.6	7.32	3.62
February 15.....	11.7	4.6	21.8	6.8	32.4	7.34	3.59
April 7.....	20.9	8.1	38.5	8.8	42.0	7.37	3.59
April 7.....	20.9	6.3	30.0	8.1	38.5	7.15	3.86
April 11.....	23.3	8.3	41.3	8.1	40.5	7.46	3.50
June 6.....		19.3	6.1	30.3	6.5	32.5	7.15
			25.5		57.0	7.34	3.73

saturation of the hemoglobin at varying pH values. The per cent saturation with  $O_2$  and CO, the oxygen tension and pH were determined using the Van Slyke-Stadie, Haldane and Cullen method respectively. The values for  $K_o$  thus obtained

are compared with  $K_o$  determinations using oxygen alone.<sup>2</sup> The results are given in figure 1 and table 1. There is excellent agreement.

**EFFECT OF CHANGE OF PH OF THE BLOOD ON THE OXYGEN DISSOCIATION  
CURVE IN CARBON MONOXIDE POISONING**

By means of Equation (5) the oxygen dissociation curve of whole blood may be drawn when the blood is *constantly* saturated with CO to any definite and fixed degree. Fixing the CO saturation at 50 per cent we have for an average human blood the following normal conditions as contrasted with an acidotic condition easily attained by inhalation of  $CO_2$ .

	I	II
pH.....	7.4	7.0
$K_o$ .....	0.001	0.0009
$K_{co/o}$ .....	250	250
n.....	2.2	2.2
HbCO.....	50 per cent	50 per cent

In figure 2 are shown the curves for these two conditions calculated from equation 5.

Increasing the acidity of the blood changes  $K_o$  only according to the well established (over physiological ranges) relation

$$\Delta \log K_o = \Delta pH$$

$K_{co/o}$  and n are unaltered as has been shown by Barcroft and others.

Figure 2 shows that the presence of CO has changed markedly the form of the oxygen dissociation curve of that part of the hemoglobin uncombined with CO.

The effect of this alteration upon the rate of elimination of CO from the blood as influenced by increasing the hydrogen ion concentration only is clearly seen from the following:

At point A we have from figure 2

$$\begin{aligned}
 pH &= 7.4 \\
 HbCO &= 50 \text{ per cent} \\
 HbO_2 &= 40 \text{ per cent} \\
 P_{co} &= 0.147 \text{ mm. Hg} \\
 P_{o_2} &= 30 \text{ mm. Hg}
 \end{aligned}$$

<sup>2</sup> The control  $K_o$  values determined with oxygen alone are taken from published data. Stadie and Martin, Jour. Biol. Chem., 1924, lx, 191.

Lower the pH to 7.0 and maintain the oxygen tension constant. Then at point B we have

$\text{pH} = 7.0$   
 $\text{HbCO} = 50 \text{ per cent}$   
 $\text{HbO}_2 = 32 \text{ per cent}$   
 $P_{\text{CO}} = 0.167 \text{ mm. Hg}$   
 $P_{\text{O}_2} = 30 \text{ mm. Hg}$

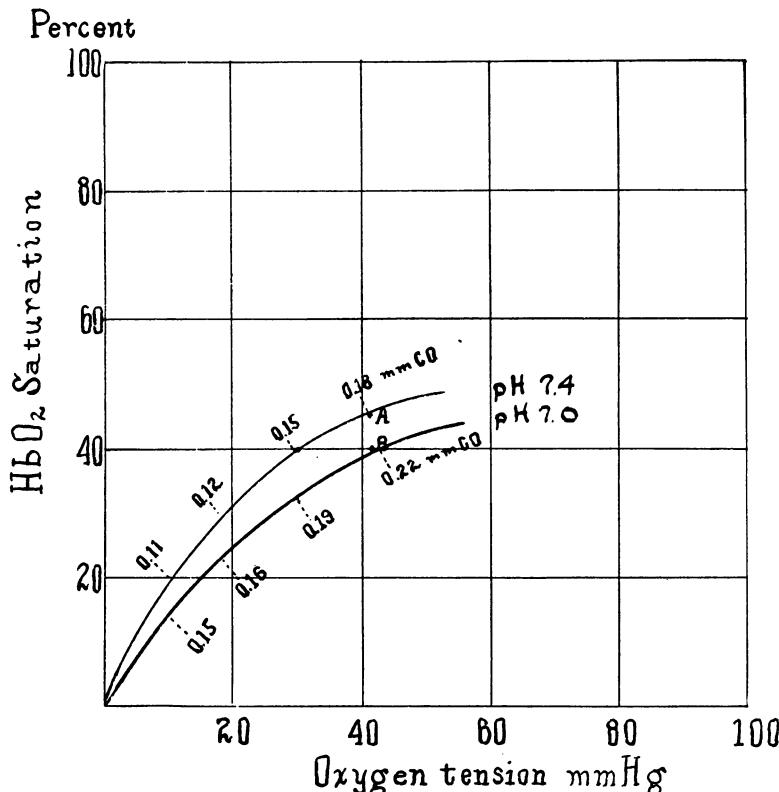


FIG. 2. OXYGEN DISSOCIATION CURVE OF BLOOD 50 PER CENT SATURATED WITH CO AND pH 7.4 AND 7.0 SHOWING THE EFFECT OF ACIDITY ON THE PARTIAL PRESSURE OF CO

At constant oxygen tension a lowering of the pH requires an increase of  $\frac{0.167 - 0.140}{0.167}$  or 20 per cent in the carbon monoxide tension to maintain the blood at 50 per cent saturation with CO.

If, as is the case in the lungs during recovery from asphyxia, the  $P_{CO}$  remains constant it is easy to show from equation 5 that the following would be the approximate conditions.

$$\begin{aligned}
 \text{pH} &= 7.0 \\
 \text{HbCO} &= 40 \text{ per cent} \\
 \text{HbO}_2 &= 40 \text{ per cent} \\
 P_{CO} &= 0.167 \text{ mm. Hg} \\
 P_{O_2} &= 30 \text{ mm. Hg}
 \end{aligned}$$

While we have arbitrarily selected a mid portion of the curves for illustration the same relations must necessarily hold true for any and all equilibrium relations, oxygen, carbon monoxide and hemoglobin.

TABLE 2  
*Elimination of CO from partially asphyxiated dogs with constant ventilatory rate and varying acidity of blood*

Time	Breathing air		Breathing 10 per cent $CO_2 + Air$		HCl intravenously		Hyperventilation	
	HbCO satn.	pH	HbCO satn.	pH	HbCO satn.	pH	HbCO satn.	pH
	minutes	per cent	per cent	per cent	per cent	per cent	per cent	per cent
0	73	7.40	95	7.38	91	7.34	80	7.58
15	55	7.42	57	7.13	48	7.02	57	7.50
30	49	7.40	44	7.08	35	6.94	47	7.48
60	37	7.38	22	7.08	21	6.92	35	7.53
120	28	7.48	6	7.00	10	6.80	23	7.50
Oxygen capacity, volumes per cent..		15.7		21.93		21.6		22.6

It is at once evident from the above that increasing acidity of the blood from whatever cause hastens the elimination of carbon monoxide from the blood independently of ventilatory rate.

To test this deduction the following experiments on asphyxiated dogs were done. The results are recorded in Table 2.

The rate of elimination of CO from the blood was studied under the following conditions:

1. Animal breathing air with constant ventilatory rate. Blood pH normal.
2. Blood pH decreased by breathing 10 per cent  $CO_2$  with constant ventilatory rate.

3. Giving dilute hydrochloric acid intravenously with constant ventilatory rate.

4. Hyperventilation with air.

This experimental portion of the work was made possible by the Department of Surgery placing at our disposal their laboratories. We are indebted to Dr. Robert Kapsinow for his kindness in performing the animal surgery necessary.

#### EXPERIMENTAL

Medium size dogs were used throughout. Operative technic, anesthesia, gassing, blood sampling and blood analysis were the same in all of the experiments. Except in experiment 4 the ventilatory rate was the same throughout the series.

*Anesthesia:* 30 to 40 cc. of paraldehyde was given by stomach tube three quarters to one hour before the experiment was started. This was found to be sufficient to obtain complete relaxation for two to three hours.

*Operation:* After the animal was completely anesthetized it was placed on the operating table and a trachea cannula was inserted and connected to an artificial respiration machine. The thoracic cavity was opened by making an incision to the left of the sternum and removing portions of three ribs over the heart. A flap was turned back which gave an opening over the heart of about 10 by 14 cm. Respiration was controlled by an artificial respiration apparatus. Great care was taken to prevent loss of blood. The right femoral artery was exposed for blood sampling. The mediastinal partition was punctured. This caused collapse of the lungs. The rate and degree of expansion and contraction of the lungs were set and maintained at a constant throughout experiments 1, 2, 3 by means of a motor driven artificial respiration machine. The pulmonary ventilation was set at about the normal minute volume and was totally independent of the animal's own respiratory effort.

*Gassing:* The animal was given pure illuminating gas through the artificial respiration apparatus at 15 to 20-second intervals until the blood became about 60 to 80 per cent saturated with carbon monoxide. After a little experience the desired saturation could be estimated by the animal's heart action.

*Blood sampling:* Five to 10 cc. samples of blood were drawn from the right femoral artery at intervals with a 10 cc. Luer syringe, and delivered into oxalated sampling tubes under oil.

*Blood analysis:* Oxygen capacity, oxygen and carbon dioxide content, carbon monoxide content were determined by the Van Slyke (1924) method. The hydrogen ion concentration of the blood was determined colorimetrically by Cullen's method (1923). The results are given in tables 1 and 2 and figure 1.

In experiment 1 it was found that the blood pH fell slightly during the first half hour of the experiment. To eliminate this complicating factor 10 gm. of  $\text{NaHCO}_3$

was given intravenously. This was found to maintain the blood pH within normal limits.

#### DISCUSSION

For simplicity of comparison we have plotted the data of table 2 in figure 3, the initial saturation with CO being the same.

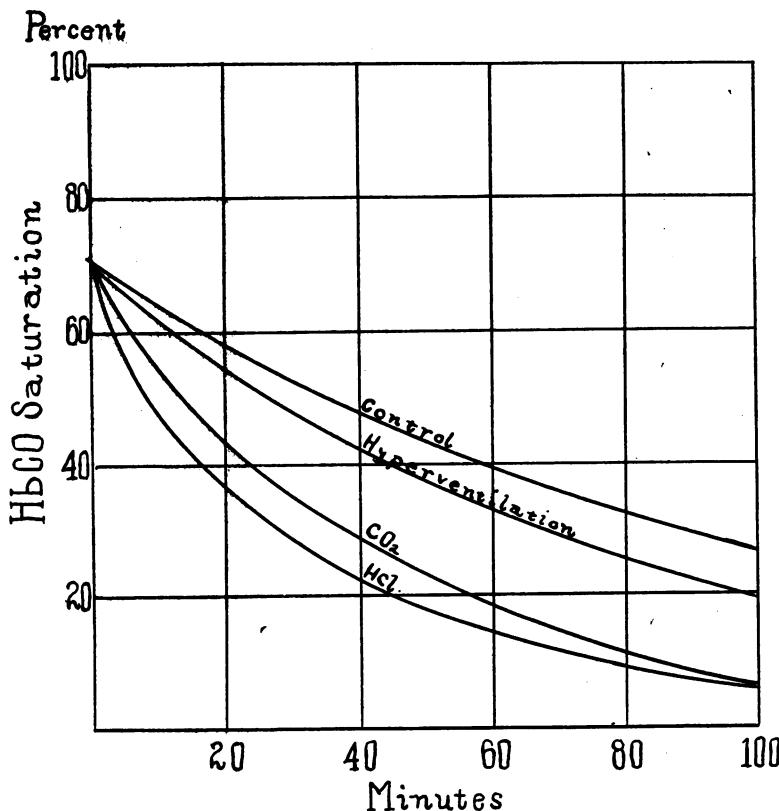


FIG. 3. CURVES SHOWING THE RATE OF ELIMINATION OF CARBON MONOXIDE FROM THE BLOOD OF PARTIALLY ASPHYXIATED DOGS UNDER DIFFERENT CONDITIONS

In all cases except one (hyper-ventilation) the ventilatory rate was the same.

The rate of elimination of CO at any instant is proportional to the concentration of CO in the blood, i.e.,

$$\frac{dS}{dt} = S$$

where S is the per cent of saturation of blood with CO. Integrating

$$\log \frac{S_i}{S_t} = kt$$

Where S is the initial saturation and S<sub>t</sub> the saturation at time t. If the data of table 2 be plotted using  $\log \frac{S_i}{S_t}$  as ordinates and t as abscissae straight line should result. This is exactly the case. The slopes of the lines give k for the four different conditions and with these k values figure 2 is calculated. This allows one to start the curves from a common point and bring out the differences in a striking fashion.

Little comment is needed. It is clear that hyperventilation itself is of minor importance in the elimination of CO. Decreasing pH by any acid, CO<sub>2</sub> or HCl causes a great increase in the rate of elimination and is the most important factor.

It must be strongly emphasized, however, that CO<sub>2</sub> administered to asphyxiated subjects has a powerful stimulating effect on respiration. While hyperventilation plays a minor rôle yet it is a distinct one. The asphyxiated subject has usually a decreased pulmonary ventilation. This slows CO elimination. Any means of increasing ventilatory rate is beneficial. CO<sub>2</sub> has a double function through the same mechanism. It increases blood hydrogen ion concentration which in itself favors CO elimination. This double function makes it the ideal therapy to employ: the addition of pure oxygen while helpful is far less important.

*The alteration in the oxygen dissociation curve by CO as the cause of the anoxemia*

An old experiment by Haldane (1895) would force us to believe that CO by itself is non-poisonous. He placed mice in a chamber with sufficient CO to saturate completely the hemoglobin. It could no longer serve to transport oxygen to the tissues and the mice would have died promptly (as did the controls) had it not been for the fact that the chambers also contained oxygen under several atmospheres of pressure. Under these conditions 3 to 4 volumes per cent of oxygen could be carried by the blood in physical solution. This was sufficient for the needs of the animals and they remained perfectly well. While

it is not entirely clear that these results can be carried over to human beings, since the symptoms of CO poisoning are somewhat anomalous as pure symptoms of anoxemia, yet tentatively we may accept the hypothesis that CO poisoning causes harm solely by depriving the

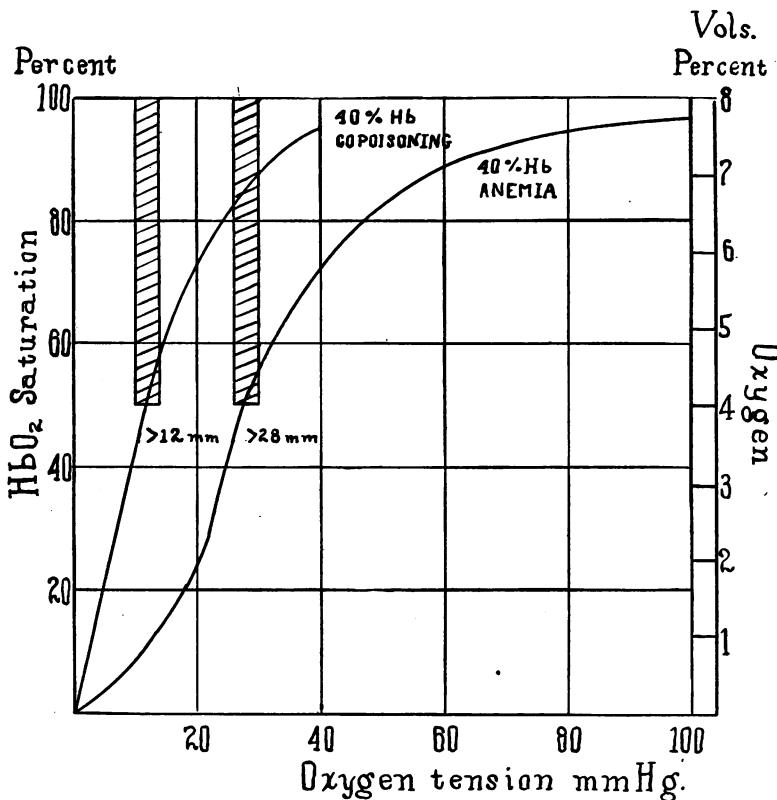


FIG. 4. OXYGEN DISSOCIATION CURVE OF THE BLOOD OF A CASE OF CARBON MONOXIDE POISONING 60 PER CENT SATURATED WITH CO CONTRASTED WITH THE CURVE OF A CASE OF PERNICIOUS ANEMIA WITH THE SAME AMOUNT OF AVAILABLE OXYHEMOGLOBIN, VIZ., 40 PER CENT OF NORMAL

tissue of oxygen. There is current, however, a misconception of the mechanism of this anoxemia which figure 4 makes clear. By means of equation 5 we have calculated the oxygen dissociation curve of blood when *constantly* saturated 50 per cent with CO. The form of this curve so calculated is in complete accord with the experi-

mentally determined curve for mouse blood under the same conditions as reported by Haldane (1912). Forty per cent of the total hemoglobin is available for combination with oxygen and the saturation of this residue of hemoglobin with oxygen is plotted against oxygen tension. In contrast the oxygen dissociation curve of a case of pernicious anemia having 40 per cent of the normal amount of hemoglobin is plotted. The curve in the latter case is unaltered as one of us has determined<sup>3</sup> but the CO case shows a marked alteration in the shape and position of the curve. It is this alteration which causes the anoxemia with its train of profound acute symptoms in marked contrast to the relatively normal condition of the anemia case. In both cases the maximum amount of oxygen available is the same, 8 volumes per cent. In both cases, the physiologic needs of the tissues is the same, say about 4 volumes per cent or half the maximum available. For the anemic case, however, this physiologic oxygen requirement (indicated by the hatched column) is dissociable at a partial pressure greater than 28 mm. of oxygen. Evidently at or above this pressure tissue metabolism is normal.

But in the case of CO poisoning, the giving up of 4 volumes of oxygen requires descent to a partial pressure of 12 mm. of oxygen. Indeed three-fourths of the needed oxygen is dissociated between 28 mm. Hg, the minimum for the anemic case, and 12 mm. Now it is quite conceivable that the partial pressure at which oxygen is available in the capillaries for tissue-metabolism is important. Krogh has pictured a single capillary as supplying a cylinder of tissue. In order adequately to supply the periphery of the cylinder with oxygen, the oxygen pressure at the capillary wall cannot fall below a certain minimum or else the rate of diffusion of oxygen to the periphery which varies directly as this pressure head will fall below the physiologic requirement. Presumably this partial pressure lies somewhere between 12 and 20 mm. of Hg approximately.

Despite the presence in the blood of two or three times the amount of oxygen necessary for normal tissue function profound anoxemia results in CO poisoning. This is due to an alteration of the shape and posi-

<sup>3</sup> Stadie: Unpublished data.

tion of the oxygen dissociation curve causing a marked lowering of the partial pressure at which oxygen is available for tissue metabolism.

#### SUMMARY

An equation is derived showing the relation between hemoglobin, oxygen, carbon monoxide and pH at equilibrium.

Experiments *in vitro* are given substantiating the equation.

By means of this relation it is possible to predict the effect of increasing acidity on the elimination of CO from asphyxiated animals. It is shown that increasing hydrogen ion concentration in itself will hasten elimination regardless of the ventilatory rate. Experiments on dogs showed this to be so.

It is further shown by the equation that the oxygen dissociation curve of hemoglobin is altered by carbon monoxide. Accepting the hypothesis that carbon monoxide is in itself completely non-poisonous, the altered curve shows that even though twice or three times the physiologic requirements of oxygen are present in the blood there is a marked lowering of the partial pressure of oxygen in the capillaries. This conceivably depresses the rate of diffusion of oxygen to the tissues, thus causing anoxemia.

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