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ESTIMATION OF RADIATION DOSAGE AND TRANSMUTATION EFFECT OF ^{14}C INVOLVED IN MEASURING RATE OF ALBUMIN SYNTHESIS WITH ^{14}C-CARBONATE

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For direct measurement of the rate of albumin synthesis $Na_2{}^{14}CO_3$ was used intravenously. The assessment of the radiation hazard involved in the study was based on the knowledge of the minimum dose of $Na_2{}^{14}CO_3$ necessary for a sufficient incorporation of ^{14}C in the guanidine-C of arginine in albumin to obtain measurable radioactivity. By measurement of expired $^{14}CO_2$ and excreted ^{14}C-urea in the urine during a 5-hr period following intravenous administration of $Na_2{}^{14}CO_3$ in five subjects, some quantitative data on ^{14}C retention and radiation dosage were obtained. In comparison with animal studies, the rate of expiration of $^{14}CO_2$ in man is slower. About 50% of the total radioactivity injected was lost through the respiratory route in the first hour. The total amount of expired ^{14}C during the 5 hr of investigation was about 75% of the injected dose for the five subjects. The amount of ^{14}C excreted as urinary ^{14}C-urea during the 5 hr of investigation is very small in comparison with the expired ^{14}C; it was only about 0.5% of the dose injected. The total absorbed radiation dose after complete elimination of ^{14}C from the body was calculated with various assumptions. The extra risk of genetic damage due to disintegration of retained ^{14}C in comparison with that of natural ^{14}C in the body during 30 living years is about 50%.

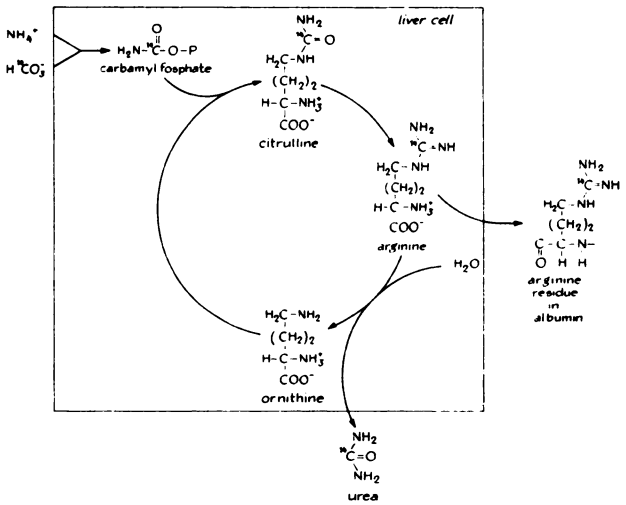

FIG. 1. Emergence of ^{14}C from $H^{14}CO_3^-$ into both urea and guanidine group of arginine in albumin.

The incorporation of ^{14}C after injection of $Na_2{}^{14}CO_3$ into organic and inorganic compounds has been well established (*1–4*). In 1946 Delluva and Wilson (*5*) observed that intravenous injection of $Na_2{}^{14}CO_3$ leads to a labeling of guanidine-C of arginine in proteins produced in the liver cell. Using the precursor–product relationship, McFarlane (*6*) introduced in 1963 a method for the direct measurement of the rate of albumin synthesis after intravenous injection of ^{14}C-carbonate. The ^{14}C-arginine produced in the liver cell from ^{14}C-carbonate is the common precursor for ^{14}C-urea and ^{14}C-guanidine of arginine in albumin. Figure 1 shows the emergence

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of ^{14}C from $H^{14}CO_3^-$ into both urea and the guanidine group of arginine in albumin. Under well-defined conditions the specific activity of all products of a single labeled precursor pool must be equal to that of the precursor. The amount of albumin synthesized in time interval ($t_1 - t_0$) is then given by the following expression: total radioactivity incorporated into albumin ÷ total radioactivity incorporated into urea × amount urea synthesized in time ($t_1 - t_0$). The activity of albumin is expressed as the activity of guanidine-C of arginine in albumin.

After the introduction of this method by McFarlane, measurements of the rate of albumin synthesis using ^{14}C-carbonate in patients with liver diseases or gastrointestinal disorders were published (*7–13*). Although this direct method of measurement has obvious advantages in comparison with the indirect method using ^{131}I-albumin, a potential drawback is the radiation dose and the transmutation effect because of the fact that ^{14}C has a half-life of about 5,750 years and because of the passage of ^{14}C into both organic and inorganic compounds. In spite of the relatively low energy, the beta particles of ^{14}C emit radiation that can affect living cells and additionally, transmute by decay to nitrogen which has different chemical characteristics. If the hazard accompanying the use of this isotope is to be properly assessed, more information about the degree and duration of tissue exposure following intake of ^{14}C compounds is required. The degree of tissue exposure by ^{14}C is dependent on the concentration of the isotope and this is dependent, in turn, on the biologic half-life.

Assessing the radiation hazard involved in the study of measurement of albumin synthesis in man is based on knowledge of the minimum dose of $Na_2{}^{14}CO_3$ necessary for a sufficient incorporation of ^{14}C in the guanidine-C of arginine in albumin to obtain measurable radioactivity, i.e., a counting rate equal to a factor of 2 or 3 of the radioactivity of the background. The minimum dose is 100 μCi for normal subjects and patients with only moderate hypoalbuminemia and 200 μCi for patients with cirrhotic liver and profound hypoalbuminemia as suggested by Tavill, et al (*13*).

From data provided by McFarlane and from a review of animal studies Tavill, et al (*13*) concluded that in man the major part of the administered dose of $Na_2{}^{14}CO_3$ is excreted within 24 hr and probably less than 2% of the dose is permanently retained within the body. Until now, as far as we know, no studies have been performed in man on the amount of ^{14}C retention calculated by measurement of expired $^{14}CO_2$ and urinary ^{14}C urea following intravenous administration of $Na_2{}^{14}CO_3$.

TABLE 1. INTRAVENOUSLY ADMINISTERED DOSE OF $Na_2{}^{14}CO_3$ TO FIVE SUBJECTS STUDIED

No.	Sex	Age (yrs)	Weight (kg)	Length (m)	Administered dose (pCi)
1	M	51	61.3	1.67	12.8×10^7
2	F	56	70.5	1.67	15.5×10^7
3	M	49	78.8	1.84	17.5×10^7
4	M	54	82.5	1.74	17.9×10^7
5	M	53	68.4	1.81	14.0×10^7

This paper describes some of the experiments used to obtain quantitative data on the ^{14}C retention and the radiation dosage that patients receive from ^{14}C-carbonate involved in the measurement of the rate of albumin synthesis.

MATERIALS AND METHODS

Albumin synthesis was measured in five subjects; three were treated conservatively for a peptic ulcer, one suffered from liver cirrhosis, and one had upper abdominal complaints due to aortic aneurysm. They had all normal renal function tests. Some data concerning the five subjects and the administered dose of $Na_2{}^{14}CO_3$ are given in Table 1.

To prevent pollution of the equipment such as Douglas bag, spirometer, and Scholander analyzer with ^{14}C, the investigation was carried out on two consecutive days. On the first day a study was performed on the average amount of CO_2 expired per minute while on the second day immediately after the injection of the dose, the specific activity of expired CO_2 was investigated. Both studies were conducted over a 5-hr experimental period. The expired air of the sitting subject was collected nine to ten times at regular intervals in Douglas bags over the 5 hr of investigation. Each collection period had a mean duration of 11.2 min (range, 9.2–15.7 min). The bag content was analyzed for volume (in a 300-liter spirometer) and for percentage of CO_2 and O_2 (with the micro-Scholander technique). Details of the method are given by Consolazio, et al (*14*). The amount of expired CO_2 per unit of time was corrected in BTPS (i.e., body temperature 37°C, day's barometric pressure, and 100% saturation). As the mean values for expired CO_2 per minute measured on the first day were used on the second day to calculate the radioactivity expired per minute, the conditions of the subjects (diet, physical activity) and of the room (temperature, moisture) were kept constant as far as possible on both days.

On the second day subjects received an average of 155 μCi (range, 128–179 μCi) $Na_2{}^{14}CO_3$ intravenously and starting immediately after the injection the specific activity of expired CO_2 (radioactivity/

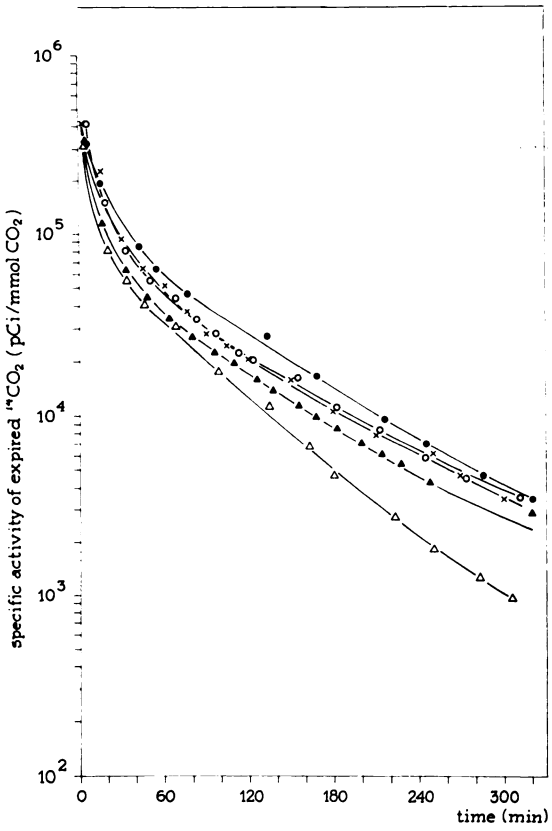

FIG. 2. Decrease of specific activity of expired $^{14}CO_2$ for five subjects after intravenous injection of ^{14}C-carbonate. Symbols on curves represent different subjects studied.

mmole CO_2) was measured regularly. The air breathed out by the five subjects was blown through a drying tube with $CaSO_4$ into a counting vessel containing 2 ml hyamine (0.25 *M*) and 2 ml ethanol with thymolphtalein (0.12 mg) as indicator. Quiet breathing during a period of 3–4 min was sufficient to turn the fluid in the vessel from blue to colorless. This indicates that a complete neutralization of the hyamine occurred and that about 0.4 mmole CO_2 had been absorbed in the fluid. The exact concentration of hyamine was determined by titration with 0.1 *M* HCl. The radioactivity was counted after adding 9.5 ml toluene scintillator in a liquid scintillation counter (Searle Radiographics). The radioactivity expired per minute at time t (radioactivity/min) was obtained by multiplying the average expired CO_2 per minute (mmole CO_2/min) with the specific activity of the expired CO_2 (radioactivity/mmole CO_2) at time t after intravenous administration of $Na_2{}^{14}CO_3$.

The ^{14}C-urea excretion was measured by collection of urine at 2-hr intervals over an 8-hr period after administration of $Na_2{}^{14}CO_3$. The determination of ^{14}C-urea radioactivity in urine was carried out as described previously (*15*).

Toluene scintillator was prepared by adding 5 gm PPO (2,5 diphenyloxazole) and 0.5 gm POPOP (2,2-p-phenylene bis (5-phenyloxazole)) to 1,000 ml toluene. The $Na_2{}^{14}CO_3$ was obtained from the Radiochemical Centre, Amersham, England.

RESULTS

During the 5-hr investigation, the specific activity of expired CO_2 was measured regularly. The results were plotted against time as shown in Fig. 2. After a rapid rise of the specific activity of the expired CO_2 in the first minutes after injection of ^{14}C-carbonate, a gradual decrease took place. If the amount of expired $^{14}CO_2$ per minute is expressed as the percentage of the administered dose of ^{14}C, the curve of the mean values obtained for the five subjects could be described by the function (Fig. 3):

$$y = 2.4607\, e^{-0.0951t} + 0.6142\, e^{-0.0123t}$$

The two components of this curve have half-time values of 7 and 56 min, respectively.

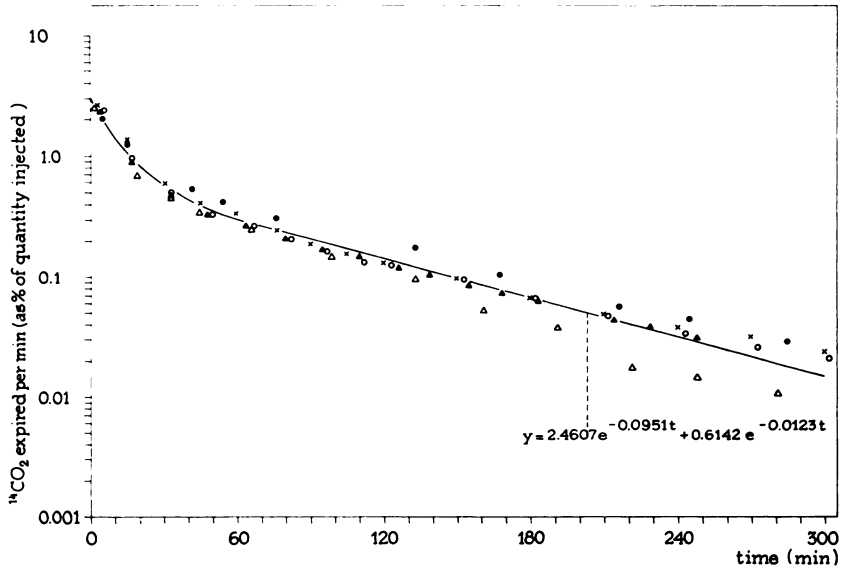

FIG. 3. Amount of $^{14}CO_2$ expired per minute as percentage of dose injected. Average value of five subjects is plotted. Symbols represent same subjects as in Fig. 2.

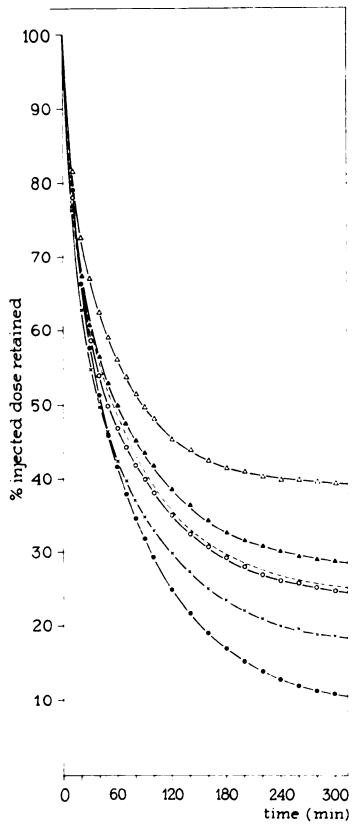

FIG. 4. Retention of ^{14}C as percentage of injected dose for five subjects during first 5 hr after intravenous injection of ^{14}C-carbonate. Symbols represent same subjects as in Fig. 2. Average value of five subjects is represented by dotted line.

Figure 4 shows the retention of ^{14}C as percentage of the injected dose. About 50% of the total radioactivity injected was lost through the respiratory route in the first hour. The total amount of expired ^{14}C during the 5 hr of investigation was about 75% of the injected dose for the five subjects.

The radioactivity of urea in urine collected at 2-hr intervals is demonstrated in Fig. 5. The total amount of ^{14}C excreted as urinary ^{14}C-urea during the 8 hr of investigation is very small in comparison with the expired ^{14}C. It is only 0.6% of the dose injected.

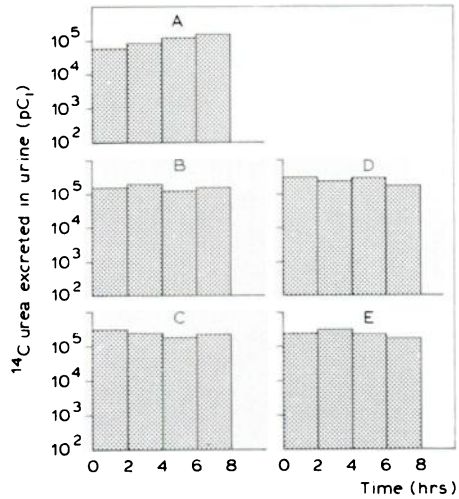

FIG. 5. Excreted ^{14}C-urea in urine collected at 2-hr intervals after intravenous injection of ^{14}C-carbonate.

ESTIMATION OF THE RADIATION DOSAGE

From the findings of this study and with the assumption that all ^{14}C retained after 5 hr is incorporated in the tissues, it is possible to calculate the radiation dose after an intravenous injection of 100–200 μCi $Na_2{}^{14}CO_3$. It is also possible to compare the risk of genetic damage due to transmutation of retained ^{14}C to nitrogen with that of natural ^{14}C. The calculations listed below have been made on the following basis:

1. The amount of $^{14}CO_2$ expired per minute during the 5 hr of investigation after intravenous injection of $Na_2{}^{14}CO_3$ and expressed as percentage of the dose injected is described by the function $Y = 2.4607\ e^{-0.0951t} + 0.6142\ e^{-0.0123t}$.
2. The dose of ^{14}C retained in the body at any time t during the first 5 hr of investigation can be expressed as: $R(t) = 100 \int_0^t Y(x)\,dx$ (in percent of the administered dose).
3. It is assumed that the dose of ^{14}C retained during the first 5 hr is uniformly distributed throughout the blood and the lung.
4. The retention of ^{14}C after 5 hr is expressed as: R(300 min) = 100% — E(300 min) — U(300 min); E(300 min) : total amount of ^{14}C expired at CO_2 during the first 5 hr in percentage of injected dose (about 75%); and U(300 min) : total amount of ^{14}C excreted as urinary urea during the first 5 hr, in percentage of administered dose (about 0.6%).
5. The dose of ^{14}C retained after 5 hr is distributed according to fraction in organ of reference of that in total body (f_2) as given by Committee II of the International Commission on Radiological Protection (ICRP) in 1959 (*16*). For fat tissue this distribution fraction is 0.6, for bone 0.1, and for the remaining part of the body 0.3. The ^{14}C-labeled compounds disappear from the tissues according to half-life values as given by ICRP. The $T_{1/2}$ for fat tissue is 12 days, for bone 40 days, and for the remaining part of the body 10 days.

The results of the calculation of the total absorbed radiation dose after complete elimination of ^{14}C from the body are: fat tissue, 111 mrems; bone, 453 mrems; lung, 15 mrems; and gonads, 9 mrems (as given in Table 2).

TABLE 2. SOME DATA USED FOR THE CALCULATION AND RESULTS OF THE TOTAL ABSORBED RADIATION DOSE

	Fat	Bone	Remaining part of the body
f_2 (fraction in organ of reference of that in total body)	0.6	0.1	0.3
$T_{1/2}$ (days)	12	40	10
$E_{eff.}$ (MeV)	0.054	0.27	0.054
Mass (gm)	10.000	7.000	53.000
Ac (μCi) ($f_2 \times 40\ \mu$Ci)	$0.6 \times 40 = 24$	$0.1 \times 40 = 4$	$0.3 \times 40 = 12$
$\dot{D}_0$ (rads/day)	66.25×10^{-4}	7.887×10^{-3}	0.625×10^{-3}
D^{∞} (mrems)	111	453	9*
maximum permissible dose for individuals (ICRP II, 1959) (mrems/year)	1,500	3,000	500

* For gonads the total radiation dosage is 9 mrems (the remaining part of the body). For lung and blood, this value (9 mrems) should be added to the radiation dosage of the first 5 hr of investigation, that is:

$$R(t) = 100 - \int_0^t Y(x)\,dx$$

$$R(t) = 24.23 + 25.87\,e^{-0.0951t} + 49.9\,e^{-0.0123t}$$

$$\dot{D}_0 = \frac{2.13 \times 0.054 \times 160}{6{,}400} \times 24 \text{ rads/day (mass of lung: 1,000 gm; mass of blood: 5,400 gm)}$$

$$= 4.8 \times 10^{-5} \text{ rads/min}$$

$$D_{300\ min} = \dot{D}_0 \times \frac{1}{100} \times \int_0^{300} R(t)\,dt$$

$$= 4.8 \times 10^{-5} \times \frac{1}{100} \times \int_0^{300} R(t)\,dt$$

$$= 5.57 \text{ mrems.}$$

It is known that in the "standard man" (70 kg), the amount of ^{14}C acquired from natural sources is about 0.1 μCi (*17*). Assuming that at the moment of administering $Na_2{}^{14}CO_3$, the distribution of C-atoms between DNA molecules and non-DNA molecules is similar to this distribution of C-atoms during the reproductive period of 30 years, the extra risk of genetic damage due to disintegration of retained ^{14}C in comparison with that of natural ^{14}C is about 50% (see Appendix 2).

DISCUSSION

In comparison with animal studies, the rate of expiration of $^{14}CO_2$ in man as described in the present paper is slower. Skipper, et al (*18–20*) found in mice a recovery in the expired air of 96% of intraperitoneal administered $NaH^{14}CO_3$ within 24 hr, 50% having been expired within the first 10 min and 92.8% in the first hour. Experiments in rats (*21*) are very similar to those in mice, values of 93–98% being recovered. The rate of $^{14}CO_2$ expiration is slightly slower; 50% of the injected dose of ^{14}C was found in the first 18 min. Kornberg, et al (*22*) demonstrated that in cats 50% of an intravenous administered dose of $NaH^{14}CO_3$ was expired in the first 30 min. The total amount of ^{14}C expired in the 5-hr investigation period was 79–81%.

The biologic hazard of ^{14}C has been discussed by many authors (*17,23–25*). Although, in general, the hazards are negligible when viewed on a short-term basis or in a restricted sample of individuals as concluded by Purdom (*25*), the somatic effects of ^{14}C as leukemia, bone cancer, and diseases caused by radiation in other tissues are possible (*17*). However ^{14}C is known as the least carcinogenic radioisotope (*26*). It is believed that the relatively small hazard in spite of its long half-life is due to its rapid elimination from the tissues and relatively small retention in the bones (*26*). The greatest potential hazard is possibly the transmutation of the ^{14}C atom in DNA molecule to nitrogen. However Purdom (*25*) mentioned that there was no experimental evidence that transmutation of a ^{14}C atom in DNA produces gene mutations (*25*). It has been found that ^{14}C incorporated into snapdragon plants produces an increase in the frequency of color mutant spots in flower petals but the relative importance of transmutation and beta-irradiation could not be determined. From these considerations, therefore, it is difficult to assess critically the biologic hazard of ^{14}C involved in our experiments. To give some impression of the risk in using this isotope to measure the rate of albumin synthesis, it may be useful to compare the risk of radiation dosage and genetic damage due to transmutation of retained ^{14}C to nitrogen with the risk of natural radioactivity. In this context it is of interest that the radiation dosage of natural

^{14}C is only about 1% of the total natural radioactivity (*17*).

From the data given by Libby (*27*) the total radiation dosages from the natural radioactivities and cosmic rays is approximately 150 mrads/year. The variations in natural dosage are very large and under certain conditions the natural dosage may be nearly 100 times higher than the minimum value—the dosage at sea level. Compared with these data, the total absorbed radiation dosage resulting from the experiment previously described is much less than that of the natural background (9 as opposed to 150 mrads) and for bone it is only 15% of the maximal permissible radiation dosage per year as given by ICRP (see Appendix 1). If assumptions as already described in our estimation of radiation dosage are valid, the extra risk of genetic damage due to disintegration of retained ^{14}C resulting from our experiment is about 50% in comparison with that of natural ^{14}C during 30 living years.

Totter, et al (*23*) concluded that the transmutation effect of ^{14}C can lead to about the same number of genetic mutations as the radiation effect. With this calculation, the genetic damage estimated for the ^{14}C radiation dose has to be multiplied by a factor of 2 to take into account the transmutation effect. On this assumption, the radiation and transmutation effect received by the gonads (2 × 9 mrads) arising from our experiment is approximately 12% of the total natural radioactivities per year (150 mrads/year) or about 4% of the maximal permissible dose per year (500 mrads/year) as given by ICRP. The radiation dosage and the transmutation effect of ^{14}C involved in the measurement of the rate of albumin synthesis (18 mrads/150 μCi/gonad dose) is not greater than in other studies using radioisotopes such as ^{131}I-albumin employed in the estimation of degradation rate of albumin (100 mrads/100 μCi–gonad dose) and ^{58}Co-cyanocobalamin used in the study of vitamin B_{12} absorption (40 mrads/0.5 μCi–gonad dose) (*28*).

The relatively nonhazardous nature of ^{14}C is attested to by the fact that the administration of readily metabolized ^{14}C compound in tracer doses up to 0.5–1.0 mCi to adult subjects is not considered to be unethical or to violate accepted standards of maximum permissible dose (*29,30*). It can therefore be concluded that the administration of 150 μCi ^{14}C-sodium carbonate for the estimation of albumin synthesis is an acceptable procedure which gives less radiation hazard than, e.g., ^{131}I-albumin studies for the estimation of albumin degradation. This does not mean that an uncontrolled administration of ^{14}C-carbonate is acceptable. Caution in every administration of radioisotopes remains required.

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APPENDIX 1. CACULATION OF THE TOTAL ABSORBED RADIATION DOSE AFTER ELIMINATION OF ^{14}C FROM THE BODY

For the calculation of the radiation dose, the following formulas are used:

$$D^{\infty} = 1.44 \times \dot{D}_0 \times T_{1/2} \text{ rad.}$$

$$\dot{D}_0 = \frac{2.13 \times E_{.eff.} \times Ac}{m} \times 24 \text{ rads/day (28).}$$

m = mass of organ (in gm).

$E_{.eff.}$ = effective energy of the beta particles of ^{14}C in MeV

→ (for bone this energy has to be multiplied by 5).

Ac = amount of ^{14}C (in μCi) present in organ at t_0.

$T_{1/2}$ = effective half-life (in days) (for ^{14}C effective half-life is equal to biologic half-life).

D^{∞} = the total absorbed radiation dose after complete elimination of ^{14}C from the body.

$\dot{D}_0$ = radiation dose rate at time zero.

The retention of ^{14}C after 300 minutes is 25% of the injected dose. The average amount of ^{14}C present in total body after 300 min is then 25% of the 160 μCi or 40 μCi.

The total radiation dosage for lungs and blood, therefore, is approximately 15 mrems (9 + 5.75 mrems).

APPENDIX 2. CARBON-14 ACQUIRED FROM NATURAL SOURCES DURING 30 LIVING YEARS = 30 × 0.1 μCi

$$\dot{D}_0 = \frac{2.13\ E_{.eff.} \times 0.1 \times 24}{m} \text{ rads/day.}$$

$$D_{30 \text{ years}} = \dot{D}_0 \times 365 \times 30 \text{ rads.}$$

^{14}C retained, 300 minutes after intravenous injection of $Na_2{}^{14}CO_3$ = 40 μCi.

$$\dot{D}_0 = \frac{2.13 \times E_{.eff.} \times 40 \times 24}{m} \text{ rads/day.}$$

$$\dot{D}_s = 1.44 \times T_{1/2} \times \dot{D}_0$$

$$= \frac{1.44 \times 10 \times 2.13 \times E_{.eff.} \times 40 \times 24}{m} \text{ rads.}$$

Extra risk of genetic damage due to retained ^{14}C is then:

$$\frac{D_s \text{ retained } ^{14}C}{D_{30\text{ years}} \text{ } ^{14}C \text{ from natural sources}} \times 100\%$$

$$= \frac{1.44 \times 10 \times 2.13 \times E_{.eff.} \times 40 \times 24 \times \frac{1}{m}}{365 \times 30 \times 2.13 \times E_{.eff.} \times 0.1 \times 24 \times \frac{1}{m}}$$

$$\times 100\% = \pm 50\%.$$

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