THE METABOLISM OF GLYCINE-2-C¹⁴ IN MAN. III. THE URINARY EXCRETION OF C¹⁴ AND CUMULATIVE RADIATION DOSIMETRY¹

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In previous communications it was reported that following the intravenous administration of 100 microcuries of carbon-14 as methylene labeled glycine (8.0 mg.) 86 per cent of the injected dose was excreted via the lungs as C¹⁴O₂ (1), and that autopsy data showed there was present a component of elimination of carbon-14 from the tissues having an average half-time of 50 days (2). The present communication is to report the urinary excretion of carbon-14 in patients given 100 microcuries of carbon-14 methylene labeled glycine and to consider the radiation dosage received by these patients.

METHODS

Five patients were given 100 microcuries of glycine-2-C¹⁴ (8.0 mg.) intravenously; these do not include the four patients whose pulmonary C¹⁴ excreted has been reported (1). The time and volume of each spontaneous urinary voiding was noted for the first 10 days; thereafter an aliquot of a spontaneous morning voiding was collected once per week. An aliquot (5 or 10 ml.) was dried *in vacuo*, then combusted to carbon dioxide with a chromic-sulfuric acid mixture (3). The carbon dioxide was converted to barium carbonate, the specific activity of which was measured in a proportional counter if greater than 10 dis/min./mg. BaCO₃; if less, the sample was reconverted to carbon dioxide and introduced into a 100 cc. ionization chamber operating at atmospheric pressure, a vibrating reed electrometer and recording potentiometer were used to measure the rate of voltage change in the ionization chamber (4, 5).

RESULTS

Figure 1 shows the specific activity of the urinary carbon-14 in patient EP and is typical of the data obtained. Table I summarizes the data for the 5 patients. Figure 2 shows the cumulative urinary carbon-14 excretion in patient EP and is calculated by integration of the data presented

in Figure 1 and Table I from the following equation:

$$N = Q \int_0^{\infty} N_{0(1)} e^{-\frac{0.693 t}{T_{1(1)}}} + N_{0(2)} e^{-\frac{0.693 t}{T_{1(2)}}} + N_{0(3)} e^{-\frac{0.693 t}{T_{1(3)}}}$$

where Q = total C¹⁴ excreted per day, as gm. BaCO₃.

N₀ = extrapolated zero time value for a given component.

T₁ = half-time for a given component.

The amount of total carbon excreted per day was calculated from the amount produced during the first 10 days.

DISCUSSION

Excretion rates

The data indicate that these patients excrete in the urine on the average 11.8 per cent of the carbon-14 administered and that the excretion may be described in terms of three rate components having average half-times of 0.26, 2.5, and 53 days. The urinary carbon-14 radioactivity was followed until it could no longer be measured satisfactorily. Almost complete excretion of carbon-14 via this route would require approximately 200 to 250 days, *i.e.*, five times the half-time of the slowest known component. It should be noted in Figure 1 that during the period from 60 to 85 days the specific activity of the urinary carbon-14 showed a definite increase, occurring at the same time that

TABLE I

The per cent of the administered dose excreted and half-time for each of the three rate processes

Patient	T ₁ (½)		T ₂ (½)		T ₃ (½)		BaCO ₃ excreted/day	Total per cent excreted
	days	%	days	%	days	%		
EP	0.10	0.9	1.4	0.9	48	5.7	90.6	7.5
LY	0.37	3.7	2.4	1.5	45	9.0	140.0	14.2
WF	0.17	8.5	1.4	3.3	44	0.6	304.7	12.4
							(diabetic)	
MM	0.45	5.5	5.0	2.7	84	3.5	82.2	11.7
ESP	0.30	5.7	2.3	1.3	43	6.4	100.9	13.4

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FIG. 1. THE SPECIFIC ACTIVITY OF THE URINARY CARBON IN PATIENT E. P. (IN DIS/MIN./MG. BaCO_3)

this patient (with chronic myelogenous leukemia) destroyed the majority of the red cells which had carbon-14 incorporated in their hemoglobin. This probably represents the excretion in the urine of some of the end products of hemoglobin catabolism. It is of interest to note that after four days the specific activity of the urinary carbon gradually becomes much greater than the breath carbon (see Fig. 3, *J. Clin. Invest.*, 1951, 30, 73). This would indicate a certain independence of the sources of the carbon in these two end-products.

FIG. 2. THE CUMULATIVE URINARY CARBON-14 EXCRETION IN PATIENT E. P.

As has been pointed out with respect to the breath excretion, the biochemical significance of each of these components is not evident. The 53-day urine component is mirrored in the 50-day tissue component both with regard to half-time and to quantity. Thus this 53-day urinary component probably represents the major route of excretion of the 50-day tissue component.

These data now make possible almost complete accountability for the injected carbon-14: 86 per cent is excreted via the lungs; 12 per cent via the urine and 2 per cent is retained for a longer period of time, but must be excreted. No appreciable amount of activity (< 1 per cent) is eliminated in the feces.

The carbon-14 in any given compound will be present largely as the result of synthesis at the time when the precursors have a high specific activity since exchange of carbon atoms in a carbon skeleton is usually not possible without extensive changes to the molecule. Only compounds that are being synthesized will contain carbon-14 and as most compounds are in a steady state there must be a corresponding catabolism and replacement of the carbon-14 by carbon-12 since in the intervening time the precursor specific activity will decrease. It is, however, possible that units such as amino acids can exchange in peptides and perhaps in more complicated proteins. Should such an exchange occur, it would continue and again the carbon-14 concentration must gradually approach natural concentration (6, 7). The autopsy data indicate that the rate of elimination of this small fraction (approximately 2 per cent of the dose) must have a half-time of several hundred days or more. Furthermore, there may be more than one of these very slow components. The route of excretion for this last 1 to 2 per cent will be difficult to determine and will probably involve special preparation of the samples and measuring instruments of great sensitivity.

Calculation of Radiation Dose

The problem of the hazard in the use of carbon-14 in clinical investigation has received considerable attention (8-12). In part the difficulties stem from fundamental lack of knowledge of the effects of ionizing radiation, a fact well recognized by the International Commission on Radiological Pro-

tection (13) (see preface to 1950 recommendations).

However, for the purpose of comparative evaluation, it is of some interest to interpret the results of our studies in terms of radiation dosage. It is acknowledged that several assumptions (detailed below) are necessary in order to make these calculations. The potential error introduced in these assumptions is also estimated.

If it is assumed that this radioactive carbon is uniformly distributed throughout the body, it is possible to make some calculations of the radia-

TABLE II
Cumulative elimination of 100 μ c. carbon-14
injected as glycine-2-C¹⁴

Time	Microcuries Carbon-14 eliminated			Mrep/day of remaining C ¹⁴
	Breath	Urine	Total	
0	0	0	0	4.36
1 hr.			4.8	4.15
2 hrs.			10.2	3.91
4 hrs.			18.7	3.54
8 hrs.			27.0	3.18
12 hrs.			32.2	2.95
1 day	40	2	42	2.53
3 days	62	6	68	1.40
5 days	70	6.5	76.5	1.03
10 days	78	8	86	0.61
20 days	80	8	88	0.52
40 days	84	9	93	0.31
60 days	86	10	96	0.175
100 days	86	11	97	0.131
200 days	86	12	98	0.087

tion dose delivered to the tissues (14). At zero time the dose rate will be:

$$\text{mrep/day} = \frac{(N) (\overline{E\beta}) (\text{erg/ev})}{(\text{erg/gm./rep}) (\text{wt. gm.})}$$

$$N = \text{No. of } \beta\text{'s/day}$$

$$\overline{E\beta} = 50,000 \text{ ev (average energy of C-14}\beta\text{s.)}$$

$$\text{wt.} = 70 \text{ Kg.}$$

$$\text{ergs/gm./rep} = \frac{83}{1,000}$$

$$\text{mrep/day/100 } \mu\text{c. C-14} = 4.36$$

In a similar manner, the dose rate at various times may be calculated from the retention of carbon-14. These data are given in Table II and Figure 3. In this figure the "normal" radiation dose is indicated by a horizontal line and is about one-third due to potassium-40 and rubidium-87 (15), one-third to cosmic radiation (16), and one-third from the earth's surface (17). Following

FIG. 3. THE DAILY RADIATION DOSAGE RATE DUE TO CARBON-14

The radiation dosage rate from the naturally occurring radioactive isotopes and cosmic radiation is indicated as being 0.3 mrep/day.

the administration of 100 microcuries of carbon-14 the mean radiation dose falls by 40 days to 0.3 mrep/day which is an average "normal" dosage rate.

The data listed in Table II were integrated graphically and the cumulative radiation dose determined (see Table III). It must be remembered that these calculations have been made on the assumption of uniform distribution of radioactivity. This is not the true situation and in recommending doses for the use of glycine-2-C¹⁴ in patients some factor must be included for this nonuniform distribution. This lack of uniformity may be greatest during the first few days following the injection of the carbon-14. However, in

TABLE III
Cumulative carbon-14 radiation dosage for a 70-Kg. man
given 100 microcuries glycine-2-C¹⁴ assuming
uniform distribution

Time interval	Dose, mrep
0-1 day	3.18
0-7 days	11.0
0-3 months (13 weeks)	36.9
0-6 months (26 weeks)	45.2

Table III it is seen that the cumulative dose during this period is only about 10 to 20 per cent of the first quarter's total figure, so it is not as critical as inhomogeneities occurring after the first four to five days. The autopsy data (2) and mice data (9) indicate that upper maximum variation from the average tissue activity in this later period is not more than a factor of 2 to 3 so that a factor of 5 (10) for inhomogeneity would probably be a reasonable value. Certainly, at present, the use of 100 μ curies of C^{14} as glycine-2- C^{14} has been sufficient to carry out these studies and yet not exceed the dose permitted by the Atomic Energy Commission for use in patients, with incurable disease and with life expectancy of two years or less.

SUMMARY

1. The urinary excretion of carbon-14 following the intravenous administration of 100 microcuries of carbon-14 as glycine-2- C^{14} may be described in terms of three rate components having half-times of $\frac{1}{4}$, $2\frac{1}{2}$, and 53 days and amounts to 11.8 per cent of the dose. The 53-day component probably represents the route of excretion of the 50-day tissue component.

2. Complete accountability for the injected carbon-14 is now possible permitting calculation of the dosage rate. For 100 microcuries of glycine-2- C^{14} given to a 70 Kg. man the cumulative radiation doses are: 0 to 1 days, 3.08 mrep; 0 to 7 days, 11.0 mrep; 0 to 3 months, 36.9 mrep.

3. The average internal radiation level from the carbon-14 falls to natural radiation levels in 40 days.

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