er during the first trimester of pregnancy (Fig. 3). The amount of radioactivity measured in mouse embryos during the first trimester of pregnancy, when they are most sensitive to teratogenic agents and LSD (*2–6*), was about 2.3 percent of the initial dose.

The distribution pattern of ^{14}C-LSD in the fetus was very similar to that in the mother (Fig. 3). The highest amounts occurred in the lungs, liver, intestine, brain, and myocardium, in that order. As in the mother, the fetal blood had a very low amount of radioactivity, an indication of a rapid transport of ^{14}C-LSD through cellular membranes into the tissues. The uptake in the placenta was highest 5 minutes after injection, but a moderate concentration remained for 1 hour after injection. The greatest radioactivity concentration in fetal organs was found at 30 minutes, with a significant amount remaining for at least 2 hours. The relatively high affinity of LSD for the maternal organs, causing a rapid decrease in the blood concentration, may diminish the amount available for transfer into the fetus.

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Carbon Monoxide–Induced Arterial Hypoxemia

Abstract. *Inhalation of carbon monoxide produces an increase in the alveolar to arterial oxygen gradient in the presence of veno-arterial shunts or ventilation-perfusion imbalance but has no such effect in normal subjects. The increase in the alveolar to arterial oxygen gradient with rising concentrations of carboxyhemoglobin results from changes induced by carbon monoxide in the shape of the oxyhemoglobin dissociation curve.*

Claude Bernard first pointed out that carbon monoxide (CO) produces hypoxia through its reversible combination with blood to form carboxyhemoglobin (*1*). On combining with hemoglobin, CO causes a functional anemia by decreasing the amount of hemoglobin available for carrying oxygen. In addition, the sigmoid shape of the oxyhemoglobin dissociation curve is changed with increasing carboxyhemoglobin concentrations ([COHb]) toward that of a rectangular hyperbola, with the result that hemoglobin gives up oxygen less readily in the tissues (*2*). Tissue hypoxia produced by these two factors is considered to be the major process involved in clinical CO toxicity (*1*), although it is possible that direct effects of CO on tissue respiration are also important.

There have been few studies of the possible effects of increasing [COHb] on arterial oxygen tension (Pa_{O_2}) and on the alveolar-arterial oxygen gradient ($A\text{-}a\ D_{O_2}$). Until recently it was assumed that Pa_{O_2} was unchanged by inhalation of CO (*1*), but there had been no direct measurements of the effect of CO on Pa_{O_2} until Ayers, Giannelli, and Armstrong (*3*) presented evidence that Pa_{O_2} decreased in a group of patients who breathed concentrations of CO sufficient to produce [COHb] of 5 to 10 percent. These authors later reported, in abstract form, large decreases in Pa_{O_2} and increases in $A\text{-}a\ D_{O_2}$ in dogs given higher concentrations of CO (*4*). As an explanation for their findings they postulated that "carboxyhemoglobin containing red blood cells may impose an abnormal barrier to diffusion of oxygen," or that a "decrease in capacity of the blood to carry oxygen can be shown to magnify the physiological veno-arterial shunting."

In this report we have attempted to determine if arterial hypoxemia may be an additional cause of tissue hypoxia in CO poisoning and to define the possible mechanisms of such hypoxemia.

The effects of the combination of CO with hemoglobin can be compared to the effects of anemia, since in both situations the oxygen-carrying capacity of the blood is decreased. Figure 1 shows the upper portion of oxyhemoglobin dissociation curves calculated for the functional anemia resulting from increasing [COHb] and for the anemia resulting from decreased hemoglobin in the blood. An important difference between the two curves is that the sigmoid shape of the dissociation curve is changed with increasing [COHb] but is not altered with increasing degrees of anemia. It has long been recognized that the shape of

Table 1. Change in $A\text{-}a\ D_{O_2}$ with increased [COHb]. There were no significant changes in oxygen uptake, respiratory quotient, or alveolar ventilation following CO inhalation in any of the subjects. The right to left shunt was 24 percent of cardiac output in patient A.S. and 37 percent cardiac output in patient G.S. The number of normal subjects is given in parentheses; S.D., standard deviation.

Subject	[COHb] (%)		$A\text{-}a\ D_{O_2}$ (mm-Hg)	
	Initial	Final	Initial	Final
Normals (5)	0.9	11.7	12.1	11.6
S.D.	±0.1	±4.7	±4.9	±5.9
P value		< .005		> .5
Shunt				
A.S.	2.1	12.8	36.5	46.9
G.S.*	1.0	12.7	56.7	62.8
$\dot{V}/\dot{Q}$				
J.J.	2.1	12.8	38.0	41.0
R.G.	1.7	11.5	39.8	42.6

* 2, 3-Diphosphoglycerate was elevated in this patient (*8*) which suggests that the oxyhemoglobin dissociation curve was shifted to the right (*9*). This shift might, in part, counteract the effect of [COHb] on $A\text{-}a\ D_{O_2}$.

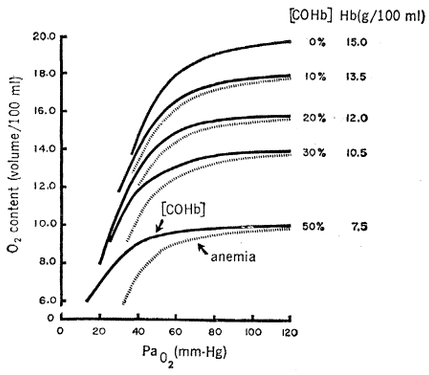

Fig. 1. The effect of [COHb] on the oxyhemoglobin dissociation curve (solid lines). Curves were calulated by the method of Roughton and Darling (*10*). The effect of anemia equivalent to that produced by CO binding of hemoglobin is shown by the interrupted lines.

the oxyhemoglobin dissociation curve is an important determinant of the effect of the relation between the rates of ventilation and perfusion ($\dot{V}/\dot{Q}$) and veno-arterial shunts on the *A-a* D_{O_2} (*5*).

To investigate the effect of CO on *A-a* D_{O_2}, and to compare the CO effect with that which might result from anemia alone, we calculated *A-a* D_{O_2} for levels of [COHb] from 0 to 50 percent and for levels of hemoglobin from 15 g/100 ml to 7.5 g/100 ml under conditions of veno-arterial shunting and $\dot{V}/\dot{Q}$ imbalance. For the former case the standard shunt equation was used (*6*). All calculations were made for an alveolar P_{O_2} of 100 mm-Hg and arterial-venous oxygen difference 5 ml/100 ml. Arterial oxygen content was calculated and *A-a* D_{O_2} was computed by obtaining

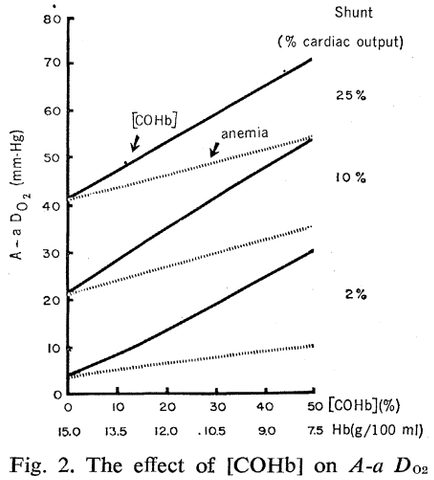

Fig. 2. The effect of [COHb] on *A-a* D_{O_2} in the presence of veno-arterial shunts (solid lines). The effect of equivalent degrees of anemia is shown by the interrupted lines. See text for explanation.

Pa_{O_2} graphically from the curves shown in Fig. 1. Results of these calculations are illustrated in Fig. 2, which shows that increasing [COHb] to 10 percent causes an increase in *A-a* D_{O_2} in the presence of shunts as small as 2 percent of cardiac output. The increase in *A-a* D_{O_2} exceeds 30 mm-Hg at a [COHb] of 50 percent. There was no significant change of the *A-a* D_{O_2} in the presence of shunts that were less than 1 percent of cardiac output. The effect of an anemia equivalent to that produced by CO binding of hemoglobin is considerably less than that of rising [COHb]. For the situation with $\dot{V}/\dot{Q}$ imbalance, we assumed a two-compartment lung model and made calculations for three different sets of $\dot{V}/\dot{Q}$ ratios. Blood flow to each compartment was considered to be equal and ventilation was varied to produce the $\dot{V}/\dot{Q}$ ratios. Arterial oxygen content was calculated and Pa_{O_2} was determined graphically from the dissociation curves in Fig. 1. The results are shown in Fig. 3. The changes in *A-a* D_{O_2} with $\dot{V}/\dot{Q}$ abnormalities are smaller than with veno-arterial shunts. As in the case of shunts, the effect of true anemia is less than that of increasing [COHb]. The ratios of 1.0 and 0.6 correspond to the nonuniformity found in normal man (*6*).

These calculations show that the effect of CO on *A-a* D_{O_2} in the presence of veno-arterial shunts or $\dot{V}/\dot{Q}$ imbalance should be in large part due to the shift to the left of the oxyhemoglobin dissociation curve, with a small increase in *A-a* D_{O_2} being due to flattening of the curve which results from the function anemia that is produced by CO binding of hemoglobin. We assumed that the arteriovenous oxygen difference remained constant in our calculations. Small changes in the arteriovenous oxygen difference of the magnitude found by Ayers and his co-workers (*3*) would account for only a 2 to 3 mm-Hg rise in *A-a* D_{O_2} in the absence of a change in the shape of the oxyhemoglobin dissociation curve.

In order to test the validity of our calculations we measured *A-a* D_{O_2} before and after inhalation of CO in five normal subjects, two patients with intracardiac shunts, and two patients with $\dot{V}/\dot{Q}$ imbalance. The results of these studies are presented in Table 1 and are in agreement with our theoretical calculations.

These findings have several important implications in CO toxicity. The tissue hypoxia produced with rising [COHb]

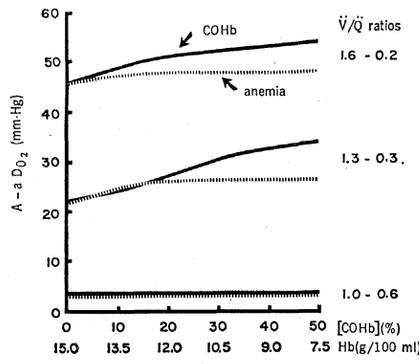

Fig. 3. The effect of [COHb] on *A-a* D_{O_2} in the presence of nonuniform $\dot{V}/\dot{Q}$ ratios (solid lines). The effect of equivalent degrees of anemia is shown by the interrupted lines. See text for explanation.

may be accentuated by arterial hypoxemia in the presence of abnormal $\dot{V}/\dot{Q}$ or veno-arterial shunts by the mechanisms described above. Arterial hypoxemia may even play an important role in CO poisoning of subjects with normal lungs if they develop $\dot{V}/\dot{Q}$ imbalance or veno-arterial shunts when unconscious. The mechanisms of increased *A-a* D_{O_2} that we have described may also explain a portion of the increased *A-a* D_{O_2} that has been reported in chronic smokers (*7*), since [COHb] of 5 to 10 percent (levels commonly found in heavy smokers) may increase *A-a* D_{O_2} in the presence of shunts as small as 2 percent.

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