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THE ELIMINATION OF CARBON MONOXIDE FROM THE HUMAN BODY WITH REFERENCE TO THE POSSIBLE CONVERSION OF CO TO CO_2

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C. A. TOBIAS, J. H. LAWRENCE, F. J. W. ROUGHTON, W. S. ROOT AND M. I. GREGERSEN

From the Aero Medical Laboratory, University of California, Berkeley, and Department of Physiology, Columbia University, New York

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THE ELIMINATION OF CARBON MONOXIDE FROM THE HUMAN BODY WITH REFERENCE TO THE POSSIBLE CONVERSION OF CO TO CO_2

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The effect of carbon monoxide upon respiratory metabolism has been the subject of long controversy: Is the only effect of CO that of combination with hemoglobin, thus depriving the blood of some of its oxygen, or does CO react in some additional manner in the body? Is there any possible conversion of CO into CO_2 or other compound, or is there any other way in which the body can take up and store CO?

In addition to their theoretical implications, these questions are of practical importance, both in industrial and in military problems. Thus in the present war, in certain types of planes, tanks, cargo ships and in other situations, many fighting men may be exposed to low concentrations of CO for comparatively long periods of time and may suffer from carbon monoxide poisoning of a more or less severe degree. Therefore, the questions outlined above carry added significance.

In the past, considerable work has been done in this field, but there is only space here to refer to some of the more important observations. J. S. Haldane (1) exposed mice to a gas mixture containing 1 atmosphere of carbon monoxide and 2 atmospheres of oxygen. Under these conditions the hemoglobin of the blood was almost entirely combined with CO but enough oxygen was dissolved in the blood to maintain life. The behavior of the mice was practically normal, and Haldane thus concluded that CO was entirely inert except for its power to combine with hemoglobin. One year later Haldane and Smith (2) showed that when a very low pressure of carbon monoxide in a rubber bladder is in equilibrium with that in the human body in a closed respiratory system so that no CO can escape, the percentage of COHb in the blood remains the same (33 per cent) for as long as 60 minutes. This result was interpreted as ruling out metabolism of CO or slow accumulation of CO in any organ (e.g., the spleen) for then the blood COHb level would decrease progressively, and the concentration of CO in the bladder would fall off. Such a conclusion is, however, open to criticism (see 9).

[1] The work described in this paper was done under contracts, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the University of California and Columbia University.

We are grateful for the technical assistance of Messrs. Ellis Myers, Frank Turpin and Robert Weitbrecht, and we wish to thank Dr. J. G. Hamilton and the Berkeley cyclotron crew for bombarding the targets.

[2] From the Division of Medical Physics and Medicine, University of California.

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Since these experiments were done, the measuring techniques have been greatly improved, and the study of the effects of high concentrations of CO has been considerably advanced. In 1926 Warburg (3) showed that CO combines with a respiratory ferment in yeast and inhibits respiration. J. B. S. Haldane presented some evidence (4) pointing to a toxic effect of CO on rats when exposed to a mixture of 2 atmospheres of CO with 2 atmospheres of O_2. In 1932 Fenn and Cobb (5) observed that CO has a stimulating effect on the normal resting metabolism of frog and rat muscle (skeletal and cardiac) when exposed to gas mixtures containing high percentages of CO; e.g., 80 per cent CO and 20 per cent O_2. This was confirmed by Schmitt and Scott (6), who also drew attention to concurrent inhibition of oxidation in the presence of CO. These phenomena have been analyzed more recently by Stannard (7), who definitely concludes that the effect of CO on muscle is dual, consisting under certain conditions of an inhibition of the Warburg-Keilin cytochrome oxidase system together with a catalytic oxidation of CO to CO_2 by enzymes separable from the known resting and active systems. In the latter connection he quotes Negelein's demonstration (8) that CO can be burned to CO_2 in alkaline solution by green and "mischfarbene" hemins at low O_2 pressures.

No information has, however, been available on the magnitude of any possible "tissue" effects of CO when administered in very low concentrations (up to 0.01 per cent in the inspired air), so two of us recently (9) tried to recover CO, previously absorbed by man, by continued breathing of oxygen or air. The blood concentrations of COHb were obtained after venepuncture. The total amount of CO in the blood was estimated from the known blood volume and COHb concentration, and the CO content of all the exhaled air was also determined. The tests were continued for one hour after the absorption of CO and, in general, about 30 to 40 per cent of the amount of CO disappearing from the blood did not appear in the exhaled air. It seemed reasonable to suppose that some of the missing CO might have been oxidized to CO_2, since the previous evidence against this happening to a slight extent in man did not appear to us conclusive, and furthermore a calculation kindly made for us by Dr. W. O. Fenn indicated that if (a) the rate of CO oxidation by muscle remains proportional to the CO pressure down to the very low values met with in human blood and (b) the results on the isolated muscle at 22°C. can be extrapolated to the whole musculature of the human body at 37°C., then about 5 per cent of the CO lost from the blood in our experiments (9) might have been oxidized. Muscle in vivo might well be more effective than in vitro. We therefore thought it well worth while to apply the radioactive tracer technique to determine whether in the human body there might be any oxidation of CO to CO_2. The radioactive isotope $_6C^{11}$ having positron and gamma ray activity and half-life of 21 minutes (10, 11, 12) was used in form[1] of the labeled C*O.

In general the plan of the experiments was as follows: Several human subjects were given a relatively large labeled dose of C*O, followed by the breathing of 100 per cent oxygen, and collection in soda lime of all exhaled CO_2, and measure-

[1] Radioactive carbon in form of CO will be referred to as C*O.

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METHODS. B_2O_3
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ment of the soda lime for any activity having a half-life of 21 minutes. The demonstration of such radioactivity in exhaled CO_2 would constitute evidence that CO is converted to CO_2 in the human body. At the same time, by placing counters over various areas on the body surface (thigh, chest, spleen, liver), the uptake and elimination of CO in these various regions were studied.

METHODS. B_2O_3 was fused to the target of the bombardment chamber of the cyclotron. On the average, bombardment with 20 mev deuterons (10 microamperes) lasted 30 minutes. The labeled carbon formed during the bombardment is in the form of CO and CO_2 and is partly trapped in the B_2O_3 target and partly in the target chamber. The latter was evacuated from the target chamber into an evacuated 300 cc. tonometer, containing 10 cc. of ordinary CO and 10 cc. of ordinary CO_2 as carriers. The tonometer had three-way stopcocks at each end.

It was essential to remove the radioactive CO_2 entirely from the gas in the tonometer before the latter was absorbed by the subject, otherwise entirely misleading results would have been subsequently obtained. The removal was done as follows: 10 cc. of 1 N NaOH were forced into the tonometer and the latter shaken violently by hand for 5 minutes. The NaOH solution was then drained off and the tonometer washed with ten successive 5 to 10 cc. portions of tap water. Each fraction was shaken thoroughly in the tonometer for some seconds before being drained off through the lower three-way tap and glass exit lead. The latter was also thoroughly washed each time through the side tube of the three-way tap so as to remove all drainage films of radioactive solution from its walls. A check as to the final purity of the gas from C^*O_2 was made by adding a few cubic centimeters of ordinary CO_2 as carrier and passing the mixture slowly over soda lime. Only 0.0015 per cent of the original activity was found in the soda lime, thus indicating a very high efficiency of CO_2 removal. The slight residual activity may be due to the CO_2 absorption falling just short of the theoretical end-point or to extremely slight absorption of the C^*O of the gas sample by the soda lime (or to both of these factors). Its amount was, in any case, insignificant for the purpose of the present experiments.

The activity of the remaining labeled CO was calibrated against a 1 mgm. radium standard using a gamma ray counter and a scale of eight circuit. Thereafter, it was introduced into a rubber bag into which there had previously been placed 150 cc. of ordinary CO and 2,000 cc. of O_2. The subject, after deep expiration, inhaled and exhaled in the bag three times, and then finally drew the whole contents of the bag into his lungs and held his breath for one minute. This usually resulted in an absorption of at least 95 per cent of the CO administered, and the blood CO content rose correspondingly to 2 to 3 volumes per cent. Thereafter, the subject exhaled and breathed air for seven minutes. He then was given 100 per cent oxygen and all exhaled air was passed through a glass tube (about 10 inches long and 1 inch in diameter) containing soda lime sufficient to absorb all exhaled CO_2. In the last two tests the soda lime tube was kept cool by packing in cracked ice. At 10 or 15 minute intervals a fresh soda lime tube was inserted and any radioactivity of the absorbed CO_2 was measured.

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This was done with a gamma ray counter, the soda lime being poured into a glass cylinder surrounding the Geiger-Muller tube. In some experiments the total exhaled air was collected in a Douglas bag and later analyzed for CO content. Frequent venous blood samples were taken and analyzed for CO content (13, 14, 15). With the blood data, including blood volume and the Douglas bag data it was possible to calculate the amount of CO which had disappeared from the blood but which had not appeared in exhaled breath. During some of the experiments the subject was exposed to Geiger counters which pointed through a lead slit system to definite regions of the body—one counter was placed over the heart and spleen, another over the liver, and a third one over the muscles of the thigh. These made it possible to plot the curves of uptake and disappearance of labeled CO in these areas of the body.

In all activity measurements the background count was first subtracted and the resulting activity at the time of measurement, t, corrected for the decay from the starting time, t_0, by multiplying it by $e^{0.033(t-t_0)}$, times being measured in minutes.

RESULTS OF THE EXPERIMENTS WITH C*O. Table 1 summarizes the results with respect to the possible conversion of CO to CO_2. Any CO_2 so formed would be distributed throughout the body in the form of CO_2 and HCO_3 so that only a fraction would appear in the expired air. Allowance is duly made for this factor in the table. In brief, the data show that less than 0.1 per cent of the CO lost from the blood during the first hour after CO administration is converted to CO_2. In only one instance out of 19 samples was the activity in the soda lime significantly above background (table 1, column 5). We have no explanation for this anomalous result except for a possible contamination, unnoticed at the time of its occurrence, of this particular soda lime with extraneous radioactive material. The same subject in a repeated experiment showed entirely negative results along with the other ones. The very small activities (usually less than 0.1 per cent of absorbed CO) indicating possible conversion might also be due in whole or in part to the absorption of extremely minute traces of CO by the soda lime, and the very sensitive radioactive technique detects this. These experiments however do not rule out the possibility of conversion of CO to CO_2 during longer periods of time. In two cases the urine was collected at the end of the experiment and in neither case was activity detectable.

In the interpretation of the experiments wherein the relative uptake and elimination of radioactive CO are measured, one must proceed with caution since each of the curves shown in figures 1, 2, and 3 undoubtedly contains components arising from sources other than the particular object of observation, i.e., the spleen, the liver, and the thigh. The usual type of curve observed from venous blood analyses for CO is very similar to that in figure 1. (Here the counter was placed under the posterior thigh, about 10 inches from the hip; a 1½ inch wide slit mounted crosswise to the thigh limited the solid angle of the counter which was 2½ inches from the skin.) During the first 1½ minutes there was an initial rise, probably related to the mixing of CO in the lungs. At the

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The appe

NAME	
J. H. L. (1)	
M. I. G.	
B. R. B. (1)	
C. A. T. (1)	4
B. R. B. (2)	
J. H. L. (2) (soda lime cooled in ice)	4
C. A. T. (2) (soda lime cooled in ice)	4
Average.....	

* All counts/min. a
subtracted.
** The C*O_2 which
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† This is the amoun
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end of 1½ minutes the elimination of CO started. In the thigh, (fig. 1) due to mixing and continued uptake by the blood, the activity continued to rise for

TABLE 1

The appearance of C^*O_2 in the exhaled air after breathing C^*O

	DATE	C^*O SAMPLE TAKEN IN THROUGH LUNGS	TIME SODA LIME EXPOSED TO EXHALED AIR	NET CTS/MIN. ABSORBED IN SODA LIME*	RATIO OF C^*O_2 FORMED TO RADIO ACTIVITY OF ORIGINAL SAMPLE**	PER CENT CO EVOLVED IN SAME PERIOD†	CO BURNT / CO LOST IN SAME PERIOD
	1945	*cts./min.*	*min.*		*per cent*		*per cent*
[redacted] (1)	3-22	1,080,000	0-15	0	0.000	28.0	0.00
[redacted] (1)	3-23	1,830,000	0-15	42	0.016	26.4	0.06
[redacted] (1)	3-24	795,000	0-15	130	0.114	29.0	0.39
[redacted] (1)	4-3	2,200,000	0-15	13	0.004	14.0	0.03
			15-30	5,600	1.820	8.5	21.40
			30-45	33	0.011	6.0	0.18
[redacted] (2)	4-6	3,540,000	0-10	16	0.005	10.0	0.05
			10-20	34	0.010	9.0	0.11
			20-30	31	0.009	8.0	0.11
			30-40	30	0.009	7.0	0.12
			40-50	0	0.000	6.0	0.00
			50-60	0	0.000	5.0	0.00
[redacted] (2) (soda lime cooled in ice)	4-6	2,940,000	0-15	0	0.000		0.00
			15-30	11	0.003	14.4	0.02
			30-45	26	0.006	13.0	0.05
[redacted] (2) (soda lime cooled in ice)	4-7	3,610,000	0-15	12	0.002	14.0	0.02
			15-30	6	0.001	8.5	0.01
			30-45	0	0.000	6.0	0.00
			45-60	1	0.000		0.00
Average		2,230,000	in 15 minute period	24	0.012	14.5	0.072

* All counts/min. are corrected for decay to the starting time. Background has been subtracted.

** The C^*O_2 which may form should be distributed evenly between the amount in the body and that exhaled. It was assumed that a person exhales 300 to 400 cc of CO_2 per minute, or 15 × 300 = 4500 cc. in 15 minutes. However, it is estimated that the total amount of CO_2 in the body may be from 27 to 33 liters. Thus, we have roughly ⅛ of the CO_2 formed in a 15 minutes experiment available for measurement. The data are corrected for this dilution.

† This is the amount of CO which disappeared from the blood. It was calculated from 3 to 4 venous blood samples taken in each experiment.

a few minutes, then its drop followed one single exponential of the same order of half-time as the exponential decrease of CO in the venous blood of the arm. In

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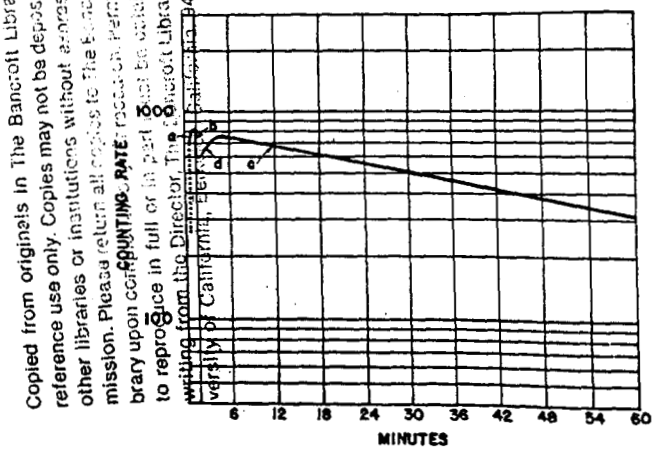

Fig. 1. Decrease of the amount of C* in the left thigh while breathing oxygen and after 1½ min. of inhaling C*O. Normal subject, F. T., 22; exp. 10; 4-7-45.
a: C*O uptake in the lungs 1½ min.
b: C*O disappears from lungs.
c: desaturation one single exponential.
d: continued uptake of C*O from arterial blood.
Half-time of desaturation: 44 min.

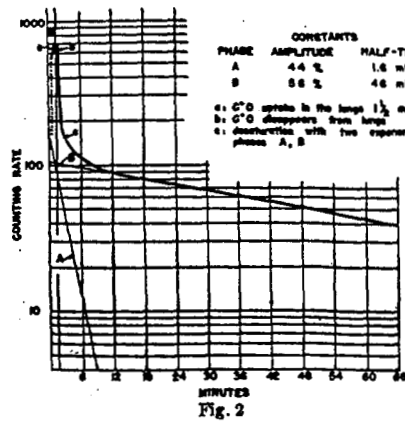

Fig. 2

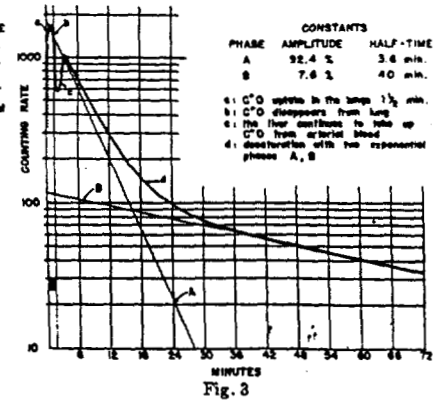

Fig. 3

Fig. 2. Decrease of the amount of C* in the region of spleen and heart while breathing oxygen and after 1½ min. of inhaling C*O Normal subject, C. A. T., 27; exp. 9; 4-7-45.
Fig. 3. Decrease of the amount of C* in the region of liver while breathing oxygen and after 1½ min. of inhaling C*O. Normal subject C. A. Tobias, 27; exp. 9; 4-7-45.

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figure 2, the curve of the spleen-heart region, the initial high concentration due to CO in the lungs falls off with a two components curve, one fast indicating mixing (see Discussion) and a slow one similar to that in the thigh. Curves taken higher up on both sides of the chest above the spleen and the liver have similar components and may reflect chiefly the situation in heart and lung and not spleen at all. The most interesting case is presented in the liver curves (fig. 3) where the fast component has an amplitude 6 to 9 times that of the slow and where the counting rate at the beginning of the desaturation is several times higher than on the other side of the chest. It is also interesting to note that the liver region continues to take up C*O several minutes after C*O intake through the lungs has ceased. This secondary uptake might possibly be associated with the arrival of blood via the portal vein, which is thought to contribute about three-quarters of the blood supply to the liver.

TABLE 2

Elimination of C from the liver and spleen-heart regions*

NAME	LIVER					SPLEEN AND HEART					BLOOD
	Relative intensity	Fast Comp.		Slow Comp.		Relative intensity*	Fast Comp.		Slow Comp.		½ time disappearance CO from venous blood
		a ampl.	T_a half time	b ampl.	T_b half time		a ampl.	T_a half time	b ampl.	T_b half time	
	cts./min.*	per cent	min.	per cent	min.	cts./min.	per cent	min.	per cent	min.	
[redacted]	1,700	65	4.4	35	26	900			100	24	42
[redacted]	10,000	91	2.6	9	91	1,650	52	2.3	48	40	70
[redacted] (1)	4,500	84	4.7	16	80	1,450	51	4.6	49	120	90
[redacted] (1)	12,500	92	3.6	8	40	1,520	44	1.6	56	46	63
Mean	7,180	83	3.8	17	60	1,380	37	2.5	63	57	66

* The intensities and amplitude percentages were extrapolated to the time when CO breathing was discontinued from the bag (1½ min. after the beginning of the experiment).

Table 2 presents the constants obtained in the various experiments. There seemed to be a much higher activity over the liver region at the beginning of elimination than in the spleen-heart region, although the sensitivity of the counters and the geometry with respect to the body were similar. The high initial activity and the large fast component were not expected in the liver curve, but their presence may in part explain the discrepancy between the venous arm COHb blood levels and the amount of CO eliminated in the exhaled air, the latter being found in three of the present experiments to average only 60 per cent of that lost from the blood during the first half hour after the CO administration, thus confirming the previous results of two of us (9). During the major part of the first hour the liver continued to unload CO to the general circulation. The average of the half times of disappearance of CO from the venous blood, as measured by standard techniques agree fairly closely with the average of the half lives of the slow components of the C*O curves, though in individual cases

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the discrepancies mount as high as ±40 per cent. This may be in part due to inaccuracies brought about by the movement of subjects, during the experiments, and insufficient determination of decay curves. The significance of the data in figures 1, 2, and 3 and table 2 will be further considered in the Discussion.

Measurement of elimination of CO while breathing oxygen for four hours. In view of the lack of evidence of conversion of CO in these exploratory experiments, three subjects inhaled ordinary CO, and during a four hour period thereafter exhaled CO was quantitated. Blood CO content of each subject was measured at the beginning and at the end of each experiment. Each subject took in approximately 150 cc. of CO mixed with oxygen in one case and with air in the other two. Thereafter, oxygen inhalation was continued for four hours and the exhaled air collected in Douglas bags. The volume in each bag was measured after mixing the exhaled air in it, and 1/1,000th of the volume was saved for analysis. The first bag was taken off after 10 minutes, and its CO content enabled one to calculate the amount of CO taken up by the body. All other samples were mixed, and at the end of the test the CO content of the mixed 1/1,000th fraction was measured. The results showed that in these three experiments 93, 97 and 97 per cent of all absorbed CO was recovered during this period of time in the exhaled air. The blood CO at the end of these tests was practically the same as before starting them so only a small correction was necessary on this account. These results are reported in detail elsewhere (9).

Discussion. From the above results it seems clear that in mild CO poisoning only a negligible, if any, proportion of CO is burned to CO_2 in the body within the first 60 minutes of oxygen breathing. The experiments were limited to one hour owing to the relatively short half life of the radioactive carbon; oxygen was used in place of air because the elimination of CO from the blood is thereby speeded up about six times, whereas the proportion of CO recovered in the expired air is still the same, viz., 60 to 70 per cent of that currently lost from the blood (9). (It should be pointed out that the amount of CO lost from the blood in periods up to one hour is calculated from venous blood COHb values and blood volume determinations by the CO method and its accuracy therefore depends on the reliability of the latter estimations.) The absolute amount of any CO unaccounted for during the first hour is therefore six times greater when breathing oxygen than when breathing air, and the chance of finding out what happens to it should be correspondingly greater. The additional finding that almost all the absorbed CO is recovered in the expired gas if oxygen breathing is continued for four hours seems to exclude not only oxidation but also every other form of CO metabolism and seems to prove that the whole, or practically the whole, of the CO taken up by the body is reversibly combined. It will be recalled that Fenn and Cobb (5) were themselves doubtful of the applicability of their results to mammalian CO poisoning, since in the latter case the CO pressures are only of the order of one-thousandth of those they used in their muscle experiments. It is also possible that the high O_2 pressures in our experiments—both absolutely and relatively to the CO pressures—may have inhibited the catalysis,

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since Negelein (8) found that for CO to be burned to CO_2 by hemins in alkaline solution the O_2 pressure must be low enough to leave the Fe only partially oxidized. Further experiments should therefore be tried at low O_2 pressures and with much larger amounts of CO in the blood. Our present results in no sense contradict those of Fenn and Cobb, but merely show that it is not feasible to make a simple extrapolation from the latter to the entirely different conditions prevailing in mammalian CO poisoning.

The more positive, though less complete and well-controlled, findings of this paper, i.e., those obtained with Geiger counters over various parts of the body seem to merit further, if perhaps more speculative, consideration. With the method of CO administration used in this paper, the alveolar CO pressure at the beginning of the breath-holding must be about 4 per cent of an atmosphere so that the COHb in the blood leaving the lungs at this stage should be of the order of 40 to 50 per cent (i.e., about 3 times the final percentage of COHb in the blood) according to calculations based on the recent data and methods of Roughton and his colleagues (16, 17). Such a rapid initial rate of CO absorption would cause the gradient of CO pressure between the alveolar air and the blood to drop rapidly, and the arterial per cent COHb must of course follow pari passu, being practically equal, at the end of the breath-holding, to that of the mixed venous blood entering the lung capillaries at this stage. Each organ of the body correspondingly receives blood with a high initial, but rapidly dropping, percentage of COHb and radioactivity. In organs such as the muscles, in which there are no large pools of relatively stagnant blood cells, the slow component of figures 1 to 3 should be reached as soon as the blood has circulated around the body enough times to mix the CO in it thoroughly, and the amplitude of the slow component should be proportional to the amount of blood in the organ, or more correctly, in the area of the organ which is recorded by the Geiger counter. Organs which have a rapid circulation especially if they are situated close to the heart, would be expected to show an initial high radioactivity. After a short period, however, their blood mixes with blood from the other, less well supplied regions of the body and the C*O activity then will decrease, indicating mixing. This seems to be the case in curves taken over both lungs anteriorly just below the clavicles and also over the spleen-heart region. We were hoping to detect a difference in "mixing time" between the curves obtained over the spleen-heart region, and other chest curves, since it is expected from the work of Barcroft et al. (19), on rats, that the blood stored in the sinuses of the spleen would slow down the mixing of COHb. Our failure to observe such differences may, however, have been due to insufficient accuracy in the measurements.

It is remarkable that the initial phase of the liver curve is so much more pronounced and prolonged than that of the spleen-heart curve and it is difficult indeed to see how it can be wholly explained on the same basis. In dogs and cats Barcroft et al. (18) showed that, after sudden administration of CO, the lag in COHb percentage between the liver parenchyma blood and the arterial blood only amounted to two minutes at most. These results contrast markedly

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with those in the spleen (19), wherein lag periods up to 30 minutes were found, thus pointing to a much greater proportion of stagnant cells in the pulp of that organ than in the liver. No comparable figures are available for human liver and spleen though it is believed that the rôle of the spleen in man as a functional blood store is far less marked than in the dog, and it is possible that in man the liver may to some extent replace the spleen as regards blood reserve function. Even so, the ratio of the fast component to the slow component should not exceed one to one at most, unless some additional factors enter. For the highest percentage of COHb in the blood in these experiments is probably not much over 40 (see above) and, since this figure must drop rapidly during the one minute of breath-holding, the red cells of the liver can scarcely rise to higher than 30 per cent COHb by capture of CO from the cells rapidly circulating through the liver. Now the final per cent COHb reached in the mixed blood both in the liver and elsewhere averaged about 15, so that if the number of red cells in the liver that are examined by the Geiger counter remains constant throughout the experiment, the total initial activity should not have exceeded *twice* the value of the amplitude of final activity. In other words, the amplitude of the fast component would at best have been only expected to equal the amplitude of the slow component. It therefore seems that other factors must also be present if a ratio of amplitudes as high as 5 to 1 is to be explained. Two ideas suggest themselves, aside from the bare possibility that the liver handles radioactive CO in a different manner from ordinary CO: (a) The sudden arrival in the liver of blood containing a high percentage of CO might lead to a temporary engorgement of the liver with blood, (fig. 3c) followed by a contraction of the liver, expelling blood high in COHb content into other parts of the body (final steep part of curve in fig. 3). (b) The liver might contain in the Kupffer cells and elsewhere, appreciable amounts of a pigment with a far higher affinity for CO than blood hemoglobin possesses. Such a pigment would be similar to the pseudo-hemoglobin of Barkan (20), which is regarded by him as an intermediate breakdown product between blood hemoglobin and bile pigment and is calculated to have up to 10 times the affinity for CO that blood hemoglobin has. A pigment with such physico-chemical properties would be expected to take up CO very rapidly from the blood, when the COHb content of the latter is suddenly raised, and only release it slowly again to the blood as the COHb drops.

All the factors so far mentioned may well enter, in varying degrees, into the explanation of the liver curve, together with other factors which have not yet occurred to us. It is hoped to obtain further evidence in man, by simultaneous measurement of the CO content of the hepatic vein blood and other blood vessels during and after CO administration, and also by administering C*O slowly instead of in the short massive dosages used in this paper. In animals it would be desirable to carry out liver perfusion experiments and to study the affinity of liver extracts for CO directly.

Whatever may be the final explanation of the shape of the liver curve of figure 3, the matter merits further consideration in the study of acute CO poisoning and in the measurements of blood volume by the CO method.

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SUMMARY

1. Several normal men were each given, via the lungs, a relatively large dose of radioactive CO, mixed with about 150 cc. of ordinary CO. Thereafter the subjects breathed oxygen for periods up to one hour, during which their expired CO_2 was absorbed in soda lime. Tests of the latter for radioactivity showed that the CO oxidized to CO_2 by the body under these conditions amounted to less than 0.1 per cent (if any) of the CO currently lost from the blood.

2. The time course of the radioactivity in three parts of the body, viz., the thigh muscles, the spleen-heart and the liver was studied by placing Geiger counters over these regions.

3. The curves for the muscle and spleen-heart areas can be reasonably interpreted in terms of the average amount of blood present in them at any given time, and the rate of blood flow. The liver curve, however, showed an unexpectedly high and prolonged initial phase, which is difficult to explain completely in such a way. The nature of the possible additional factor present in this region is discussed.

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