

INTRA-LABORATORY CORRESPONDENCE
OAK RIDGE NATIONAL LABORATORY

SEP 16 1964

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September 15, 1964

To : Those Listed Below
From : W. S. Snyder
Subject: Internal Dose Estimation Seminar

Topic - Dose to Various Body Tissues from HTO

Speaker - W. S. Snyder

Date - Thursday, September 17, 1964

Time - 10:00 a.m.

Place - Classroom, R-207

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Human Studies Project

ESTIMATION OF INTERNAL DOSE

1. URINARY EXCRETION OF TRITIUM FOLLOWING EXPOSURE OF MAN TO HTO -- A TWO-EXPONENTIAL MODEL

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The metabolic course of HTO in the body may be considered to be relatively well understood. Numerous animal experiments supplemented by experiments on humans suggest that HTO introduced into the body becomes a part of the general pool of body fluids and is eliminated from the body via the urine, perspiration, breath, and other avenues of elimination of water from the body. The experimental data prior to 1957 is summarized in the comprehensive review of the problem by Pinson and Langham.¹ In addition, there is a wealth of experience gained in working with tritium which has revealed other factors which influence the metabolism of HTO, in particular, age and seasonal variations.

Nevertheless, there are some data to suggest that the metabolic model which assumes HTO to enter and be nonpreferentially eliminated from the general pool of body water is not entirely accurate. Thompson² has exposed mice and rats to HTO and observed that retention in a variety of tissues could be represented by a sum of two exponentials which were distinct from the single exponential representing the retention in body water. In addition to experimental work on mice which gave a multi-exponential retention, Pinson and Langham report an

¹E. A. Pinson and W. H. Langham, J. Appl. Physiol. 10, 108-26 (1957).

1148346 ²Roy C. Thompson, J. Biol. Chem. 197, 81-87 (1952); op. cit. 200, 731-43 (1953).

experiment in which one human subject was exposed to tritium over a period of eight months, and dried biopsy specimens of skin and fat taken 51 days after the end of the exposure showed a higher concentration of tritium than did urine at the time of the biopsy. Thus, there is the implication that in man, as in experimental animals, some fraction of the HTO entering the body is not eliminated at the rate characteristic of the elimination of water from the body and that this fraction may be more closely incorporated in certain tissues of the body. Subsequent to an accidental inhalation of HTO by an experimenter at this Laboratory, we have been able to measure the concentration of tritium in various body fluids and, in particular, have found that concentration in urine does follow a pattern described as a sum of two exponentials during ¹⁵⁵250 days following an intake.

The exposure occurred about the middle of the day shift on October 28, 1963. The individual was working with a source of HTO when a hood failure caused a release of the material to the room. An air monitor signaled the release, and the area health physicist quickly verified the presence of tritium on surfaces of the laboratory. The subject receiving the principal intake is a senior scientist, a male of age 41 years, weight 66.5 kg, height 161 cm, and apparently enjoying good health. He was aware of the general nature of the problem posed by HTO in the body, and we are indebted to him for his cooperation which made this extended study possible. After the first samples were evaluated, it was agreed that he would not attempt any drastic increase in his normal fluid intake, although he was encouraged to drink liberally.

During the first 11 days, samples of urine, blood serum, and sputum were obtained and analyzed for tritium.

No significant difference in the levels found in these various body fluids was noted, and this is in line with measurements reported by Pinson and Langham.¹ Also, the data appeared to follow a single exponential as expected but indicated a half-time for elimination of something under 9 days. The data for the first 13 days are shown in Fig. 1. An early evaluation of the dose to be expected was made which indicated no apparent need for measures to hasten elimination. After discussion with the subject, it was agreed that he would not attempt to deliberately alter his normal habits for the purpose of hastening the elimination of the tritium.

At time of writing, urine specimens have been collected periodically and analyzed during ~~about~~²⁵⁰ 250 days postexposure by liquid scintillation counting. All counting times were for 30 minutes. All the urine data are shown in Fig. 2, and all the postexposure data are given in Table 1. During these ~~250~~²⁵³ 250 days the subject has not been working directly with tritium. However, prior to this incident, he had shown urine concentrations in excess of the later values reported here. For example, the last sample taken before the incident was on October 25, just three days before the incident, and a concentration of 6.1×10^4 d/min/ml was measured. It is possible that this earlier exposure may have some influence on the data.

#

Fig 1

TRITIUM CONCENTRATION IN BODY FLUIDS

ORNL CASE HWM-9733

H^3 Concentration in Body Fluids (dps. per minute / liter)

- URINE (0-24 HOUR SAMPLES)
- ▽ BLOOD
- X SALIVA

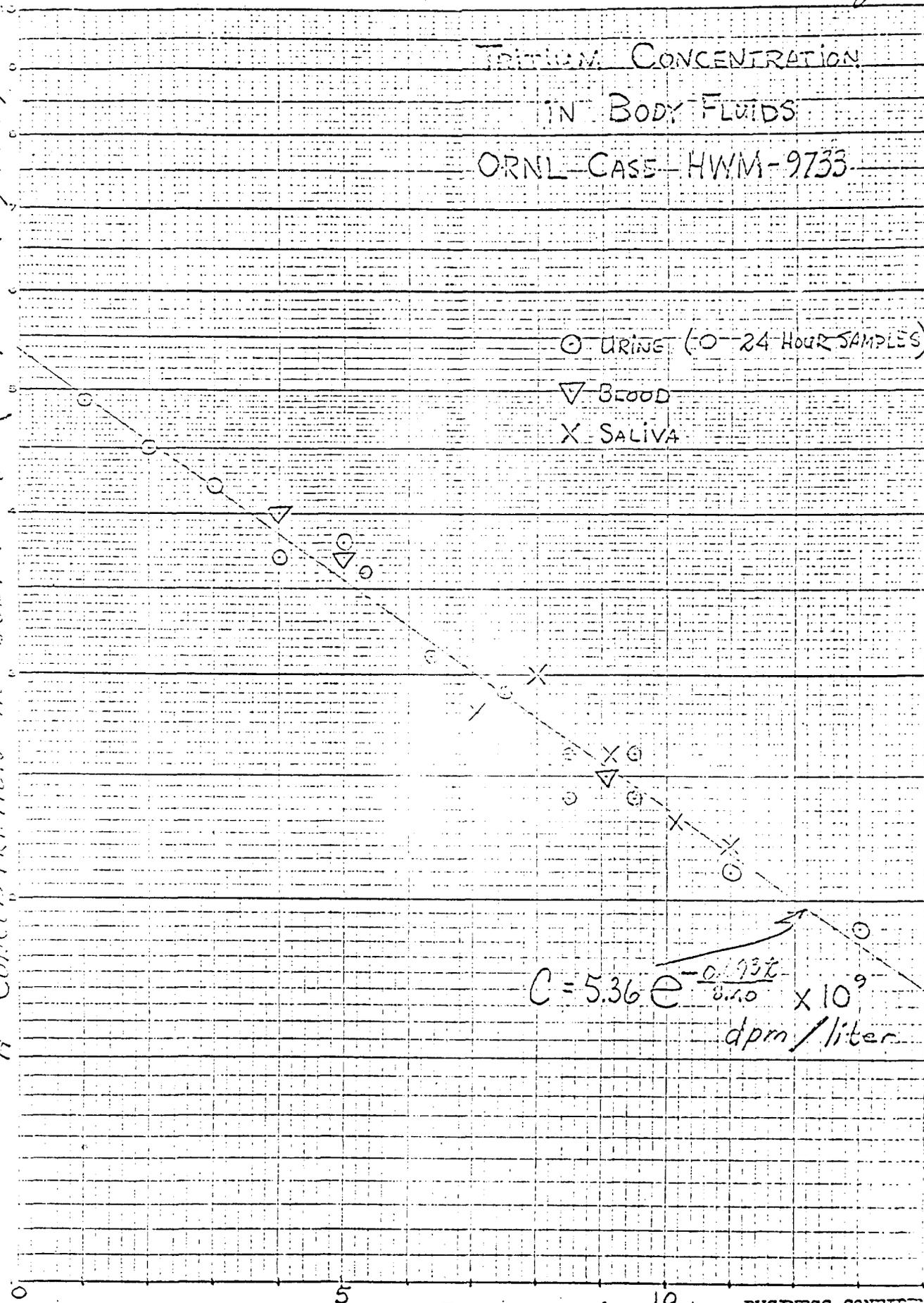
$$C = 5.36 e^{-\frac{0.138}{8.50} \times 10^9} \text{ dpm/liter}$$

TIME SINCE EXPOSURE (D^{-10})

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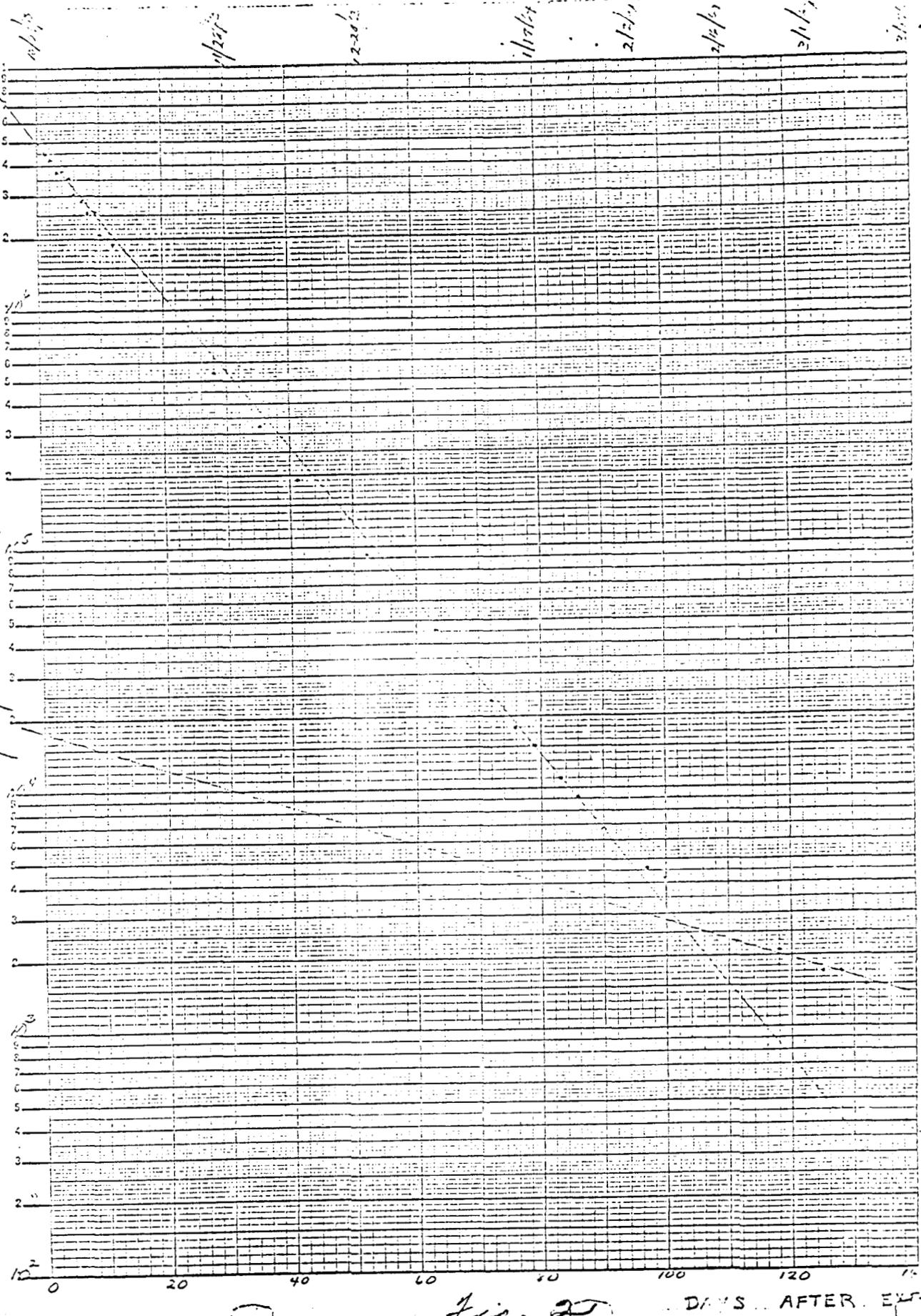


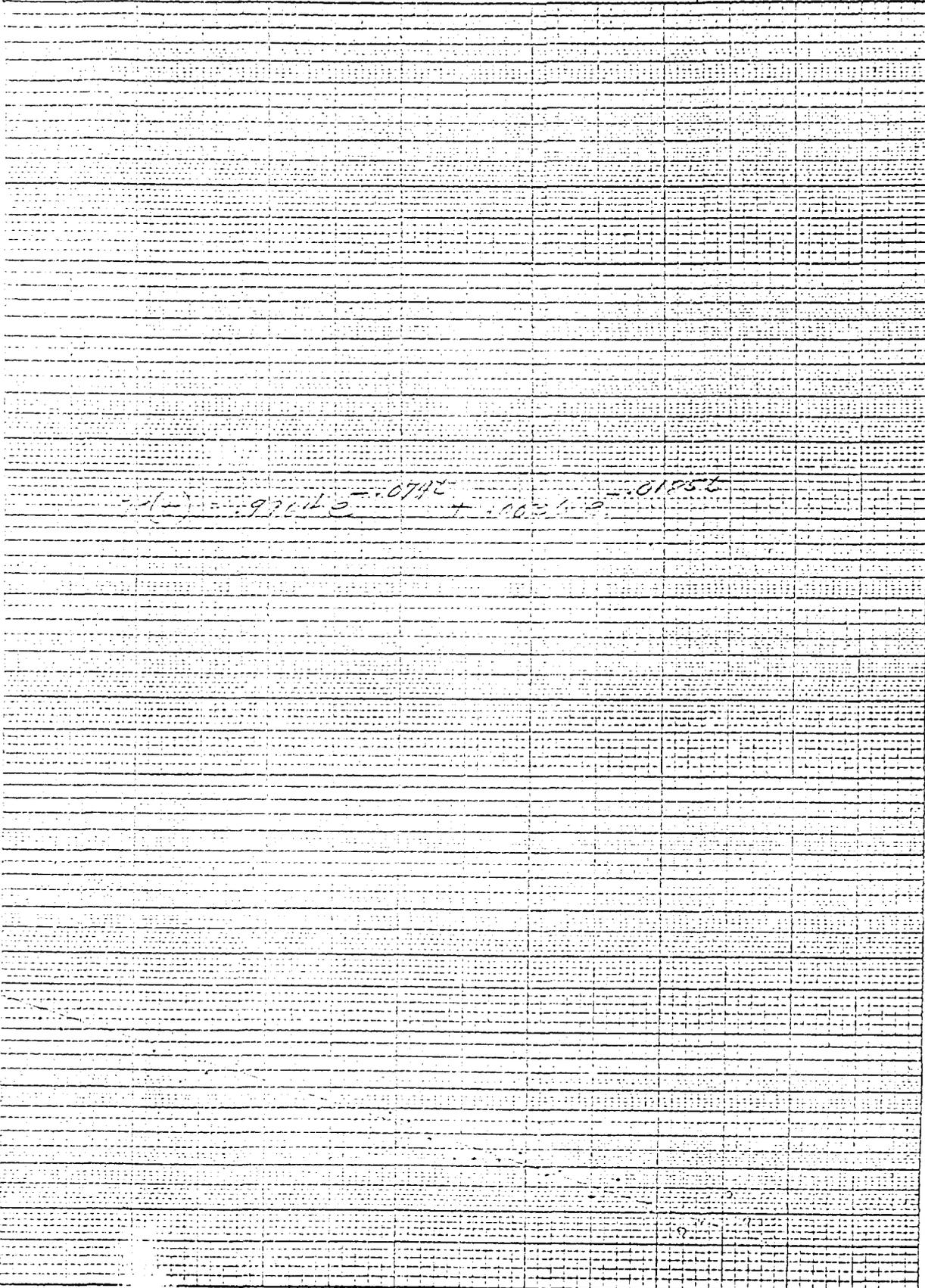
Fig. 25

DAYS AFTER EXP

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1/1 4/1 4/10 4/15 4/20 4/25 4/30 4/35 4/40 4/45



Handwritten text: $240 - 210 = 30$ and $210 - 180 = 30$

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Table 1. Concentration of Tritium in Body Fluids

Time After Exposure (days)	Concentration (dis/min/ml) *		
	Urine	Blood Serum	Sputum
1	$4.9 \times 10^6 \pm 5.1 \times 10^3$		
2	$4.5 \times 10^6 \pm 5.1 \times 10^3$		
3	$4.2 \times 10^6 \pm 3.5 \times 10^3$		
4	$3.7 \times 10^6 \pm 4.6 \times 10^3$	$4.0 \times 10^6 \pm 3.4 \times 10^3$	$3.3 \times 10^6 \pm 4.4 \times 10^3$
5	$3.8 \times 10^6 \pm 3.4 \times 10^3$	$3.7 \times 10^6 \pm 3.3 \times 10^3$	
6**	$3.6 \times 10^6 \pm 3.3 \times 10^3$		
7**	$3.1 \times 10^6 \pm 3.0 \times 10^3$		$2.8 \times 10^6 \pm 2.9 \times 10^3$
8**	$2.9 \times 10^6 \pm 2.9 \times 10^3$		$3.0 \times 10^6 \pm 3.1 \times 10^3$
9**	$2.6 \times 10^6 \pm 2.8 \times 10^3$	$2.5 \times 10^6 \pm 1.5 \times 10^3$	$2.6 \times 10^6 \pm 8.8 \times 10^2$
9	$2.4 \times 10^6 \pm 2.7 \times 10^3$		
10**	$2.6 \times 10^6 \pm 2.8 \times 10^3$		$2.3 \times 10^6 \pm 3.8 \times 10^3$
10	$2.4 \times 10^6 \pm 3.9 \times 10^3$		
11	$2.1 \times 10^6 \pm 3.6 \times 10^3$		$2.2 \times 10^6 \pm 3.9 \times 10^3$
13	$1.9 \times 10^6 \pm 3.4 \times 10^3$		
18	$1.0 \times 10^6 \pm 2.0 \times 10^3$		
24	$7.9 \times 10^5 \pm 1.8 \times 10^3$		
29	$5.4 \times 10^5 \pm 1.0 \times 10^3$		
36	$3.2 \times 10^5 \pm 7.8 \times 10^2$		
42	$1.9 \times 10^5 \pm 6.2 \times 10^2$		
53	$9.4 \times 10^4 \pm 3.8 \times 10^2$		
64	$4.6 \times 10^4 \pm 2.8 \times 10^2$		
70	$3.0 \times 10^4 \pm 2.2 \times 10^2$		
73	$2.3 \times 10^4 \pm 2.0 \times 10^2$		
77	$1.8 \times 10^4 \pm 1.8 \times 10^2$		
80	$1.5 \times 10^4 \pm 1.7 \times 10^2$		
84	$1.1 \times 10^4 \pm 1.5 \times 10^2$		

* mean disintegration rate \pm one standard deviation

** 24-hour samples; all others are spot samples

Table 1. Concentration of Tritium in Body Fluids (cont'd)

Time After Exposure (days)	Concentration (dis/min/ml)*		
	Urine	Blood Serum	Sputum
87	$9.2 \times 10^3 \pm 1.7 \times 10^2$		
91	$6.7 \times 10^3 \pm 1.3 \times 10^2$		
98	$4.6 \times 10^3 \pm 1.3 \times 10^2$		
101	$4.2 \times 10^3 \pm 92$		
105	$3.5 \times 10^3 \pm 86$		
108	$3.0 \times 10^3 \pm 82$		$3.0 \times 10^3 \pm 47$
112	$2.3 \times 10^3 \pm 71$		
115	$2.2 \times 10^3 \pm 75$		
119	$2.1 \times 10^3 \pm 73$		
122	$1.9 \times 10^3 \pm 74$		
126	$1.7 \times 10^3 \pm 59$		
129	$1.7 \times 10^3 \pm 58$		
133	$1.5 \times 10^3 \pm 56$		
147	$1.1 \times 10^3 \pm 47$		
150	$1.0 \times 10^3 \pm 46$		
154	$1.0 \times 10^3 \pm 49$		
163	$9.2 \times 10^2 \pm 30$		
164	$8.3 \times 10^2 \pm 29$		
168	$6.3 \times 10^2 \pm 28$		
172	$6.9 \times 10^2 \pm 28$		
189	$4.9 \times 10^2 \pm 24$		
200	$4.8 \times 10^2 \pm 26$		
203	$4.4 \times 10^2 \pm 25$		
206	$3.8 \times 10^2 \pm 24$		

* mean disintegration rate \pm one standard deviation

Table 1. Concentration of Tritium in Body Fluids (cont'd)

Time After Exposure (days)	Concentration (dis/min/ml)*		
	Urine	Blood Serum	Sputum
210	$3.2 \times 10^2 \pm 23$		
213	$3.2 \times 10^2 \pm 23$		
217	$3.2 \times 10^2 \pm 24$		
220	$3.4 \times 10^2 \pm 25$		
224	$2.8 \times 10^2 \pm 23$		
226	$2.9 \times 10^2 \pm 25$		
231	$2.3 \times 10^2 \pm 23$		
235	$2.7 \times 10^2 \pm 22$		
240	$2.1 \times 10^2 \pm 17$		
245	$1.7 \times 10^2 \pm 17$		
248	$1.9 \times 10^2 \pm 16$		
252	$2.4 \times 10^2 \pm 16$		
255	$1.9 \times 10^2 \pm 17$		

* mean disintegration rate \pm one standard deviation

that some tissue may accumulate a higher concentration than body water, particularly at times much later than the exposure. However, the contribution of the second exponential term to the total dose is very small, and unless some tissue concentrates the material to a rather high degree, it seems unlikely that it would contribute significantly to the dose.

A Possible Extension of the Last Two Sentences of the Annual
Report Material on the HTO Exposure Case

On the other hand, there remains the possibility that some tissue may accumulate a higher concentration than body water, particularly at times much later than the exposure. In an attempt to explore this possibility, even partially, a two-compartment model was set up to see if such a model would fit the available data. The model is shown schematically in Fig. 3. It is assumed that a unit amount ($1 \mu\text{c}$) of HTO is taken into the system at time $t = 0$. The functions $A(t)$ and $B(t)$ represent the amount of activity present in the respective compartments (see Fig. 1). The exchange rates α , β and the excretion rate γ represent fractions of the compartment contents exchanged or excreted per unit time and are, therefore, non-negative constants.

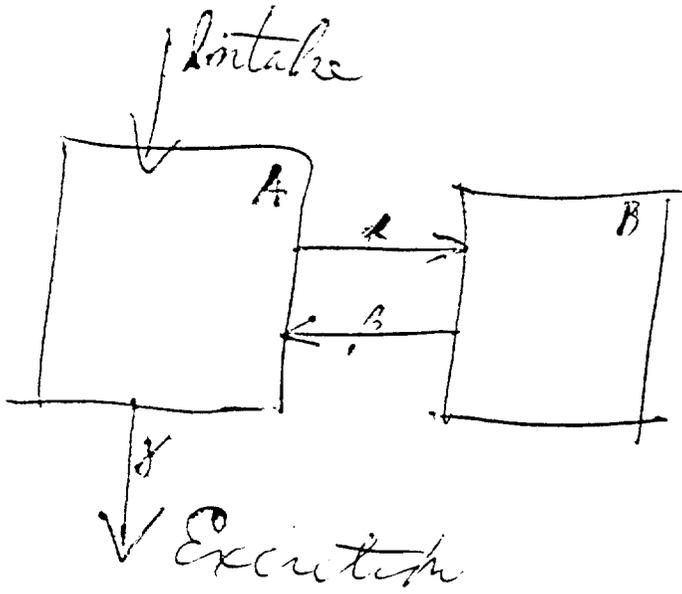
The differential equations governing such a system are the following:

$$\begin{aligned}\frac{dA}{dt} &= \beta B - (\alpha + \gamma) A \\ \frac{dB}{dt} &= \alpha A - \beta B.\end{aligned}\tag{1}$$

The solution of these equations with $A(0) = 1$ and $B(0) = 0$ as initial conditions is given by

$$\begin{aligned}A(t) &= \left[(\beta - h) e^{-ht} - (\beta - k) e^{-kt} \right] / (k - h) \\ B(t) &= \alpha \left[e^{-ht} - e^{-kt} \right] / (k - h)\end{aligned}\tag{2}$$

Fig. 3,



where k and h are the two roots of the quadratic equation

$$x^2 - (\alpha + \beta + \gamma)x + \beta\gamma = 0. \quad (3)$$

To fix the notation, we let

$$k = \left[\alpha + \beta + \gamma + \sqrt{(\alpha + \beta + \gamma)^2 - 4\beta\gamma} \right] / 2$$
$$h = \left[\alpha + \beta + \gamma - \sqrt{(\alpha + \beta + \gamma)^2 - 4\beta\gamma} \right] / 2. \quad (4)$$

These roots are easily shown to be positive, and k is greater than h . It is also easy to show that

$$\beta - k < 0 < \beta - h \quad (5)$$

so that $A(t)$ is the sum of two exponential terms with positive coefficients and B is the difference of two such terms.

From the least squares fit of the data, it is observed that the coefficients of the fitted to the excretion data exponentials are 5.3×10^6 and 2.3×10^4 d/min/ml. Although Fig. 2 represents excretion data, the pool of body water, represented by compartment A, is at the same concentration as urine, and thus the function represented in Fig. 2 is proportional to $A(t)$. When normalized for unit intake, the intercepts in Fig. 2 are given by

$$r = 0.9957 = (\beta - h)/(k - h)$$

and

$$1 - r = -(\beta - k)/(k - h). \quad (6)$$

From Fig. 2 it appears that two exponential terms are required to fit the urinary concentrations observed in this case. By courtesy of Dr. Chester Richmond of LASL, we have obtained a least squares fit of the data to a sum of two exponentials using the LASL code described in reference 3 which does not require a logarithmic transformation of the concentrations. This fitting procedure yielded a retention formula for concentration in urine of

$$R(t) = 5.3 \times 10^6 e^{-\alpha t} + 2.3 \times 10^4 e^{-\beta t}$$

with

$$\alpha = \frac{0.693}{8.7} \quad \text{and} \quad \beta = \frac{0.693}{34}$$

Cases of internal exposure at ORNL which warrant consideration of dose and intake on the basis of the characteristics of the individual are evaluated by an Internal Dose Evaluation Committee. This subject's total body water was estimated on the following bases:

1. On weight basis: for 66.5 kg body weight the human contains 0.44 to 0.70 liters water/kg...the mean, $0.52 \times 66.5 = 34.6 \approx 35$ liters.⁴
2. On age basis: humans 41 years of age contain from 0.44 to 0.65 liters water/kg...the mean, $0.525 \times 66.5 = 34.9 \approx 35$ liters.⁴
3. On the basis of weight to height ratio: weight/height = 0.41 kg/cm, the male human body weight is 18 per cent to 37 per cent fat (mean 28%). Lean body weight (LBW) $\approx (1 - 0.28) \times 66.5 = 47.9$ kg.⁵ The same reference suggests: total body water = 0.72 LBW = $34.5 \approx 35$ liters.

⁴ Biological Handbook - Blood and Other Body Fluids, Fed. Am. Soc. Exptl. Biol., 1961.

⁵ G. B. Forbes, J. Gallup, and J. B. Hursh, Science **133**, 101-2 (Jan. 13, 1961).

³ C. R. Richmond, J. E. Furchner, P. N. Dean, and P. McWilliams, Health Phys. **10**(1), 3-13 (1964).

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4. On the basis of total potassium content: the subject was counted in the ORNL Whole Body Counting Facility on November 8, 1963, with the following results: Age - 41; Weight - 66.5 kg; Height - 161 cm; Estimate 121 grams of potassium based upon ^{40}K measurement.

Total potassium content = 0.28 per cent of lean body weight (LBW);
LBW = 121 grams/0.00028 = 43.2 kg.⁶ This reference indicates that 72 per cent of the lean weight and 20 per cent of the fat weight is made up of water; thus, total body water = $0.72 \times 43.2 + 0.2 \times 23.3 = 35.76 \approx 36$ liters.

The Committee decided to use 36 ⁽¹⁾ as the amount of body water. Assuming a concentration of 5.3×10^6 d/m/ml initially and that all the tritium is in the body water at early times postexposure, this yields $5.3 \times 10^6 \times 36 \times 10^3 = 1.9 \times 10^{11}$ d/min, or 86 mc, as the initial intake. The total dose to body water is then

$$D = \frac{51 \times f_2 \mathcal{E} q(0)}{m \times 5.32 \times 10^6} \int_0^\infty dt R(t) = 15.5 \text{ rem}$$

where $f_2 = 1$, $m = 3.6 \times 10^4$ g, $\mathcal{E} = 0.01$ Mev, $q(0) = 86 \times 10^3$ μc , and

$$\begin{aligned} \int_0^\infty R(t) dt &= \frac{5.32 \times 10^6 \times 8.7}{0.693} + \frac{2.3 \times 10^4 \times 34}{0.693} \\ &= 6.65 \times 10^7 + 1.13 \times 10^6 = 6.76 \times 10^7. \end{aligned}$$

It is apparent that the second exponential term contributes only about 1.7% to the total dose. The dose in various body tissues may be somewhat less since no allowance has been made for the presence of organic material. However, there are some tissues where water constitutes a preponderant part of the mass, and so the estimate is substantially, although not precisely, correct for such tissues. On the other hand, there remains the possibility, perhaps rather the probability,

⁶E. C. Anderson, Brit. J. Radiol. Supp. 7, 27 (1957).

The values of k and h may be determined from the slopes of the lines on Fig. 2 or by the least square fit of the data. From equations (6) and (4), one obtains

$$\begin{aligned}\alpha &= \frac{r(1-r)(k-h)^2}{rk+(1-r)h} = 7.3 \times 10^{-4} \\ \beta &= rk+(1-r)h = 0.021 \\ \gamma &= \frac{hk}{rk+(1-r)h} = 0.079.\end{aligned}\tag{7}$$

The numerical evaluations given in (7) have been obtained by using the values

$$k = \frac{0.693}{8.7}, \quad h = \frac{0.693}{34}, \quad r = \frac{5 \times 10^6}{2.3 \times 10^4 + 5.3 \times 10^6} = 0.9957.$$

It appears that it is possible to select parameters in such a way that the model fits the data. To estimate a dose to the tissues representing the two compartments, the mass of these tissues is needed. In the absence of any direct biological evidence on the compartment represented by $B(t)$, it was assumed that the HTO metabolized as does H_2O . This unsupported assumption can be used to calculate an estimate of the H_2O in compartment B, and a dose can be computed on the basis of this water content. The surprising result was that this estimate did not involve the parameters α , β , γ of the model, although the model was used in making the estimate. It was found that a quite general argument could be used, and this is outlined below.

Assume HTO is taken into the body and is metabolized in exactly the same way as H_2O until the moment when the tritium disintegration takes place. Because of the

long radioactive half-life of tritium, the decay will be neglected. Let $R_i(t)$ μc be the burden of ingested tritium present in tissue i at time t following intake of $1 \mu\text{c}$ at time 0. The dose rate to tissue i at time t is then

$$\frac{R_i(t) \times 3.2 \times 10^9 \times \mathcal{E}}{M_i}$$

where $R_i(t)$ = the tissue burden in μc

$$3.2 \times 10^9 = (\text{d/day})/\mu\text{c}$$

$$\mathcal{E} = \text{Effective energy (Mev)} \times 1.6 \times 10^{-8}$$

$$M_i = \text{Mass of tissue } i \text{ (g)}.$$

The total dose, D_∞ , to tissue i is then

$$D_\infty = \frac{3.2 \times 10^9 \times \mathcal{E}}{M_i} \int_0^\infty R_i(t) dt \text{ rem.} \quad (8)$$

Assuming an intake of 1 g of H_2O per day and that tissue i is in equilibrium for intake of H from H_2O , then tissue i contains

$$\frac{1}{18} \int_0^\infty R_i(t) dt \text{ g} \quad (9)$$

of hydrogen which was ingested in the form of H_2O , 1 being the daily intake of water, g/da . The infinite range of integration is unrealistic, but it is used only to indicate effective equilibrium. The total hydrogen content, say, $h_i \text{ g}$, of tissue i must be at least the amount indicated by (9). In general, there is not a great range of variation of hydrogen content among the soft tissues, 10% being a representative value. Thus from (9) we have

$$0.1 M_i \sim h_i \geq \frac{1}{18} \int_0^{\infty} R_i(t) dt. \quad (10)$$

Combining (10) and (8), one obtains

$$\begin{aligned} D_{\infty} &= \frac{3.2 \times 10^9 \times \mathcal{E}}{h_i} \int_0^{\infty} R_i(t) dt \times \frac{h_i}{M_i} \leq \\ &\leq \frac{3.2 \times 10^9 \times \mathcal{E} \times 18}{1} \times \frac{h_i}{M_i} \sim \frac{5.8 \times 10^9 \times \mathcal{E}}{1} \text{ rem} \end{aligned} \quad (11)$$

since $\frac{h_i}{M_i} \sim 0.1$.

If the compartment represented by $A(t)$ is considered to consist essentially of water and if we denote this compartment by taking $i = 0$, then the amount of water in the compartment is at least $1 \int_0^{\infty} R_0(t) dt$ g. This follows from the assumption that HTO and H_2O metabolize in the same way and, because $R_0(t)$ being the fraction of intake present at time t , one atom of tritium corresponds to one molecule of HTO. Since $M_0 \cong 1 \int_0^{\infty} R_0(t) dt$, (8) becomes

$$D_{\infty} = \frac{3.2 \times 10^9 \times \mathcal{E}}{1} \text{ rem.} \quad (12)$$

It will be noted that the estimated dose to any tissue i given by (11) cannot exceed the dose to body water as given by (12) except by the factor $\frac{18 h_i}{M_i}$, where h_i/M_i is the fraction of the mass M_i due to hydrogen. For example, if the hydrogen is all present in the form of water, then the factor is 1. However, there is no tissue known to the authors for which the hydrogen is much in excess of 10%. Table 4 below presents data from several sources on this point. Thus it seems very unlikely that any tissue can get a dose from

Table H. Hydrogen Content of Some Body Tissues

Tissue	Tissue Weight (g)	Percent Water by Weight	Percent H by Weight
Bone	7,000	28.2	3.39
Fat	10,000	23.0	9.33
Skeletal Muscle	30,000	70.1	10.08
Skin	2,000	57.7	9.40
GI Tract	2,000	77.4	10.29
Liver	1,700	75.0	10.04
Brain	1,500	77.3	10.71
Lungs	1,000	77.3	10.09
Kidneys	300	70.6	9.99
Heart	300	63.0	9.79
Spleen	150	78.5	10.20
Pancreas	70	73.1	9.77
Spinal Cord	30	70.0	7.24
Eye	~ 0.45	68.9	9.73
Blood Plasma	3,200	92.0	10.76

ingested HTO that is markedly in excess of the dose to body water. This conclusion, while only supported by the above indirect arguments, may provide some guidance in attempting to assess the significance for the health physicist of the existence of this (these!) other compartments.