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STUDIES IN GLYCINE-2-C^{14} METABOLISM IN MAN

1. The Pulmonary Excretion of $C^{14}O_2$

N. I. Berlin, B. M. Tolbert, and J. H. Lawrence

September 1, 1950

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1. The Pulmonary Excretion of $C^{14}O_2$

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Physics Department and Radiation Laboratory
University of California, Berkeley, California

September 1, 1950

Introduction

There has been considerable discussion regarding the use of Carbon 14 in clinical investigations, particularly from the standpoint of retention in the body of a long lived (5600 years) radioactive isotope. There is evidence from animal investigations that following the intravenous injection of simple C^{14} labeled compounds occurring in normal biochemical processes most of the radioactivity will be excreted as $C^{14}O_2$ within a few days.[1,2,3,4,5] The rate of excretion in mice via the lungs and the rate of loss of Carbon 14 from the soft tissues and bone when this isotope is administered as glycine-2-C^{14} has been determined; most of the radioactivity was eliminated in the breath in the first two days and the slowest tissue component was found to have a half time of approximately 10 days.[6] There is no method available for extrapolation of this animal data to man. The present study was designed to measure the rate of pulmonary excretion of Carbon 14 as $C^{14}O_2$ when administered as glycine-2-C^{14}.

Methods

Methyl-labeled glycine was prepared by chlorination and amination of acetic acid-2-C^{14} and had a specific activity of 12.2 microcuries/mg. of glycine.[7] A series of four patients was given approximately 100 microcuries of glycine-2-C^{14} (8 mg.) intravenously in 10 ml. distilled water for the

purpose of the determination of the red blood cell life;[11] since previous investigations with radio-iron had indicated that many patients with chronic leukemia might have red blood cells with a shorter than normal life span.[12] Frequent breath samples were taken by a device (see Figure 1) designed to collect the expired air in a rubber balloon for a measured period of time. The balloon was transferred to a bubbler system (see Figure 2) and the expired air drawn through a 1N sodium hydroxide solution. The carbon dioxide thus absorbed was precipitated as $BaCO_3$ by NH_4NO_3 and $BaCl_2$. The barium carbonate was filtered, dried at 110° C and weighed to determine the amount of CO_2 excreted per minute. The samples were counted with a proportional counter* where the specific activity was greater than 10 dis./min./mg. $BaCO_3$; those with a lower activity were measured in an ionization chamber. These instruments were calibrated with the current Oak Ridge C^{14} standard millicurie by specially prepared samples.

Inasmuch as the rate of pulmonary excretion of Carbon 14 when administered in this form was not known at the start of these studies, the patients were placed in an oxygen tent although no oxygen was supplied, so that the expired air would pass through the soda-lime filter and thus absorb the carbon dioxide. In addition a vacuum pump continually exhausted the air from inside the tent to the outside of the building. These precautions were maintained for approximately 36 hours.

Results

Figure 3 shows the specific activity as a function of time of the expired carbon dioxide as $BaCO_3$. The maximum specific activity of the

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* Nucleometer - Manufactured by Radiation Counter Lab, Chicago, Illinois

expired breath occurred within the first hour following the injection. A measurable amount of radioactivity was present within the first 10 minutes following the injection. Figure 4 shows the calculated cumulative Carbon 14 excretion as determined from the amount of CO_2 excreted per minute and the rate constants obtained from Figure 1.

The rate of excretion of Carbon 14 when administered in this manner may be described in terms of three rate processes: the first having a half time of two to four hours; the second, sixteen to forty hours; and the third, seven to fourteen days. Table I shows the half times and the percentages of Carbon 14 excreted through each of the three rate processes for the other patients.

Discussion

The cumulative excretion of Carbon 14 is so rapid that in Patient I at the end of 1 day approximately 40 percent has been eliminated by this route, and by the end of 5 days 60 percent; by 20 days, approximately 83 percent (see Figure 2). Furthermore, in all 4 patients by the end of 40 to 75 days there was no significant measurable activity in the breath; i.e., less than 0.04 dis./min./mg. $BaCO_3$. It is possible that there is a slower component, the radioactivity of which could be detected by more sensitive methods[8,9]; however, this could represent only a small fraction of the administered dose.

The relation of these three different rate processes to know biochemical processes is not known. However, the measurement of the uptake of Carbon 14 in the plasma proteins and their turnover time suggests that the slowest component may represent the rate constant for protein synthesis and turnover.[10]

The finding that the slowest measured rate of excretion is of the same order of magnitude in man as in mice should permit the extrapolation to man of animal investigations with similar Carbon 14 labeled compounds. This may allow the use of such animal data as the basis for the determination of the hazard of using C^{14} in clinical investigation. In addition to the 83 to 92 percent excreted via the lungs, some 5 percent of the injected dose is excreted in the urine and a negligible amount in the feces.[10] An additional 2 percent is present in the red blood cells as hemoglobin and will not be eliminated until the red cells are destroyed at the end of approximately 120 days.[11] This would indicate that there is little or no significant retention of Carbon 14 within the body; what may possibly be retained is present in chemical compounds having a very long turnover time. However, since such compounds do have a long turnover time the amount of Carbon 14 that could be incorporated in them is small because, as Figure 2 shows, after the first 2 days there is comparatively little Carbon 14 available for anabolic processes.

Summary and Conclusion

1. The rate of excretion of Carbon 14 via the lungs when administered as Glycine-2-C^{14} in 3 patients has been presented.

2. This pulmonary excretion has been described in terms of 3 rate processes, the slowest of which has a half time of 7 to 14 days.

3. In 55 days approximately 83 to 92 percent of the Carbon 14 is excreted via the lungs, 5 percent via the urine, and 2 percent is retained in the red blood cells during their life span.

4. The lack of hazard involved in the use of Carbon 14 in the manner described is discussed from the standpoints of excretion and possible retention in chemical compounds having a long turnover time.

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TABLE I

The Percent of the Administered Dose Excreted and Half Time for Each of the Three Rate Processes

Patient	$T_1(1/2)$(Hours)	%	$T_2(1/2)$(Hours)	%	$T_3(1/2)$(Hours)	%	Total % Excreted
1	3	36	31.2	27	223	29	92
2	2.7	32	40	13	163	38	83
3	2.5	13	36	21	336	52	86
4	3.3	22	16	17	240	49	88

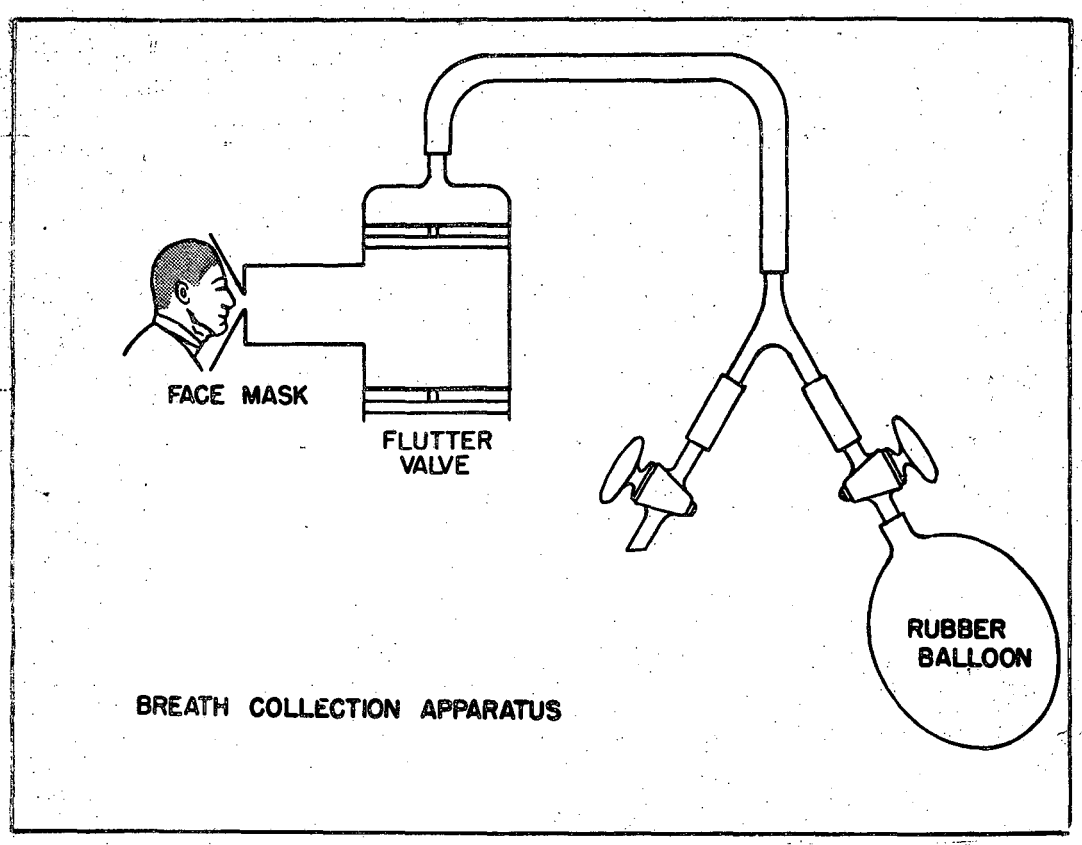
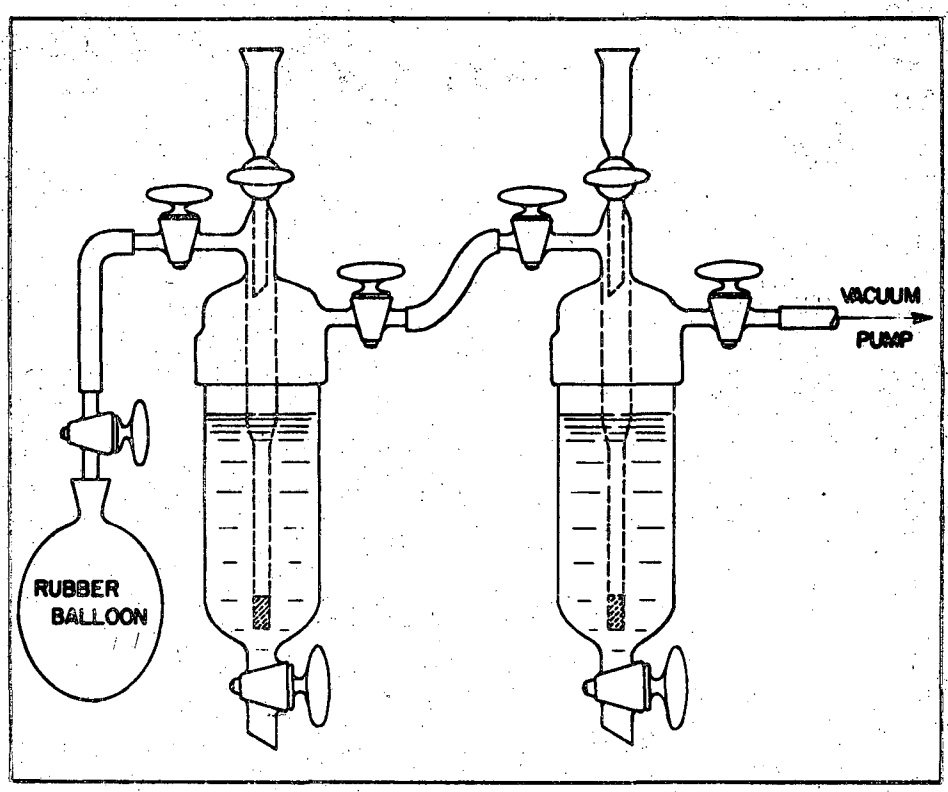


Figure 1
(Note: not drawn to scale)



APPARATUS FOR CARBON DIOXIDE ABSORPTION MU 726

Figure 2

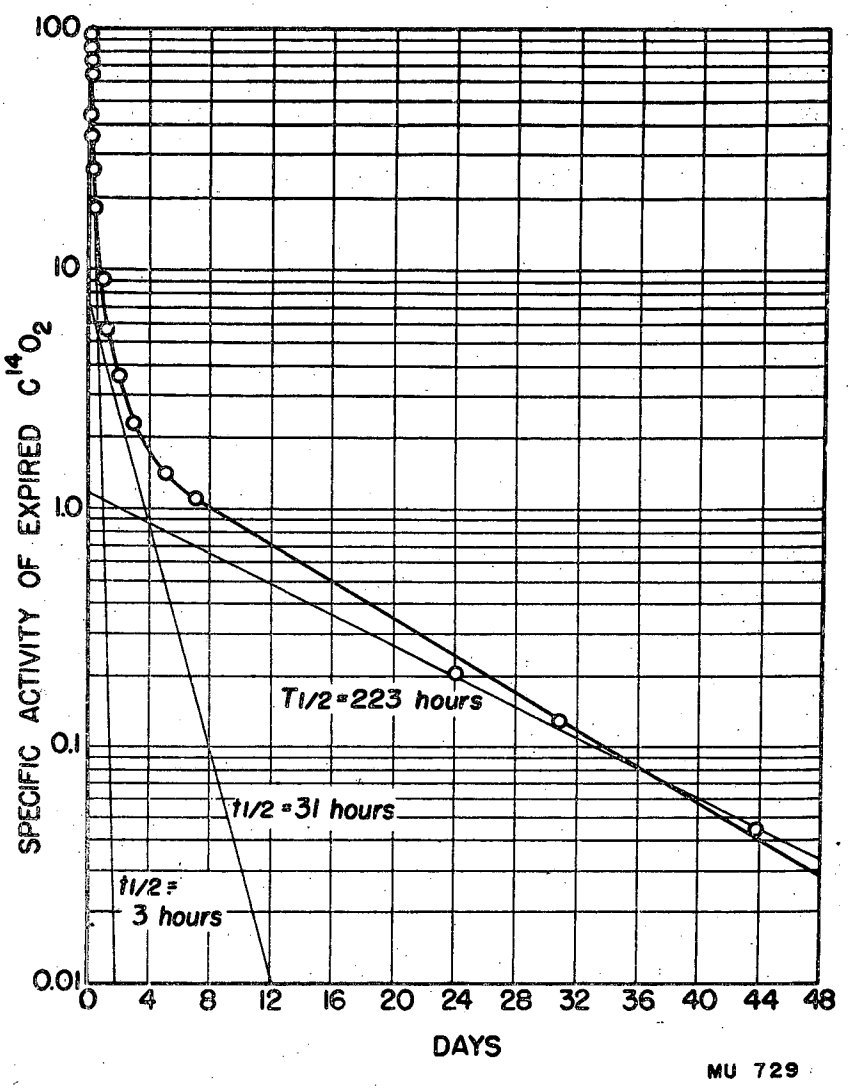


Figure 3
The specific activity of the expired breath as a function of time, in Patient I, in disintegrations per minute per mg of $BaCO_3$.

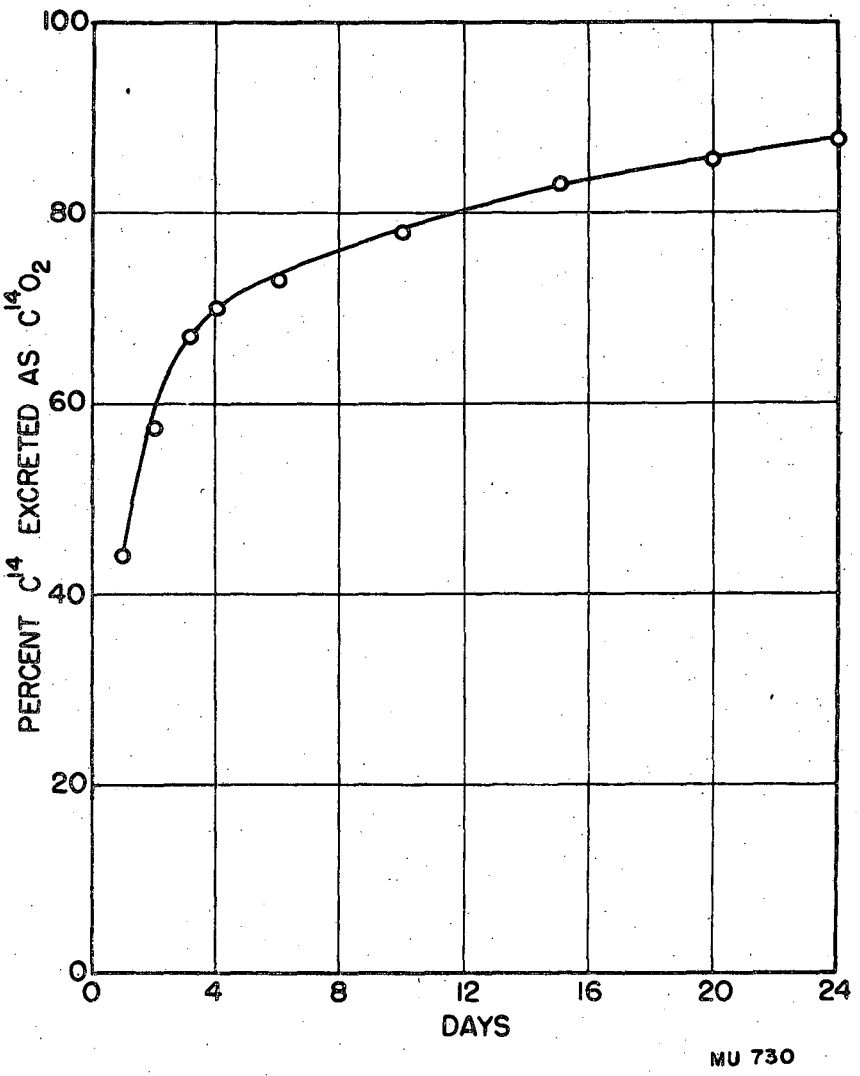


Figure 4

The cumulative C^{14} excretion as $C^{14}O_2$ in Patient I. The cumulative excretion after the 24th day is not shown, but by the 45th day it will amount to approximately 92% of the injected dose.