methionine over a long period of time (*4*). In animals on choline-deficient diets, the administration of choline caused a marked stimulation of the turnover of liver and plasma phospholipides; this effect is smaller or undetectable in animals maintained on adequate diets. In other words, in experimental animals the stimulating action of a large dose is only evident when the supply of choline or choline precursor is insufficient.

These observations suggest a tentative interpretation of our present findings on human patients. One might postulate that a definite increase in the phospholipide turnover after the administration of a single large dose of choline or methionine reflects a condition of relative deficiency in lipotropic agents. This hypothesis deserves further investigation and we are continuing our study in order to arrive at a more definite conclusion.

In certain instances of chronic hepatitis, the use of lipotropic factors is thought to be of therapeutic value. This beneficial effect is attributed largely to a stimulatory action on the formation of phospholipides. An increase in the turnover of phospholipide in plasma was noted in two patients with portal cirrhosis who received a large dose of choline or methionine. This effect was no longer demonstrable after prolonged treatment with lipotropic agents, although the patients exhibited clinical and laboratory evidence of marked improvement.

It is suggested that the stimulation of phospholipide turnover caused by a single large dose of choline or methionine may indicate a deficiency of lipotropic material, and thus provide an estimate of the anticipated response to the treatment of cirrhosis with lipotropic substances.

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Evidence for the Conversion of Carbon Monoxide to Carbon Dioxide by the Intact Animal

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Conversion of CO to CO_2 by animal tissues was suggested and to some extent demonstrated by Fenn and Cobb (*5*) to account for the marked increases in gas consumption observed when isolated tissues, particularly muscle, were exposed to an atmosphere containing about 80% CO in oxygen. The phenomenon was confirmed by Schmitt and Scott (*9*) and shown to be superimposed on inhibition of the cytochrome-cytochrome oxidase system by Stannard (*10*). The ability of an intact animal to accomplish this conversion, however, has never been demonstrated. In fact, there have been numerous arguments against the presence of such a phenomenon (*6, 7*), the most recent of which is found in the results of Tobias *et al.* (*11*), in which radioactive carbon (as $C^{11}O$) was employed. They found that less than 0.1% of the CO lost from the blood could be recovered as $C^{11}O_2$ in the expired air.

TABLE 1

DISAPPEARANCE OF CO FROM CLOSED CHAMBER (60 LITERS) WITH AND WITHOUT TURTLES*

Exp.	Time†	Total weight of turtles	Initial CO concentration	Amount consumed: With turtles	Amount consumed: Control	Amount consumed: Difference	CO consumed
	days	g	%	ml	ml	ml	%
1	8	2080	0.023	5.92	0.00	5.92	41
2	7	4826	0.020	7.71	1.20	6.51	52
3	13	4880	0.038	12.03	2.68	9.35	48
4	11	4662	0.047	14.86	1.08	13.78	49
5	10	2946	0.075	13.30	0.00	13.30	30

* Gasometric experiments, values expressed at STP.
† Number refers to duration of *each* period, control and experimental.

With the availability of C^{14} and recent refinements in methods for the determination of very small amounts of CO, it was considered of interest to repeat the experiments done in this laboratory with isolated tissue and to extend them to the intact animal. The results with isolated tissue have been reported elsewhere (*3, 4*). Suffice it to say that the oxidation of CO to CO_2 by skeletal and cardiac muscle observed earlier by indirect gasometric and volumetric procedures was quantitatively reproduced in direct experiments measuring conversion of $C^{14}O$ to $C^{14}O_2$.

In the experiments with intact animals reported here, two methods were applied: (a) gasometric measurement of the CO disappearing from a closed chamber, using a modification of the extremely sensitive Roughton-Root technique (*8*), and (b) collection of the expired CO_2 from animals residing in an atmosphere containing CO, some of which was the radioactive $C^{14}O$, and measurement of radioactivity by the method of Bale, *et al.* (*1*).

Table 1 shows the amount of CO lost, measured by the gasometric method, in five experiments with turtles. Expired CO_2 was collected in soda lime placed within the chamber, and oxygen was added automatically as needed from a small spirometer through a check-valve system. Any CO removed for sampling was replaced by introduction of an equal amount from a syringe. Samples were taken initially, after an equilibration period of 10–12 hr and then either daily or at the end of the test period.

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It is clear that the amount of CO lost when the animals are present is large compared with that disappearing when only soda lime, food, accumulated feces and urine, etc. are present. It is also large compared with the amounts required to saturate blood and tissues at the CO tensions employed. The elapsed times are far greater than those necessary for equilibration of the gas with blood, tissues, and soda lime. Furthermore, samples taken at daily intervals indicated a more or less constant rate of disappearance (i.e., the CO does not all disappear during the equilibration period).

TABLE 2

DISAPPEARANCE OF CO FROM CLOSED CHAMBER (12.5 LITERS) WITH AND WITHOUT MICE*

Time	Total weight of mice	Initial CO concentration	Amount consumed		Rate of loss
			With mice	Control	
days	g	%	ml	ml	mm³/g/hr
4	246	0.071	4.49	0.13	0.20
4	294	0.089	8.16	0.84	0.26

* Gasometric experiment, values expressed at STP.

A similar experiment with mice is shown in Table 2. The initial concentrations were somewhat higher than in the experiments with turtles, but these represent only a moderately toxic level for mice. The CO concentration was determined initially, after an equilibration period of 10–12 hr, and again at the end of the experiment. The control period duplicated the experimental except for the absence of the animals. The data indicate disappearance of CO at a rate approximating 0.24 mm³/g body wt/hr.

The C^{14}-labeled CO was prepared by release of CO_2 from $BaCO_3$ having a specific activity of 384 μc per g of carbon. This CO_2 was reduced to CO after the method of Bernstein and Taylor (*2*). The conversion was practically quantitative, and this CO was used to prepare the mixture in the exposure chamber. The apparatus and conditions were otherwise similar to those in the gasometric experiment. Radioactive measurements were made with the CO_2 in gaseous form (*1*).

The results of the two experiments using mice are summarized in Table 3. While small amounts of radioactivity appeared in the alkali in the absence of the mice, due probably to solution of CO plus conversion to formate, it is obvious that the amounts of C^{14} appearing as $C^{14}O_2$ are many orders of magnitude higher in the presence of the animals. The phenomenon is clear, and the rate of CO oxidation calculated from isotope experiments agrees remarkably well with that obtained earlier by the gasometric procedure. While the specific activities in the collected CO_2 are low compared to the original CO, actually for each gram of carbon present as CO in the chamber, 22.3% and 19.3% respectively were converted to CO_2 in the two experiments.

The CO oxidation rate by the intact mouse is about 10 times that expected from a linear extrapolation of the rates obtained with isolated frog muscle at 80% CO to those expected at 0.07% CO. Allowing for the temperature difference (from 25° to 38° C), this indicates that mammalian muscle in the body effects this conversion at rates roughly equivalent to those expected from earlier work on isolated tissue. If applied to man, this rate would predict oxidation of CO at approximately 20 ml/hr if air containing 0.07% CO is breathed. It should be stated, however, that, if the rate observed by us in mice actually occurs in man, it should have been observable by the technique used by Tobias *et al.* (*11*). However, if the conversion is slow to start, the short times involved in their experiments might have prevented observation of the phenomenon.

TABLE 3

CONVERSION OF CO TO CO_2 BY MICE*

Time	Total weight of mice	Initial CO concentration	Activity measurements of $C^{14}O_2$ collected			Rate of conversion
			With mice		Control	
days	g	%	d/min × 10³	specific activity μc/g carbon	d/min × 10³	mm³/g/hr
2.67	57	0.07	459†	0.06	0.63	0.28
2.00	47	0.07	306	0.052	2.54	0.29

* Experiment with radioactive carbon monoxide ($C^{14}O$).
† That is, 459,000 disintegrations per minute.

The possible significance of these findings will be discussed in a more complete paper. Obviously, the mechanism of this reaction in tissues and its apparent limitation to muscle presents an interesting biochemical problem.[2]

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