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THE BODY ABSORPTION, DISTRIBUTION, AND EXCRETION OF TRITIUM IN MAN AND ANIMALS

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ABSTRACT

A study has been made of the body absorption, distribution, and excretion of tritium in man and laboratory animals following exposure to tritium in the form of HT and HTO. Both respiratory and oral routes of exposure were studied. The results indicated that the major portion of tritium inspired as HTO was absorbed in the body. Very little tritium inspired as HT was absorbed. Both rat and man oxidized small amounts of HT to HTO.

From the results obtained it would appear that for man the maximum permissible level of tritium as HTO in inspired air should be 6×10^{-5} µc/cc. based on 0.3 rep./wk. and a 40 hr./wk. exposure. The maximum permissible level of tritium as HT in inspired air should be 0.6 µc/cc. In the latter case radiation doses to the lungs is the limiting factor. The principal dilution volume of tritium as HTO in the body of both man and animals on short exposure was found to be the total body water. The rate of turnover of tritium from the body fluids following acute exposure was in keeping with the rate of turnover of total body water. Mice excreted tritium from body fluids with a biological half-time of 1.5 to 2.0 days, rats 3 to 5 days, men 9 to 14 days.

Chronic exposure of mice to HTO over a period of 5 months resulted in tritium becoming distributed in the body water and in some undetermined body constituents other than water which had a biological half-time longer than one week. The study further showed

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that tritium concentration as HTO in all the body fluids and fluid excreta of man was essentially the same.

The rate of absorption of HTO through the gastro-intestinal tract was linear with time when given amounts were ingested. Tritium excretion as HTO from the body fluids of man and animals was exponential with water turnover. Absorption of HTO through the skin of man was studied by immersion of the hand and forearm in water containing HTO. Absorption through the skin was found to be approximately equal to the rate of water loss by insensible perspiration.

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THE BODY ABSORPTION, DISTRIBUTION, AND EXCRETION OF TRITIUM IN MAN AND ANIMALS

Ernest A. Pinson

Introduction

Tritium is the radioactive isotope of hydrogen of mass three. It has a half-life of 10.7 years and emits soft beta particles of 18 Kev. maximum energy. No gamma radiation is emitted. It has been used as a hydrogen tracer in the experiments here presented in amounts up to 3 millicuries. Various physiological aspects of its absorption through the skin, the respiratory and gastro-intestinal systems, its distribution within the body, and its excretion from the body have been measured in man and animals. From these measurements certain conclusions concerning the tolerance dose of tritium for man have been drawn.

Experimental Methods and Results

The method used for tritium assay when present as HTO in body fluids was as follows:

Water from the body fluid concerned was obtained by complete distillation in a vacuum at room temperature. 0.1 cc. of the water sample thus obtained was allowed to evaporate into an evacuated system, the vapor passing through a furnace filled with powdered zinc on glass wool held at 400-410°C. The reduced hydrogen and tritium were pumped into a 250 cc. Borkowski-type ion chamber by means of a Toeppler pump, which produced a pressure of about 380 mm. Hg in the chamber at room temperature. The chamber was then filled to about 100 cm. Hg

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pressure with CO_2 in order to obtain better ionization efficiency within the contained gas. The saturated ionization current was measured with a dynamic condenser electrometer with a sensitivity of 10^{-17} ampere. The observed ionization current was 1.5×10^{-12} ampere per microcurie. The background of the ion chamber was 2.4×10^{-16} ampere equivalent to 1.6×10^{-4} microcurie (360 disintegrations per minute) of tritium. The activities measured usually ranged from 10 to 100 times background. At these levels duplicate analyses differed by less than 5 per cent.

Rats were exposed continuously to various concentrations of tritium in inspired air for periods up to 145 hours. This was done in a closed system of approximately 30 liters volume. The HT exposure apparatus used is shown in Fig. 1 with the bell jar in place and in Fig. 2 with the bell jar removed so that the contained cage may be seen more clearly. The HT gas was exposed to no metals in this system. Glass, lucite, rubber, water, food, the rat, and the chemicals required to absorb water and CO_2 ($CaCl_2$ and soda lime) were the materials with which the gas came in contact when the rat was exposed to HT. Oxygen was bled into the bell jar from the oxygen supply tank through a <u>one-way</u> valve as the rat used oxygen from the bell jar. When exposure to HTO vapor was made the floor of the chamber was covered with a 0.5 N NaOH solution containing HTO in an amount to produce the required activity in the saturated atmosphere of the bell jar. The NaOH acted as CO_2 absorber. Urine and feces were collected intermittently from the bottles beneath the chamber. Gas samples were collected from the chamber in an evacuated ion chamber, through the tube at the bottom extending up into the chamber, and analyzed to determine tritium activity. The animal may be exposed

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continuously for many days in this system at an essentially constant tritium activity.

The tritium concentration to which rats were exposed in the above described apparatus was varied from 6×10^{-6} to 3×10^{-2} µc/cc. in different experiments. The length of exposure ran from 100 to 145 hours. One exposure of two hours duration to a tritium activity of 1.8 µc/cc. was made in a similar but smaller apparatus.

Fig. 3 shows the build up of tritium concentration as HTO in the body fluids in two of these experiments, one in which the rat was exposed to HT and the other to HTO. A summary of all such exposures made on rats is given in Table 1.

TABLE 1

RATE OF APPEARANCE OF HTO IN THE BODY FLUIDS OF THE RAT AS A RESULT OF THE INSPIRATION OF HT AND HTO.

Tritium Form	Inspired Amt. µc/cc.	Rate of Appearance of HTO in Body Fluids µc/cc./hr.
HT	1.8	5.0×10^{-2}
"	3.0×10^{-2}	1.7×10^{-3}
"	3.3×10^{-3}	2.0×10^{-4}
"	1.0×10^{-3}	3.0×10^{-5}
"	8.6×10^{-5}	Indetectable
"	6.0×10^{-6}	"
HTO	1.0×10^{-4}	4.0×10^{-3}
"	2.6×10^{-5}	2.0×10^{-3}

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In these experiments the rat used about 500 cc. of oxygen per hour at room temperature and 59 cm. Hg pressure. Assuming absorption of 4% of oxygen from inspired air this gave a volume of 12.5 liters of air inspired per hour. Thus it appears that when tritium was present as HTO in inspired air a major portion of all the activity inhaled was taken up in the body fluids, indicating rapid exchange and absorption of tritium water across respiratory membranes. If the tritium activity was present as HT in the inspired air, less than 0.1% of the inspired activity appeared in the body fluids of the rat as HTO. Except in one experiment the range of activities to which the rat was exposed via inspired air was not high enough for absorption of HT per se in body fluids to be detected. Apparently biological oxidation of HT to HTO takes place in the rat's body. This does not appear to be an exchange of HT with H_2O for when HT was placed in a sealed glass bulb with oxygen over a small amount of H_2O and allowed to stand at room temperature for two or three weeks, no HTO appeared in the H_2O. Since the same gas was used in this exposure as for the rat exposures it also nullifies the possibility that the HT might have been contaminated with HTO. The HT was passed through anhydrous magnesium perchlorate and through a liquid nitrogen trap for removal of HTO before use in these experiments.

Respiratory exposure of the rat to either HT or HTO took about 100 hours for HTO in the body fluid to reach a relatively steady value (Fig. 3). Beyond this time HTO excretion through the various water excretory routes balanced HTO uptake by the body through the lungs. The equilibrium value reached varied 10-15% during the day due to short

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period variations in the water turnover rate. The rat eats and drinks most of its daily water turnover at night so that the tritium activity in body fluids, on continuous exposure to a constant inspired activity, was usually lowest in the morning and highest in the evening.

After exposure of the rats was completed, they were removed from the exposure chamber, placed in a metabolism cage and the decline in HTO activity in body fluids followed. Water and food intake were noted and urine collections were made daily for analysis of tritium activity. The results of one such experiment are shown in Figs. 4 and 5. It is apparent HTO elimination from the body is an exponential function of water turnover. The water intake shown included water from food as well as H_2O ingested per se. Other experiments on rats showed a biological half-life for HTO ranging from 3 to 5 days depending on the rate of H_2O intake. The dilution volume ranged from 57% to 72% of the body weight. Since body water constitutes about 70% of the lean body weight, this suggests that body water makes up the major portion of the body volume with which HTO is diluted.

It seemed important to attempt to determine if, during chronic exposure, tritium did enter into combination with body constituents other than water and, if so, to what extent since other body constituents may have biological half-lives differing from that of water. To do this water containing 4.14 μc/cc. of tritium as HTO was fed to three mice for five montns in place of normal H_2O. When diluted with water obtained from the food this gave an average HTO activity in the body fluids of the mouse of 2.8 μc/cc. (The beta radiation from this amount

of tritium represents a radiation dose of about 6 rep. per week.) By weighing the HTO and the food ingested the H_2O resulting from the food was determined by the degree of dilution noted. It was found that about 50% of the weight of the food ingested appeared in the mouse's body to dilute the HTO which the mouse drank. This figure was used to calculate total water intake.

After five months the mice were taken off HTO water and given H_2O. The decline in HTO activity in body fluids was followed for about one month. Daily water and food intake was carefully measured during this period. The results are shown in Figs. 6, 7 and 8. Initially the decrease in HTO activity in the body fluids was very rapid, showing a biological half-life over the first ten days of 1.7, 2.0 and 1.5 days in mice 1, 2, and 3 respectively. Considering water turnover in Fig. 7, the average value for the reservoir calculated from the rate constant during this first ten day period was 83% of the body weight of the mice. Since this value was more than the percent body water it suggests the contribution of some tritium from some tissue or tissues within the body having longer half-lives than that for body water. This was confirmed subsequently in the experiment as the decay curve became less and less steep. During the last 10 days of the experiment the apparent half-life for HTO as measured in the urine lengthened to 7-10 days. At this time some body constituents other than water having a half-life in excess of one week was undoubtedly contributing considerably to the HTO activity measured in the urine. It should be noted that by this time the activity measured in the urine had decreased to less than 0.5% of the value observed at the beginning of the period of decline and maintained during

the five months period the mice were drinking HTO. Thus it seems quite apparent that mice on long exposure to HTO integrate some of the tritium into body constituents other than water and from which constituents the mice can eliminate the tritium with a half-life longer than one week.

At the end of the period shown in Fig. 6, the mice were sacrificed, dissected, and various component parts of the body separated so that samples of bone, muscle, fat, liver, etc. were obtained. It is planned to dry these tissues, burn the dried residue, collect water from the combustion, and analyze it for tritium in an effort to localize the source of the long lived components indicated above. This part of the experiment has not yet been completed.

Some tritium absorption and excretion data were also collected from man. In no case in this work was man exposed to a radiation dose in excess of the maximum permissible dose of 0.3 rep. per week established by the AEC health safety recommendations.

In a closed rebreathing system containing water and CO_2 absorbers ($CaCl_2$ and soda lime) man was exposed to tritium as HT in amounts ranging from 0.11 μc/cc. to 9 μc/cc. of inspired air for periods of two hours. The HT was dried before use by freezing water out in a dry ice trap. After drying the gas came in contact with no metals in the rebreathing system. Only glass, lucite, and rubber were used in enclosing the system. Under these conditions man also appeared to oxidize HT to HTO as did the rat, although the rate of this oxidation in man was much less per unit body weight than in the case of the rat. The results of one such experiment on man are shown in Fig. 9. In this short period of exposure

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the increase of HTO in body fluids was linear when plotted against time since the amount excreted during the experiment was negligible compared to that produced in the body. The results of three exposures of man to different activities of tritium as HT in inspired air are given in Table 2.

TABLE 2

RATE OF HTO APPEARANCE IN BODY FLUIDS OF MAN DURING INSPIRATION OF HT.

Tritium Activity as HT in Inspired Air μc/cc.	Rate of HTO Appearance in Body Fluids μc/cc./hr.
9	7.7×10^{-3}
0.6	5.0×10^{-4}
0.11	Indetectable

For these levels of activity in inspired air the HT dissolved in body fluids can be detected. However, no procedure was worked out at this time for its accurate quantitative measurement. Therefore, HT was removed from the samples to be analyzed for HTO by warming to room temperature in a vacuum. At some future time the rate and degree of HT absorption in the body will be studied. On the basis of absorption of hydrogen in water at 37°C. it may be expected that body fluids will absorb per unit volume about 1.6% of the activity per unit volume of inspired air.

The composite results of the HT and HTO inhalation experiments on man and rats are shown in Fig. 10 in relation to a maximum permissible

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dose for man of 0.3 rep. per week. No experiments on inhalation of HTO by man have yet been done. It seems fairly certain, however, on the basis of theoretical considerations and the results obtained with the rat, that the curve shown for absorption of HTO by man when inhaling HTO is a realistic one, or at least a conservative one so far as a safe permissible dose is concerned. The maximum permissible dose of tritium for man based on a 40 hour per week exposure to HTO or HT in inspired air is indicated by the point at which the vertical line crosses the appropriate diagonal line on the graph shown in Fig. 10. The dose is dependent to a certain extent on the rate of water turn over by man. A water turn over of 20 liters per week for a 70 kg. man was assumed in making the graph. This figure also points to the conclusion that a man inhaling HT may reach a maximum permissible dose of 0.3 rep. to the lungs before a maximum permissible dose of 0.3 rep. to the body in general is reached due to oxidation of HT to HTO.

In one experiment the arm of a man was immersed up to the elbow in water containing 0.1 mc/cc. of tritium as HTO. HTO activity in body fluids rose at such a rate as to indicate an absorption rate of water through the skin of 0.05 mg./cm.^{2}/minute. This approximates the rate of insensible perspiration or water loss out through the skin due to diffusion when sweat glands are inoperative. The rate of entry of tritium into the body of man through the skin is too slow to pose a serious hazard so far as maximum permissible doses are concerned. One would have to immerse the whole body in water containing 0.1 mc/cc. of tritium as HTO for more than an hour in order to absorb an amount of

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HTO through the skin which would give a radiation dose of 0.3 rep. per week.

One experiment was done on man in which 3 mc. of tritium as HTO was ingested in 200 cc. of water. Absorption into the blood stream was linear with time and was complete in about 45 minutes (Fig. 11). The tritium was diluted with about 58% of the body weight, suggesting that total body water is the principal diluent. Body water turnover was measured over a period of six days subsequent to this ingestion by weighing all food and fluid intake and all excretory output. Water intake in food including metabolic water was calculated and included. For four days water turnover was kept near normal (2.7 liters per day). During the last two days water turn over was increased to 12.8 liters per day. During both periods tritium activity as HTO in the body fluids decreased along a straight line when the log of the activity was plotted against water turnover (Fig. 12). The reservoir calculated from the rate constant was 57.5% of the body weight. Since this is essentially the same as the diluent per cent following ingestion it again suggests body water only as the principal distribution volume for tritium. Tritium excretion rates determined on eight other human subjects in which water turnover was measured less precisely indicate a reservoir ranging from 57 to 68% of the body weight. Some of these data were reported previously in LAMS - 1099.

In the experiment described above the biological half-life for tritium during the four day period of normal water intake was about 10 days. During the last two days when the water turn over was increased

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to 12.8 liters per day the tritium half-life in body fluids was reduced to approximately 2.4 days (Fig. 13). In the eight other human subjects mentioned above the biological half-life for tritium as HTO in body fluids ranged from 9.3 to 14 days on ad libitum water intake.

In the course of these several experiments on man the tritium activity in water from sweat, insensible perspiration, expired water vapor, sputum, urine and blood were measured and compared. In all fluids the tritium activity was found to be essentially the same. This leads to the generalization that isotopic dilution or concentration of tritium does not occur to any marked degree in any fluid anywhere in the body. With certain limitations imposed by the element of time any of the above mentioned fluids may be used as a measure of the tritium activity as HTO in the body fluids in general.

SUMMARY

1. The rat, and probably man, absorbed into the body the major portion of tritium inspired as HTO.
2. Both rat and man oxidized tritium inspired as HT to HTO.
3. The rat oxidized about 0.1% of HT inspired to HTO.
4. Man oxidized about 0.004% of HT inspired to HTO.
5. The principal diluent of tritium as HTO in the body of both man and animals on short exposure is the total body water.
6. Mice on long exposure to HTO showed tritium in body water and in some undetermined body constituents other than water which had a half-life longer than one week.

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7. Mice excreted tritium from body fluids with a biological half-time of 1.5 - 2.0 days; rats 3 - 5 days; men 9 - 14 days.

8. For man, the maximum permissible level of tritium as HTO in inspired air (based on 0.3 rep./wk. and a 40 hr./wk. exposure) is 6×10^{-5} uc/cc.

9. For man, the maximum permissible level of tritium as HT in inspired air (based on 0.3 rep./wk. and a 40 hr./wk exposure) is 0.6 uc/cc. In this case the radiation dose to the lungs is the limiting factor.

10. The tritium concentration as HTO in all the body fluids and fluid excreta of man was essentially the same. With certain limitations imposed by the element of time, any of the body fluids may be used as a measure of the tritium activity as HTO in the body fluids in general.

11. The rate of absorption of HTO through the gastro-intestinal tract was linear with time when a given amount was ingested.

12. Tritium excretion as HTO from the body fluids of man and animals was exponential with water turnover.

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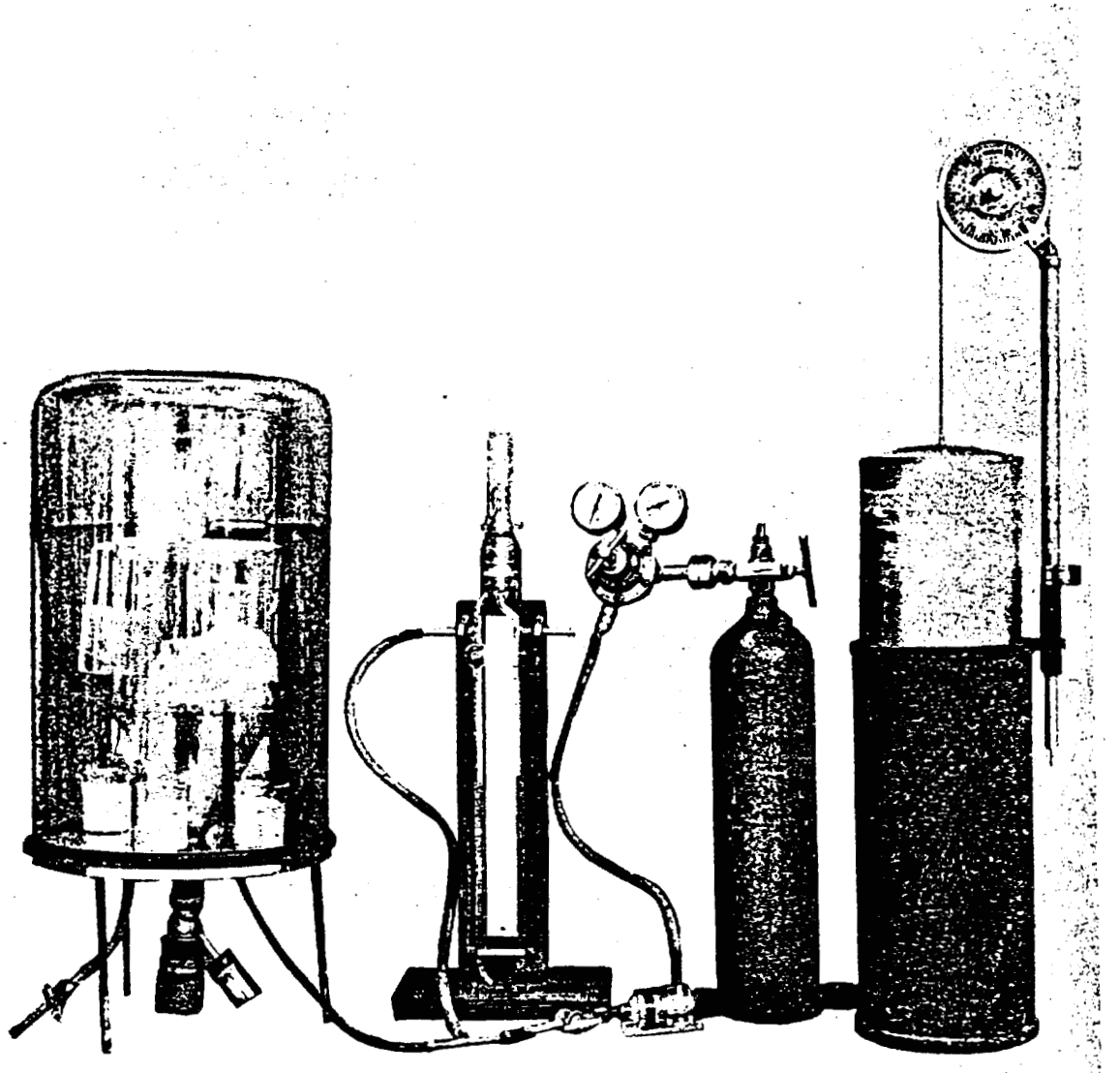

FIG. I - Apparatus for exposure of animals to HT.

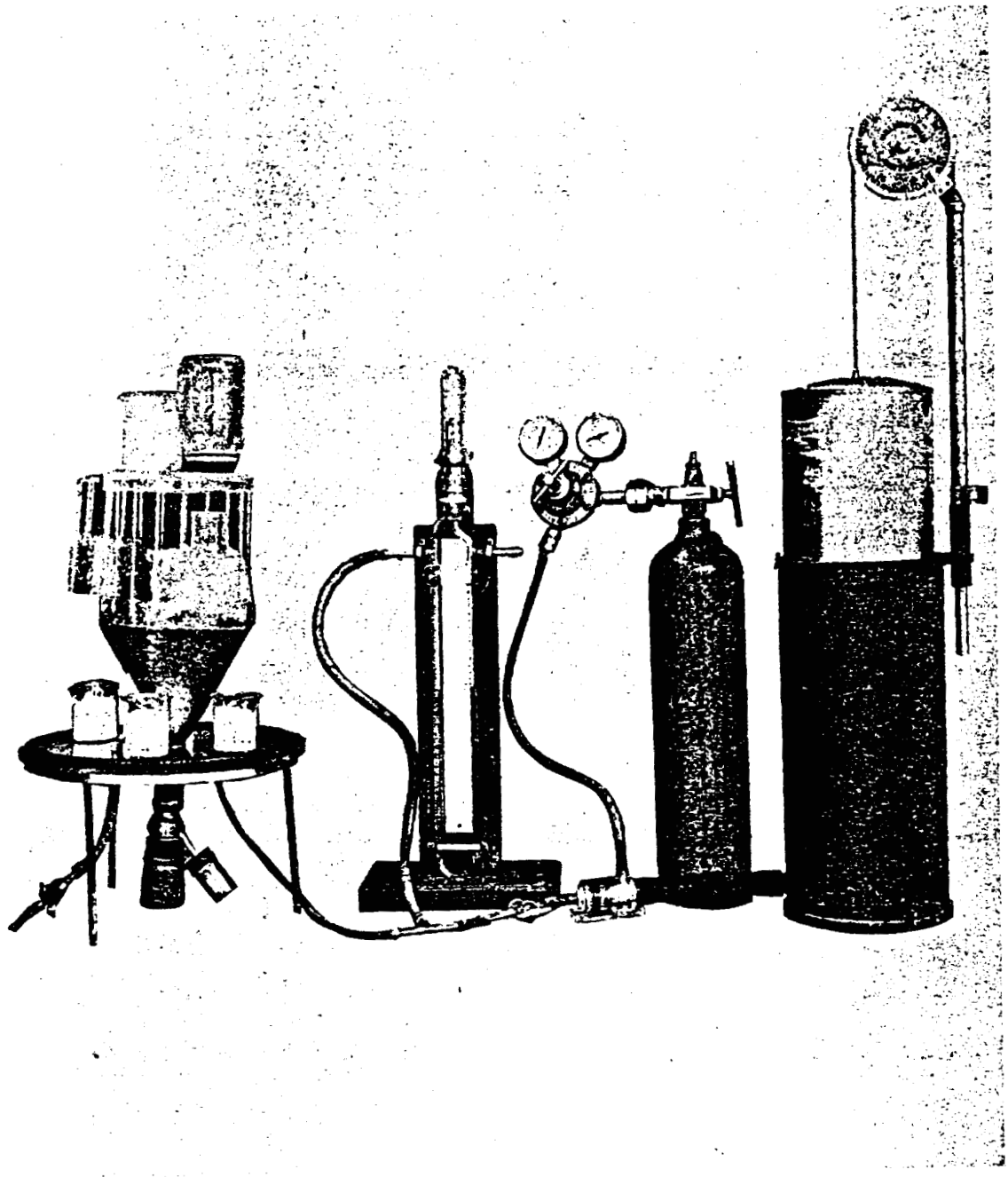

FIG. 2 - Apparatus for exposure of animals to HT (the jar removed to show cage assembly.)

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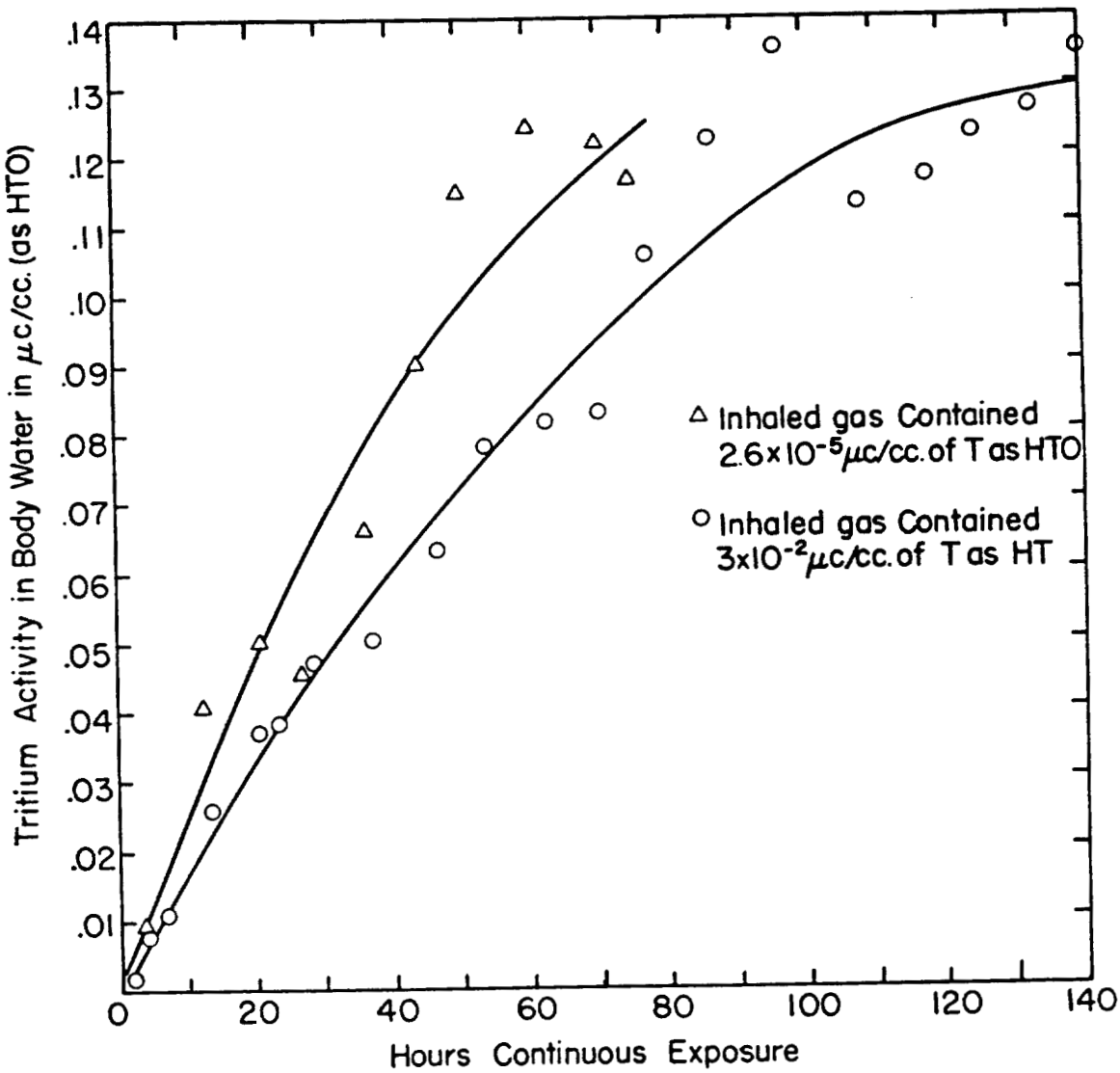

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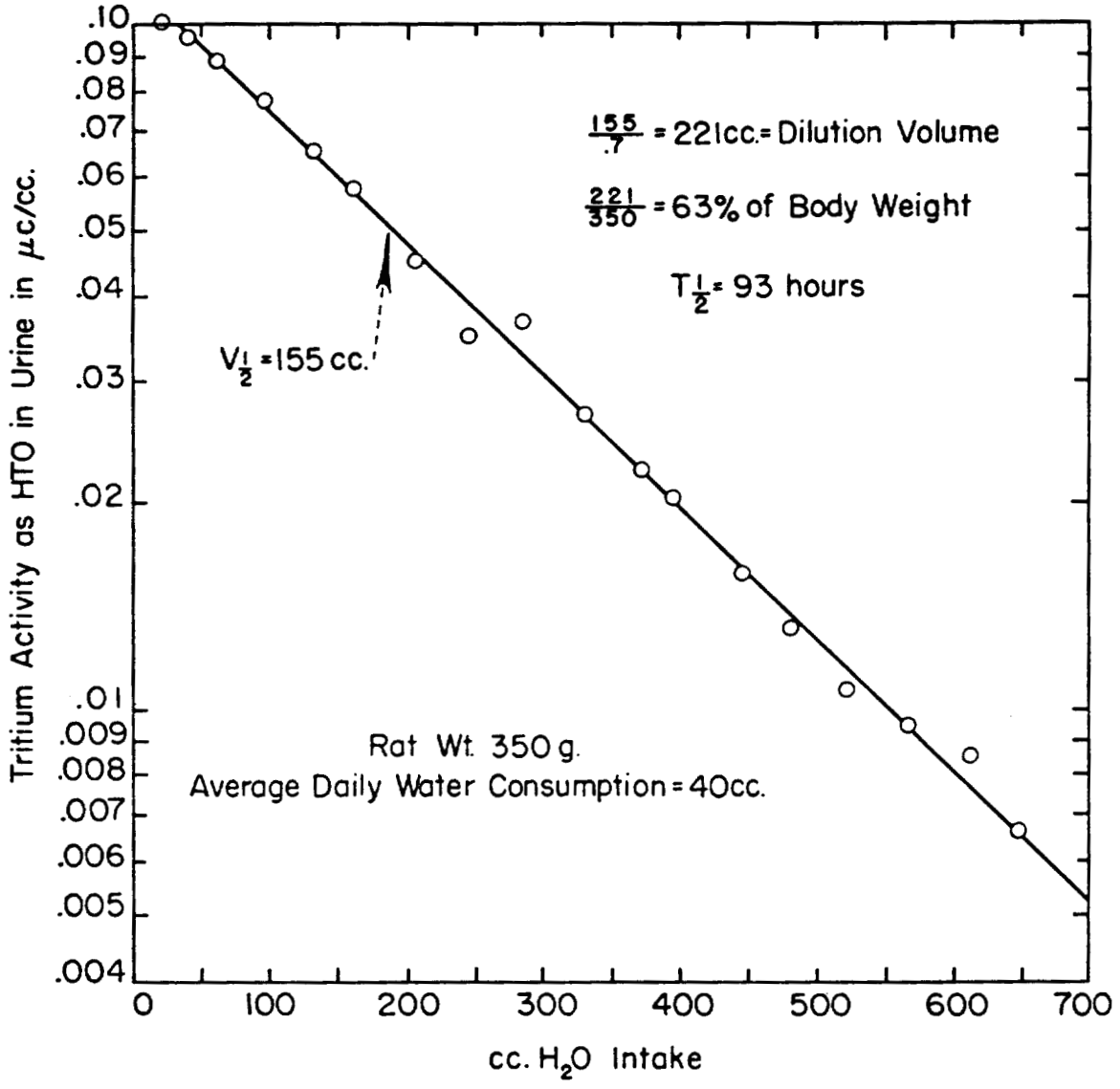

FIG. 4 - Tritium Excretion vs Water Consumption for the Rat (including Water in Food)

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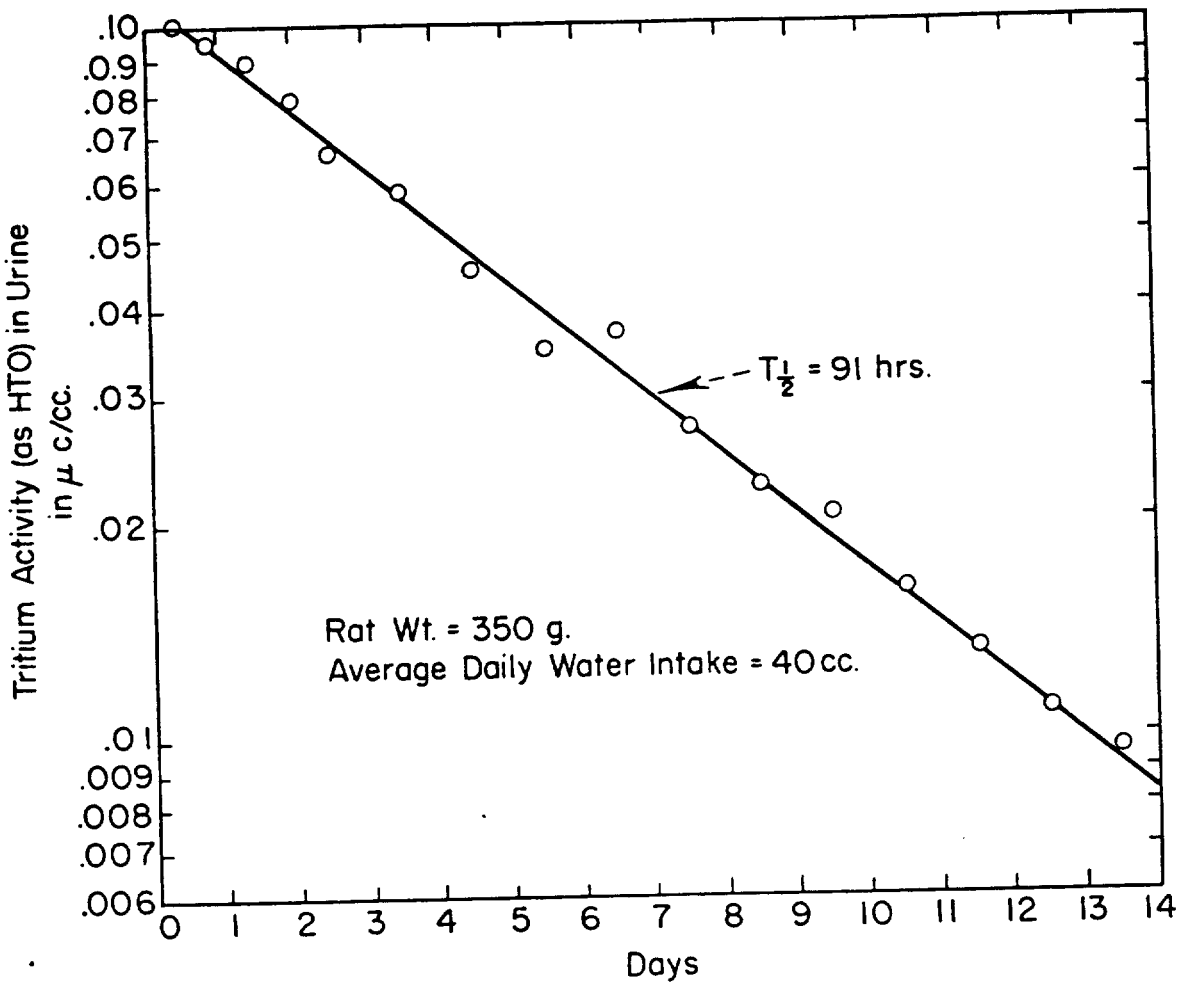

FIG. 5 - Elimination of Tritium by the rat vs. Time after exposure

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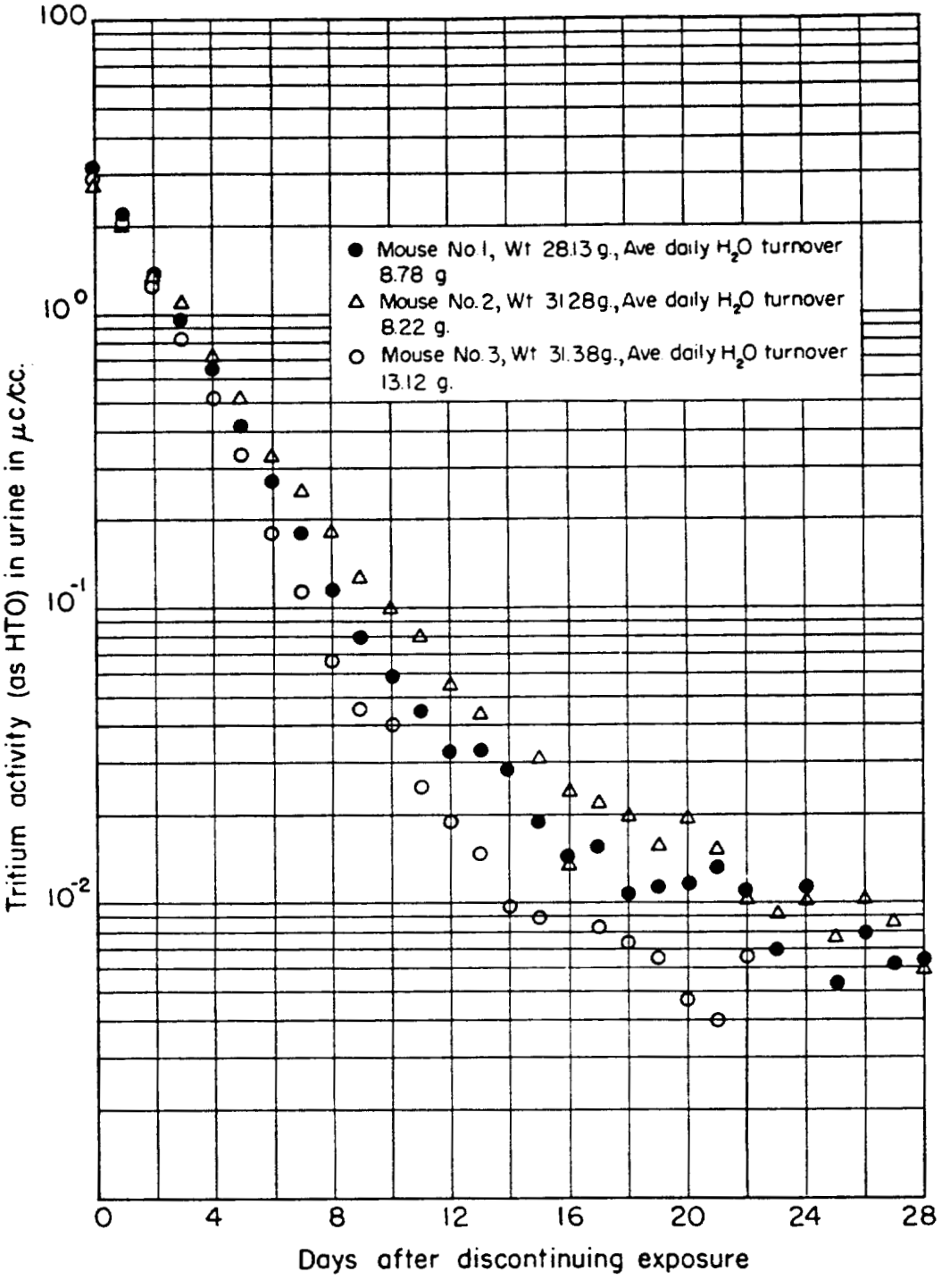

FIG. 6 - Rate of elimination of Tritium by mice following chronic exposure to ingested HTO.

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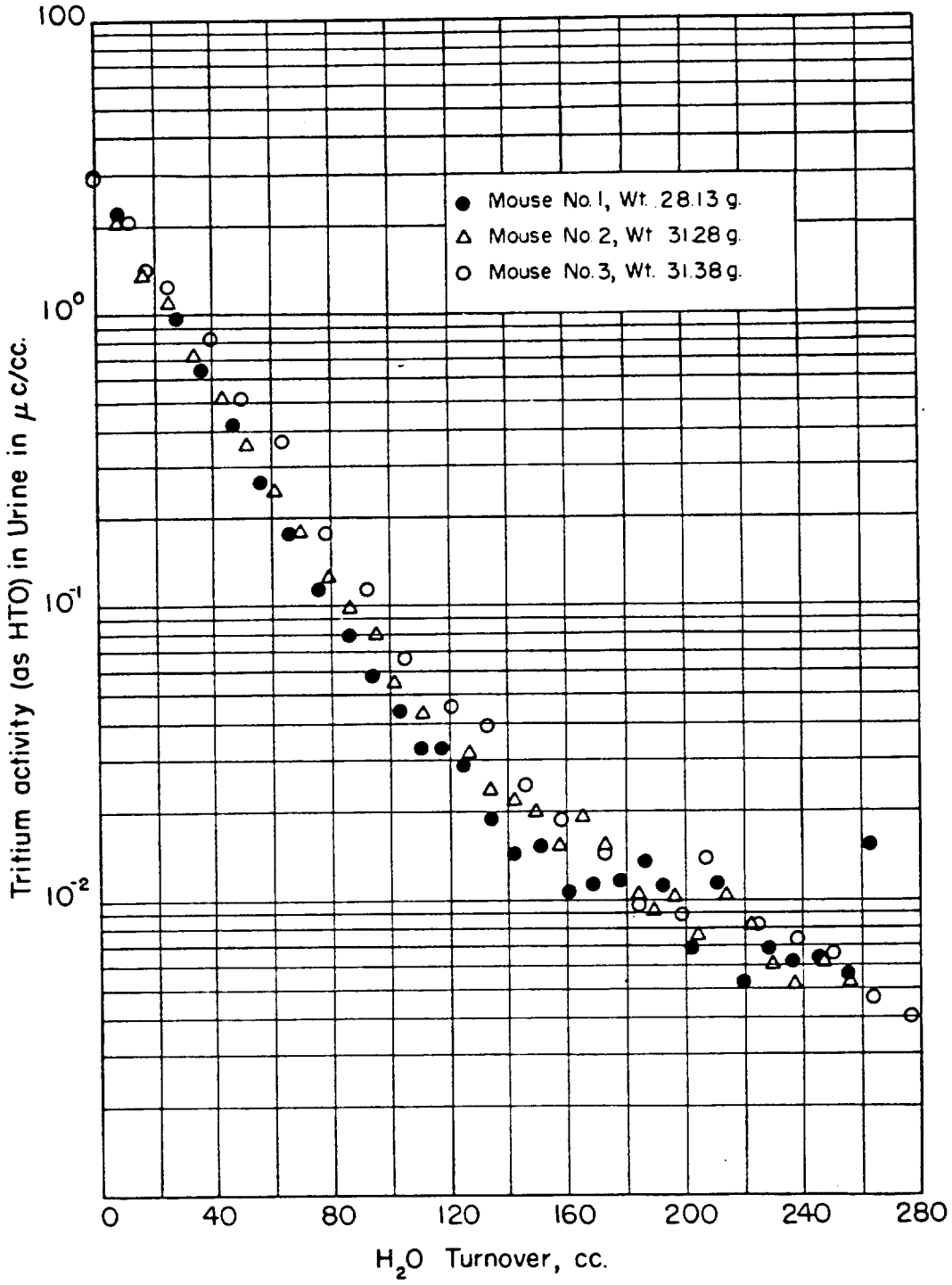

FIG. 7 - Water turnover cc. vs. Tritium activity in urine following chronic exposure of mice to ingested HTO

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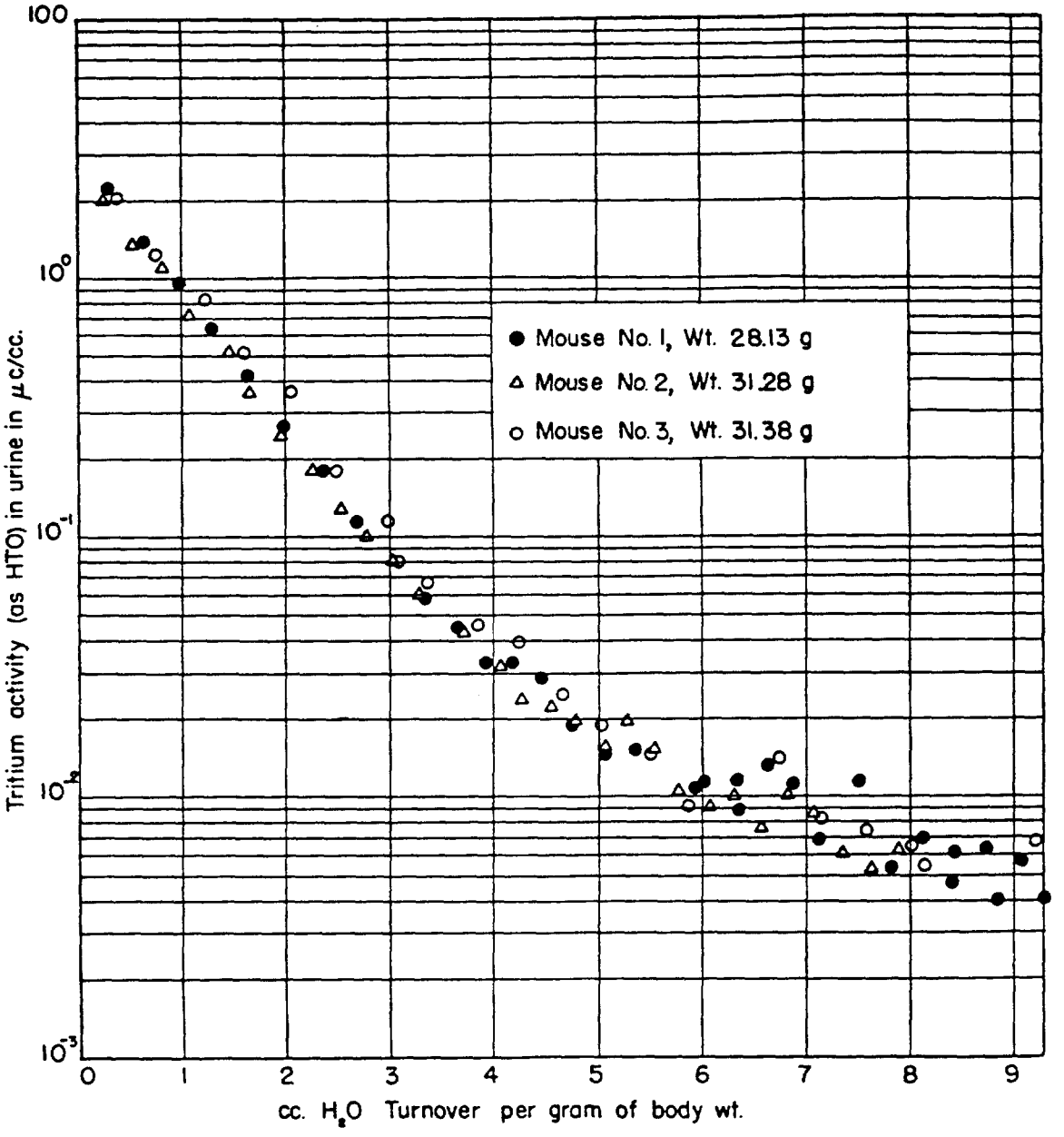

FIG. 8 - cc. Water turnover per g. body wt. vs. Tritium activity in urine following chronic exposure of mice to ingested HTO.

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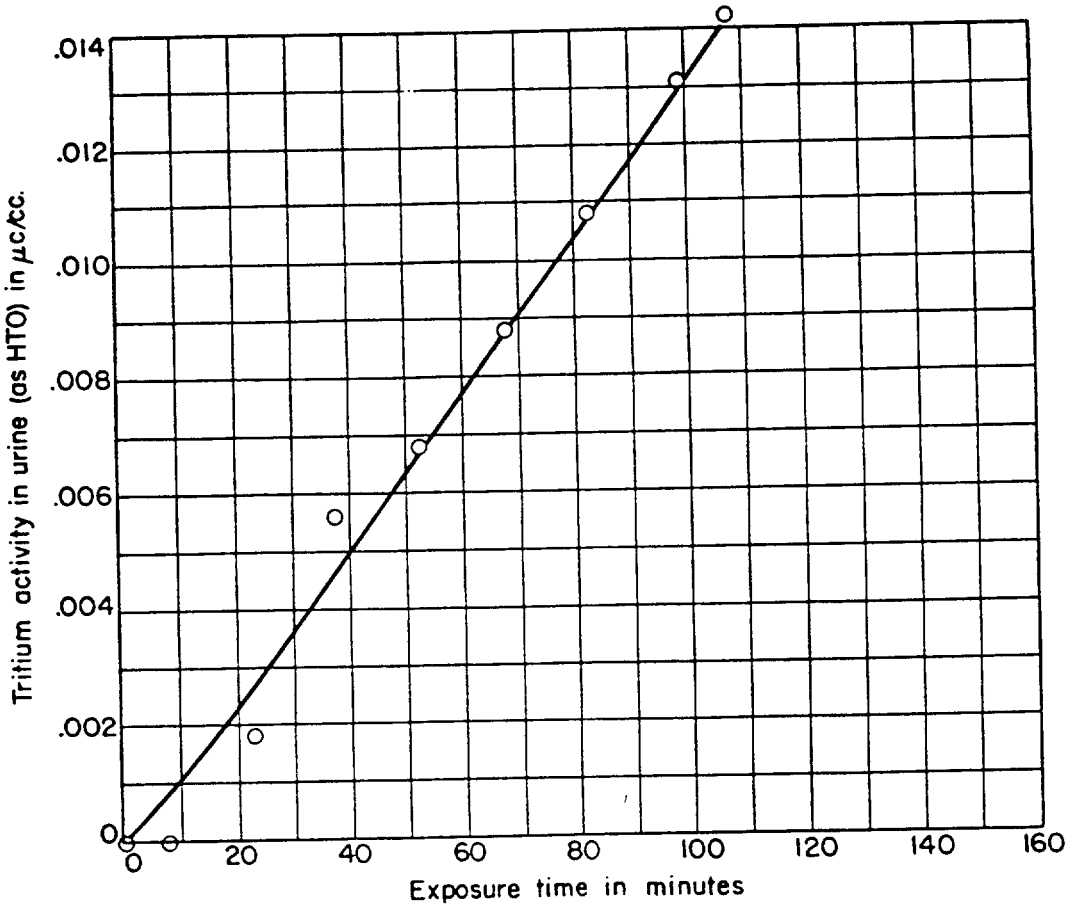

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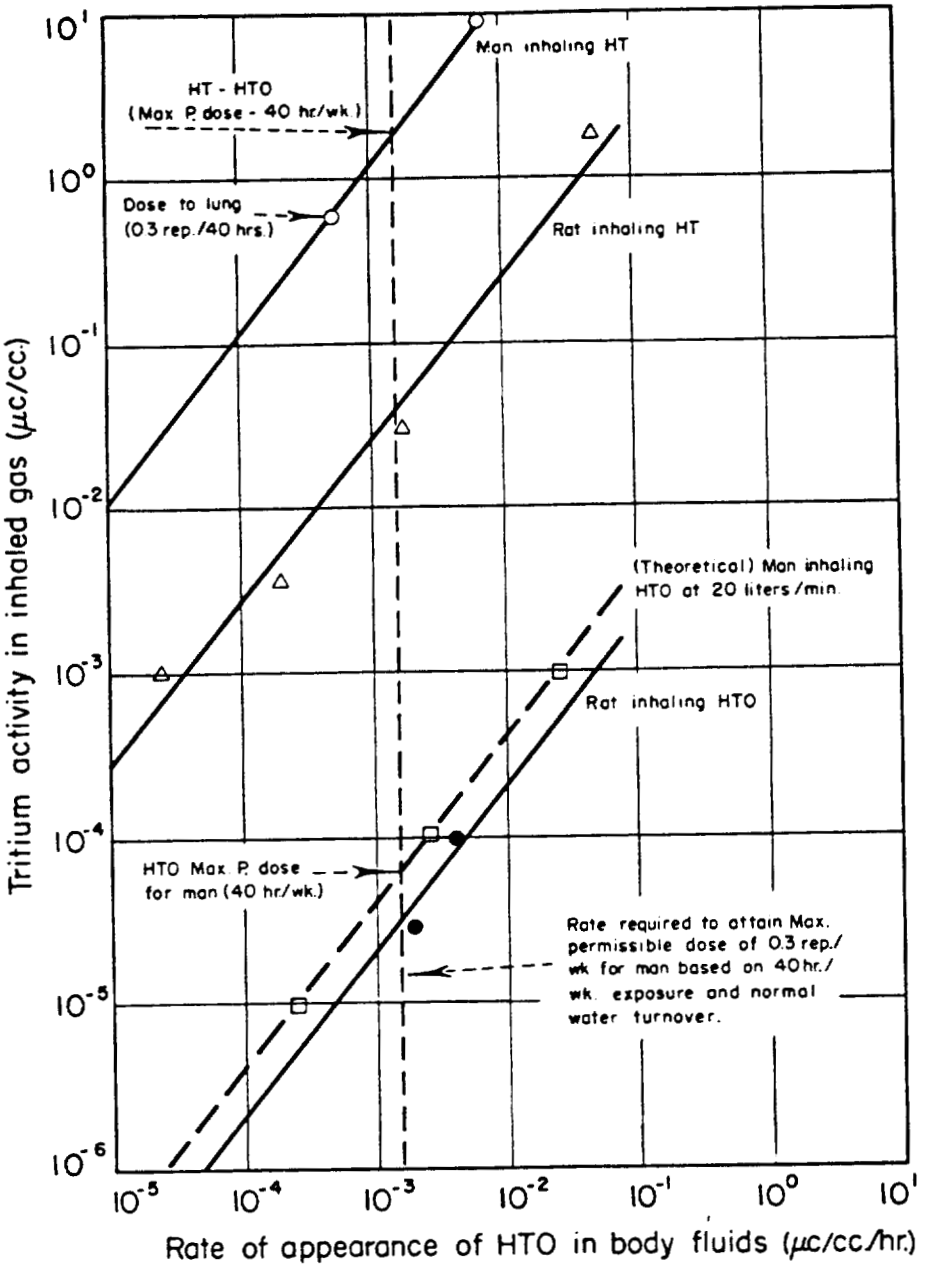

FIG. 10 - Maximum permissible dose of Tritium for man based on a 40 hr/wk. Exposure to HT or HTO in inspired air.

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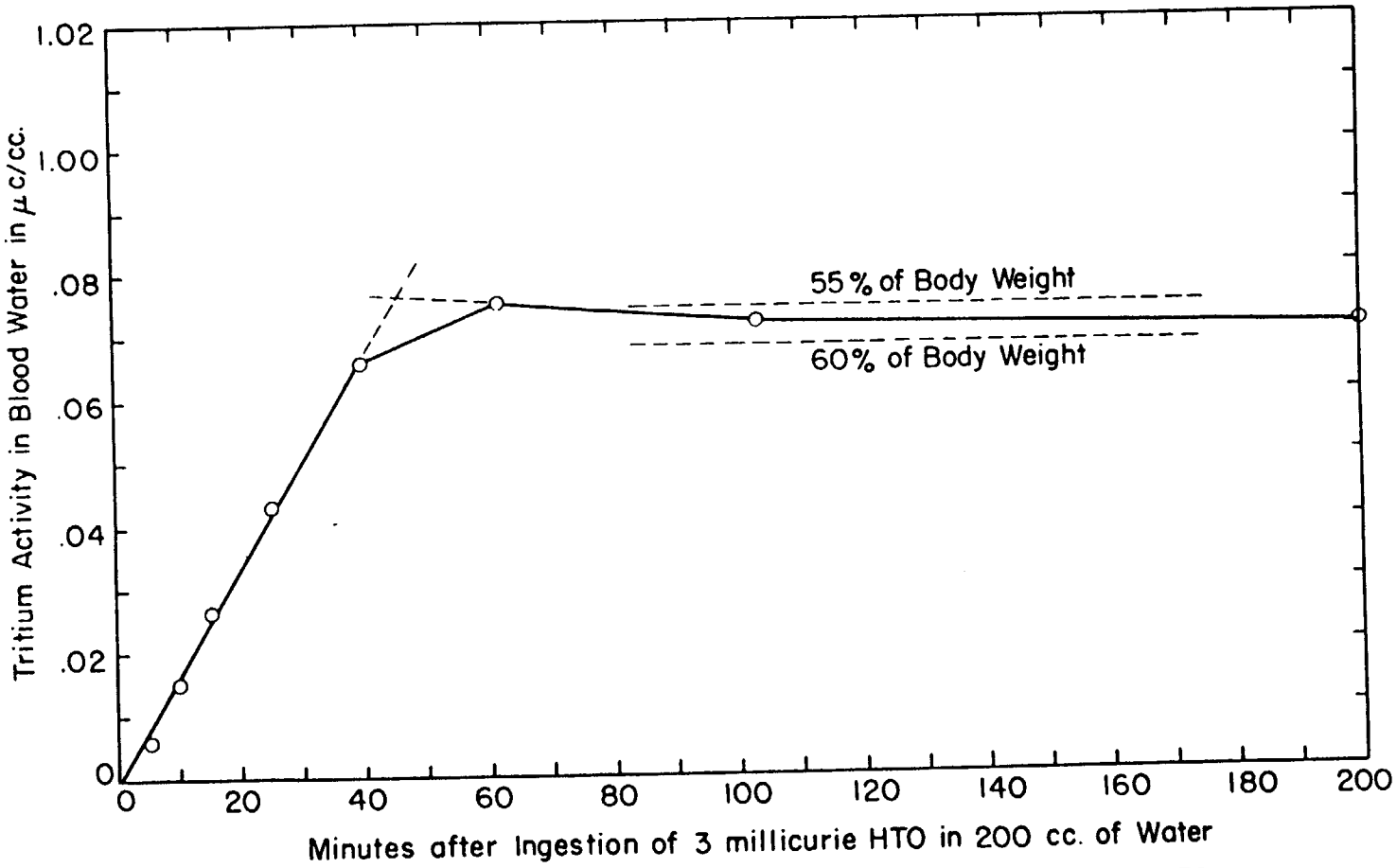

FIG.11 - Tritium Uptake in Blood Water following Ingestion of HTO
(MAN - Wt. 73.5 Kg.)

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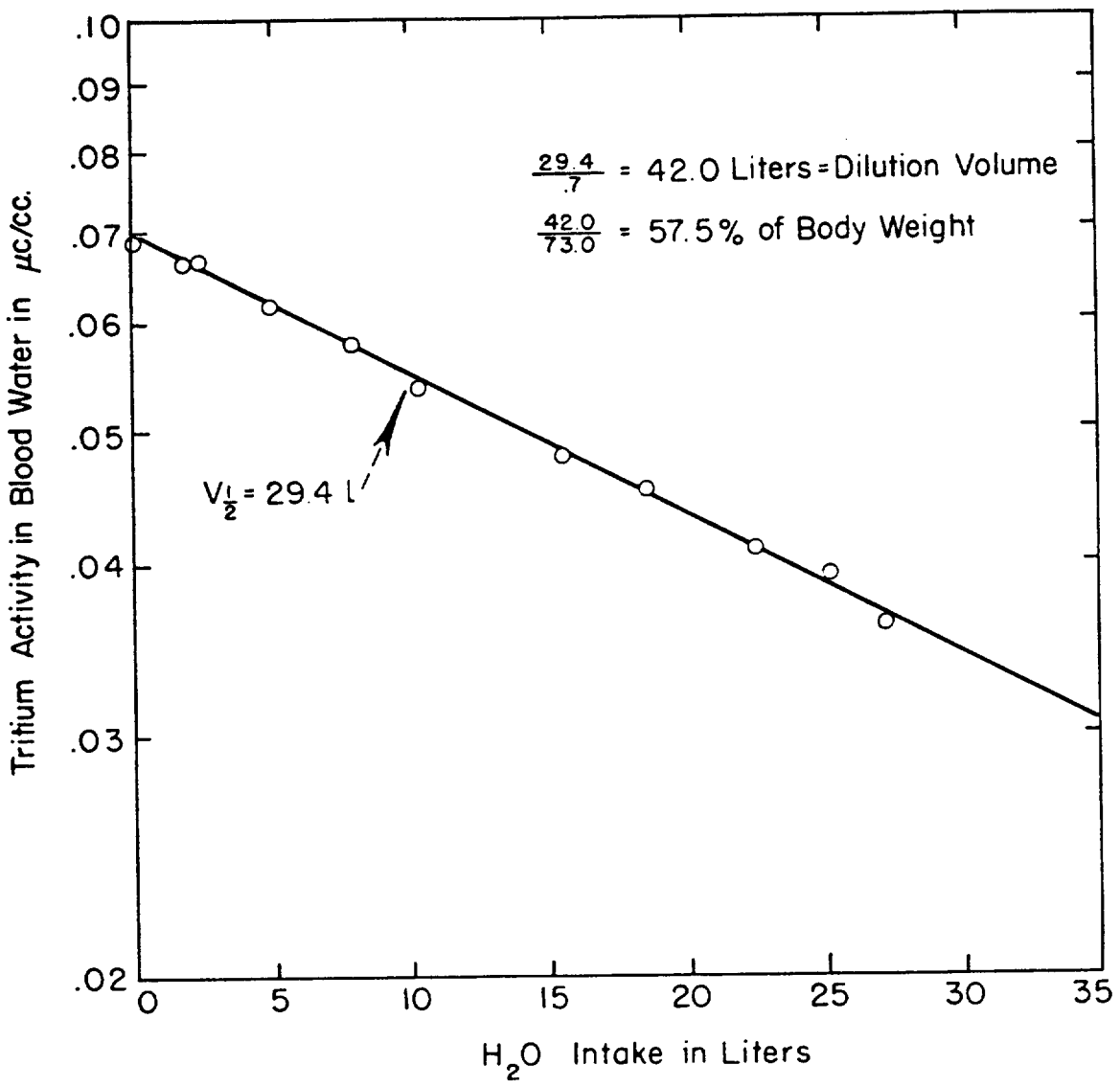

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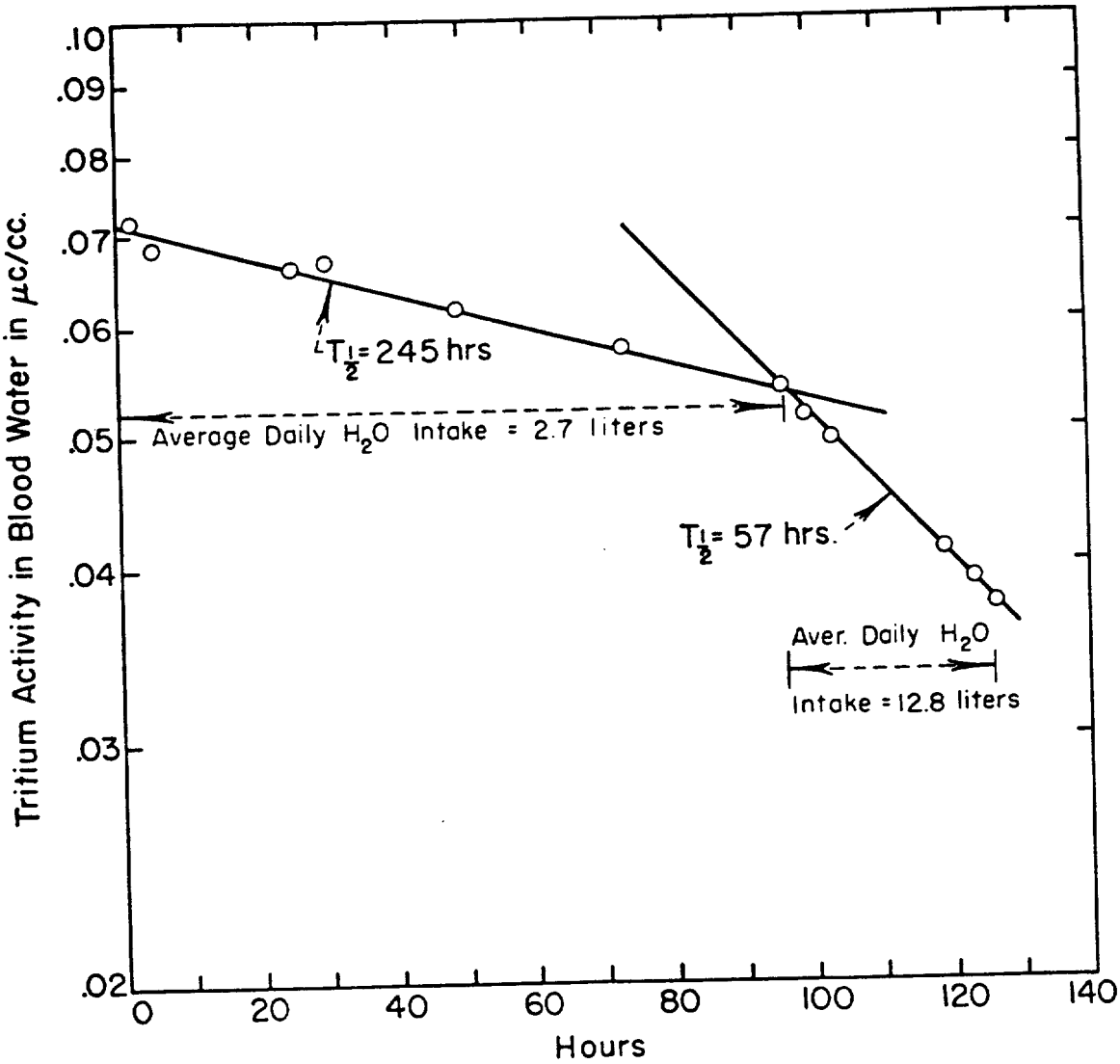

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