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THE DISTRIBUTION AND EXCRETION OF URANIUM IN MAN

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The cooperative study by the Department of Neurosurgery at Massachusetts General Hospital and the Health Physics Division at Oak Ridge National Laboratory has 2 objectives. The first is to obtain data on the excretion of uranium and its distribution in tissues for calculation of Maximum Permissible Concentrations in the body, urine, air, and drinking water of man. The second, which will not be discussed here, is to determine the potentialities which enriched uranium offers in therapy of inoperable brain tumors.

Data on the distribution and excretion of uranium in man are needed for the purpose of determining the internal radiation exposure of production workers who, through handling enriched uranium for long periods of time (10 to 13 years), have inhaled the dusts, mists, and fumes of this material and thus have uranium stored in their bodies. The conclusion that these workers have stored uranium arises from studies of many samples of air they inhale and their excreta. Air samples have shown that the enhanced material is present in measurable quantities, and characterization of the particle sizes places them in the range for penetration into and retention in the lower passages of the lung. Samples of urine reveal variable quantities of uranium. When workers are isolated from the work areas for months, measurements of their urine have shown that the levels drop rapidly after the cessation of exposure. In 1 month the levels fall to one-half, but after reaching this point they decrease more slowly. These findings support the conclusion that the workers' bodies contain stored material.

For the past several years in the Y-12 production area, it has been the practice to remove employees from uranium operations when their cumulative internal exposure exceeds the maximum permissible exposure. The cumulative internal exposure is determined by converting the uranium excreted in the urine into rem delivered to the body. This is accomplished with the following equation

$$(1) \quad \text{rem} = \frac{0.3}{7 \times 70} \sum_i \Delta t_{i-1} d_i$$

Here, d_i is the d/m excreted per day, while Δt_{i-1} is the time interval between measurements. The conversion factor outside of the summation sign merely says that the MPC for urine, 70 d/m/day, corresponds to the elimination from the body when it contains that amount to deliver 0.3 rem per week. This value, 70 d/m/day, is based on the lung as the critical organ and, therefore, corresponds to exposure to insoluble compounds of uranium. When exposure is to soluble types of compounds, the MPC for urine is 80 d/m/day, a negligible difference from the 70 d/m/day.

Figure 1 shows a graph of the cumulative internal exposure for a production worker. Urinary uranium measurements were converted with equation (1). The absorbed dose in rem is plotted on the ordinate while the time is plotted along the abscissa. The Maximum Permissible Exposure line is plotted for comparison. Note that the worker is in excess of the MPE line. His measurements show that he has an absorbed dose of 130 rem and that he should have only 85 rem. His exposure was terminated in 1954 by removing him from the enriched uranium operations and placing him in other work. He cannot return to the area until his exposure is on or below the MPE

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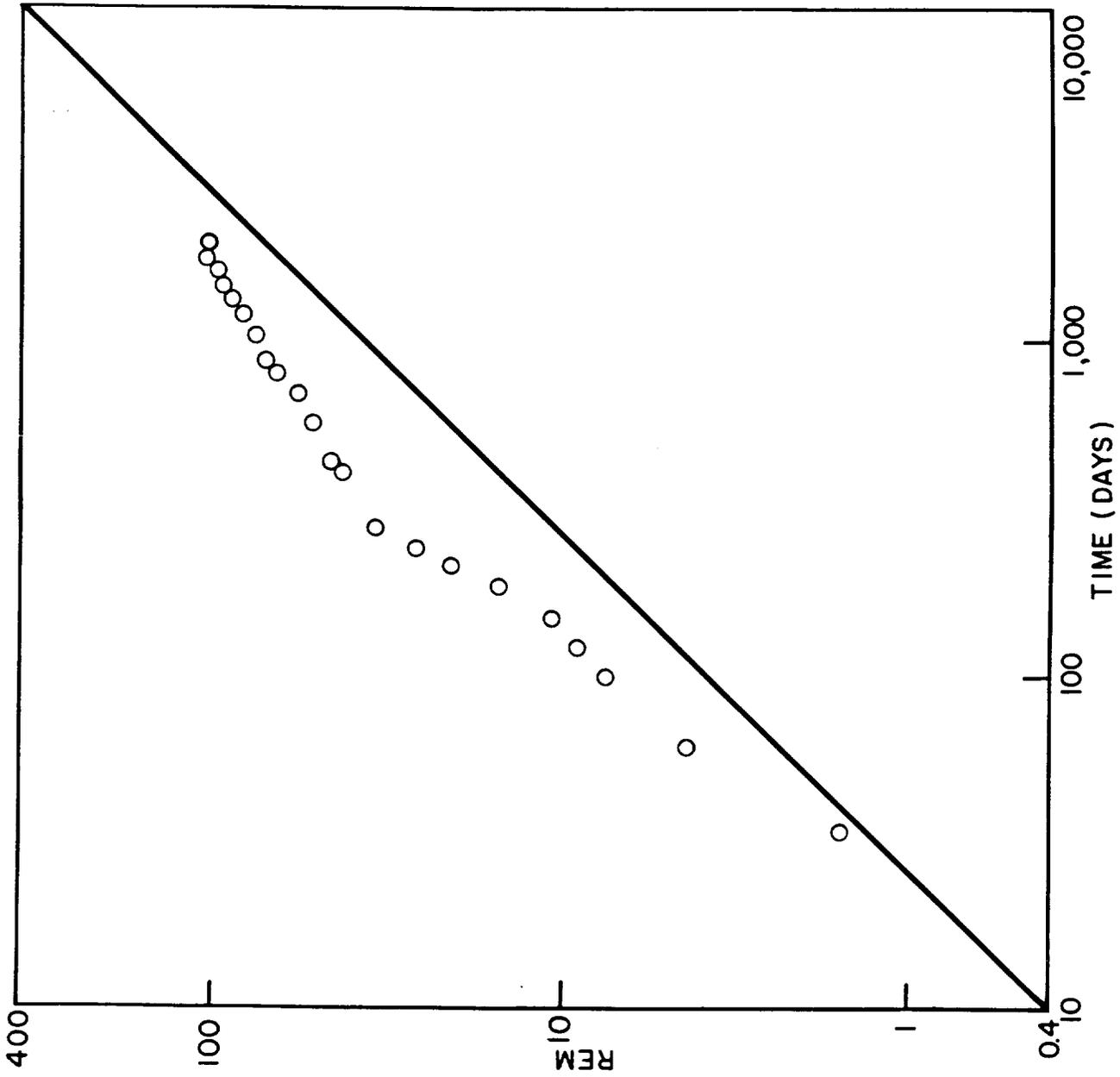


Figure 1. PLOT OF REM TO BODY BASED ON LUNG AS THE CRITICAL ORGAN - ESTIMATED FROM URINARY EXCRETION OF A PRODUCTION WORKER

line. It is estimated that 10 to 15 years will be required to reach this line.

This is not a typical case for production employees, but the highest case on record. There are many others who have been transferred from the uranium operation on this basis; in fact, about 35 have been removed in order to reduce their cumulative internal exposure below the MPE. This method for limiting internal exposure is not different from the practices for limiting external exposure. The philosophy behind its application is noted to be the same. However, the way in which the internal dose is obtained depends upon a factor which is not inherent in problems of external exposure. A reliable measure of internal radiation dose depends upon knowledge of the rate of elimination of uranium from the human body. These exposure cases dictate the need for human measurements. Our value of 70 d/m/day is based upon experimental measurements in dogs and rats.

In an effort to obtain human data for the calculation of MPC's for enriched uranium, the cooperative study of the distribution and excretion in man was initiated several years ago. To date, 11 terminal brain tumor patients have been injected with U-233 and enriched uranium. Many biopsy and autopsy samples have been obtained. All the patients have expired and autopsies were obtained on 9. We shall discuss the results of 6 of these patients here.

At the time of injection all the patients were without evidence of general pathological processes other than their cerebral disease. With the exception of 1 patient, who lived 17 months after injection, all were in a coma or semi-coma. They received the usual hospital care for comatose patients, consisting of indwelling catheters and feeding by gastric tube every 2 hours, which was at times augmented with intravenous fluids. All patients were administered uranium intravenously. Nine received uranyl nitrate hexahydrate compound buffered with a sodium acetate solution, while 2 received the compound UCl_4 . The pH of the injection solution ranged from 5.5 to 6.0. Samples of blood, urine, and spinal fluid were obtained every hour during the first 24 hours after injection. Thereafter, blood and urine samples were obtained every 12 hours during the first week, then once per week until expiration.

Figure 2 shows the blood levels plotted versus time. On the ordinate is the percent of injected dose per 10,000 milliliters of blood, while the abscissa is the time of measurement. Patients I through VI were administered the hexavalent state in amounts ranging from 4 to 50 mgms of metal. Note that Patient VII, who was administered 50 mgms of tetravalent uranium, is displaced above the other patients' values. Patient VIII was also injected with 50 mgms but he decreases along the same path as patients who received hexavalent injections. This figure shows that uranium in the blood decreases rapidly. Within minutes after injection only 25 percent remains, while at 20 hours 99 percent has disappeared and only 1 percent remains. Beyond 20 hours the blood levels, shown in Figure 3, are noted to diverge. Patient VI, who received 50 mgms of U(VI), decreases more slowly than those who received amounts ranging from 4 to 15 mgms. Also, note the increased fluctuation as the levels subside. This variation is outside the limits of analytical error.

In Figure 4 the rate of urinary excretion shows clearly a correlation with dose in the first 5 hours. As the injection dose is increased, the levels initiate at lower ordinate values and then rise until they reach a maximum at 3 to 4 hours, when they decrease along a linear path of the power function law. The excretion of tetravalent uranium, Patients VII and VIII, is noted to describe a trend different from hexavalent excretion levels.

The fecal excretion of uranium may be said to be negligible regardless of the valence state injected.

Figure 5 summarizes the measurements made upon autopsy tissues. The bones and kidneys may be said to be the organs which are chiefly concerned with storing uranium. It can be said also that the percent of injected dose in these 2 organs is not significantly different. Since the kidney is the smaller organ, it receives the greater radiation insult. Consequently, it is chosen as the critical organ.

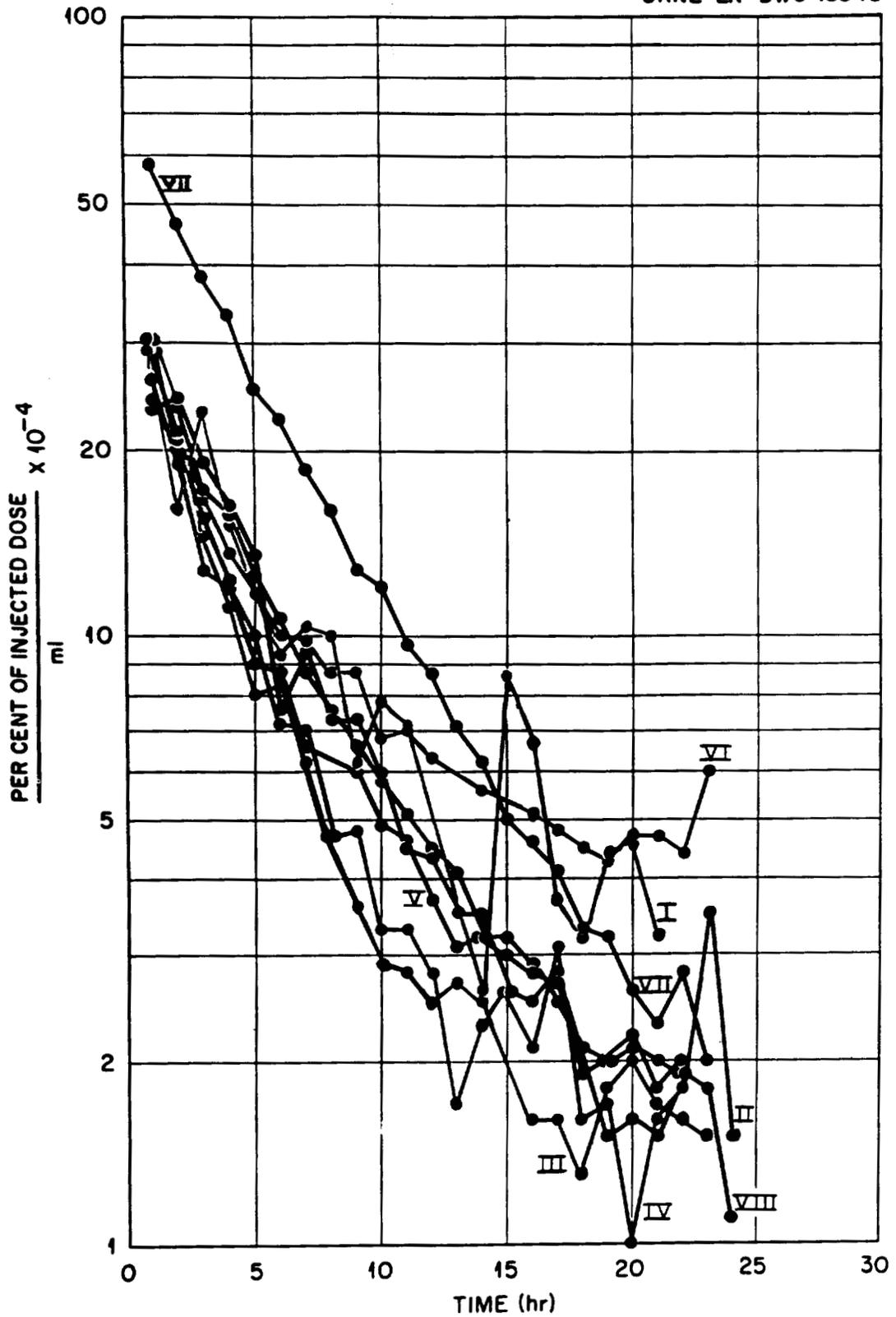


Figure 2. PERCENT OF DOSE PER MILLILITER OF BLOOD DURING FIRST DAY FOLLOWING INTRAVENOUS INJECTION FOR 8 TERMINAL BRAIN TUMOR PATIENTS

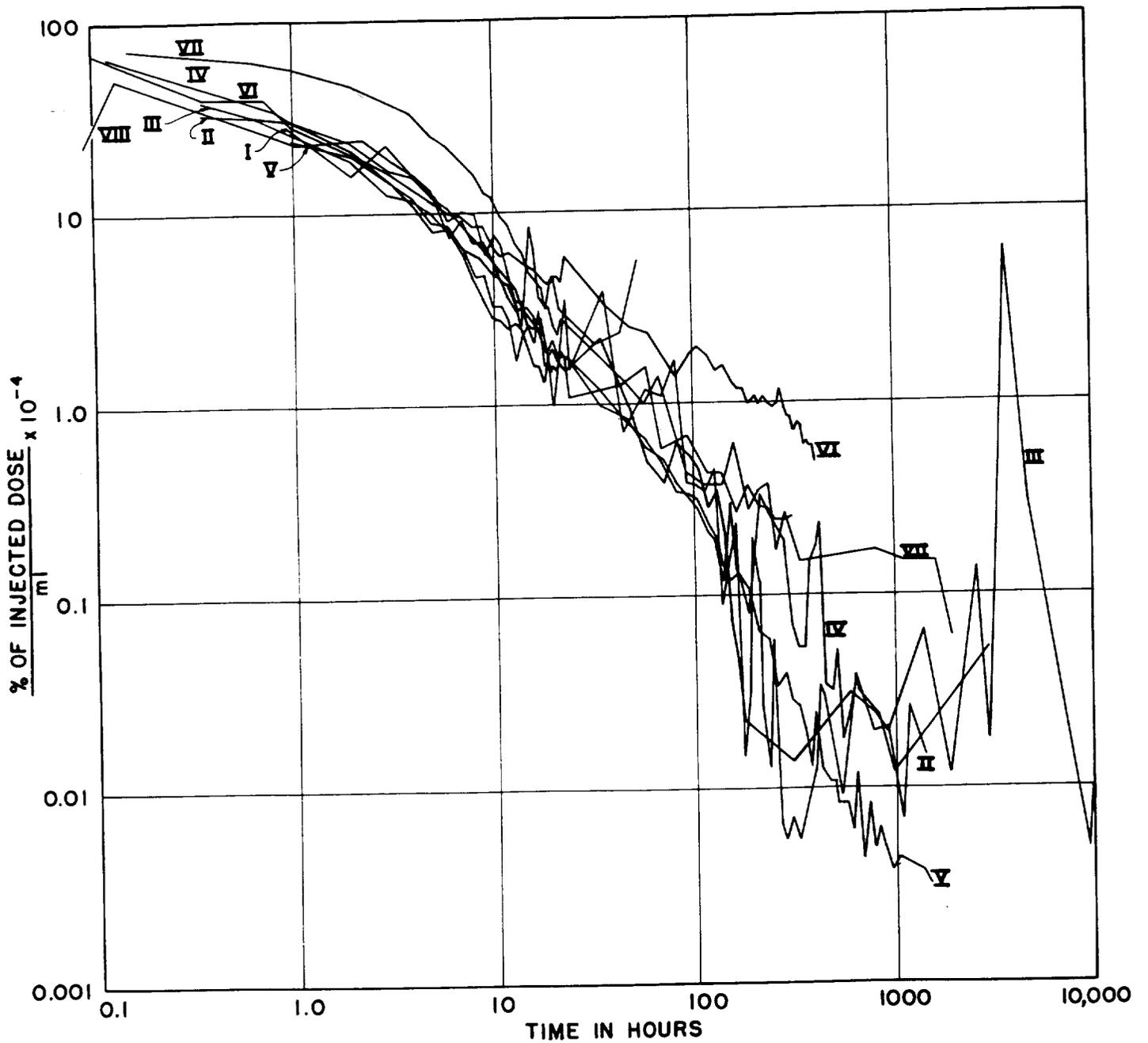


Figure 3. PERCENT OF DOSE PER MILLILITER OF BLOOD FOR 8 TERMINAL BRAIN TUMOR PATIENTS FOLLOWING INTRAVENOUS INJECTION

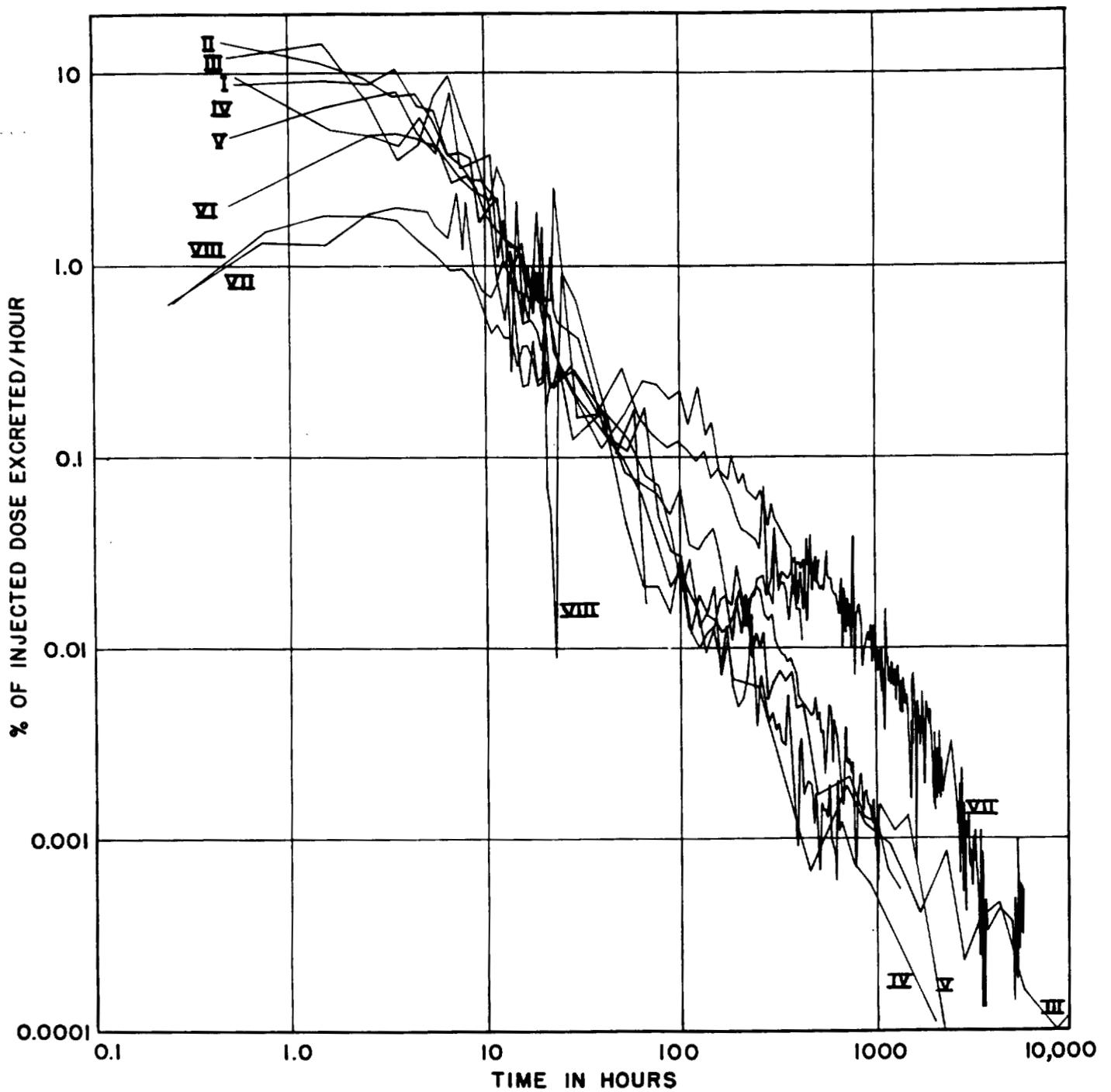


Figure 4. URINARY RATE OF EXCRETION FOR 8 TERMINAL BRAIN TUMOR PATIENTS FOLLOWING INTRAVENOUS INJECTION

INJECTION: $UO_2(NO_3)_2 \cdot 6H_2O$

EXPIRATION TIME IN DAYS		2.5	18	74	139	566
ORGAN OR TISSUE	GRAMS					
BONE	7,000	10.0	4.9	1.4	0.6	1.3
KIDNEY	300	16.6	7.2	0.7	1.2	0.4
MUSCLE	30,000	1.2	2.1	0.9	0.3	0.06
SKIN AND SUBCUTANEOUS TISSUES	6,100	1.8	1.0	0.1	0.06	-----
FAT	10,000	0.6	0.6	-----	-----	0.04
RED MARROW	1,500	-----	-----	0.02	0.03	0.1
YELLOW MARROW	1,500	-----	-----	-----	-----	-----
BLOOD	5,400	1.0	0.2	0.005	0.002	0.004
LOWER LARGE INTESTINE	150	-----	-----	-----	-----	-----
STOMACH	250	0.88	0.02	0.003	0.001	0.001
SMALL INTESTINE	1,100	0.2	0.2	0.03	0.01	0.006
UPPER LARGE INTESTINE	135	-----	-----	-----	-----	-----
LIVER	1,700	1.8	1.1	0.2	0.2	0.05
BRAIN	1,500	-----	-----	-----	-----	-----
LUNGS	1,000	0.5	0.4	0.03	0.02	0.008
LYMPHOID TISSUE	700	-----	-----	-----	-----	-----
HEART	300	0.06	0.02	0.003	0.006	0.002
SPLEEN	300	0.6	0.2	0.1	0.02	0.006
URINARY BLADDER	150	0.03	-----	0.002	0.001	0.0003
PANCREAS	70	0.7	0.008	0.008	0.0006	0.0004
SALIVARY GLANDS	50	-----	-----	-----	-----	-----
TESTES	40	-----	0.01	0.008	0.002	0.002
SPINAL CORD	30	-----	-----	-----	-----	-----
EYES	30	-----	-----	-----	-----	-----
THYROID GLAND	20	-----	0.003	0.0002	0.0001	0.0002
TEETH	20	-----	-----	-----	-----	-----
PROSTATE GLAND	20	-----	0.003	0.0004	0.0004	0.0001
ADRENAL GLAND	20	0.02	0.01	0.003	0.001	0.0004
THYMUS	10	-----	-----	-----	-----	-----
MISC. TISSUES (BLOOD VESSELS, CARTILAGE, NERVES, ETC.)	390	0.3	0.2	0.04	0.002	0.002
URINE (% OF DOSE ACCUMULATED)		61	63	92	84	98.2
BODY CONTENT = 100-% IN URINE		39	37	8	16	1.8
TOTAL IN TISSUES						

Figure 5. PERCENT OF INJECTED DOSE PER STANDARD MAN ORGAN OR TISSUE FOR 5 TERMINAL BRAIN TUMOR PATIENTS

These human findings can be compared with the results of small animal experiments. The notable differences are:

1. In small animals, U(VI) is stored chiefly in bone. From the human data it can be seen that bone and kidney store identical amounts of uranium.
2. The biological half-life for uranium in rat kidney is ~ 4 to 6 days. From these data, averaged over a 70-year period, the biological half-life is 300 days.
3. The disappearance of U(VI) and U(IV) from the bloodstream of humans is slower. In rats, 99 percent disappears in as little as 2 hours. Our data reveal that 20 hours are required.
4. In rats, two-thirds of the injected uranium is excreted in 24 hours. On the average, 70 percent is excreted by these patients. However, a correlation with dose appears to exist. Fifty percent of the injected dose is excreted when 50 mgms are injected; 84 percent when 4 mgms are injected.
5. Small animals, when injected with tetravalent salts of uranium, excrete sizeable amounts, 40 percent of the injected dose, in feces. Humans excrete negligible amounts via the G.I. tract.

We have attempted analysis of this dynamic process of distribution and excretion of U(VI) with a linear model shown in Figure 6. This model was based on small animal distribution and excretion data. It permits one to obtain estimates of the amounts of uranium in the chief organs as a function of time. The procedure for its application is to fit the excretion data with 3 exponential terms, thereby determining the parameters of the distribution. This model has been applied to the distribution and excretion data of the second patient in order to illustrate its use. The results of this application appear in Figure 7. Two curves band the excretion measurements to include the error in estimating the parameters. When these 2 sets of parameters are operated upon with the procedure dictated by this linear model, the percent of injected dose may be estimated for the organs. Note in Figure 8 that the model underestimates the percent of injected dose appearing in the kidneys.

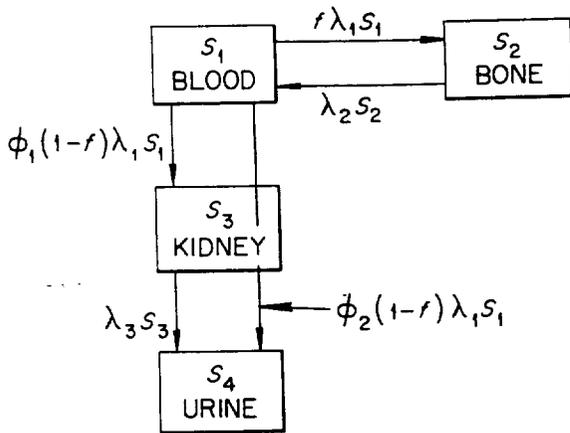
This model is presently being modified to give closer agreement with these human experimental results. It appears that better agreement with the experimental data will be obtained by incorporating a mechanism to simulate the diffusible-non-diffusible complex formation in the bloodstream and also to include a pathway from kidney back to blood, thereby simulating reabsorption from the tubules. These modifications are presently being made.

The power function model has been applied to these human data. The excretion measurements were expressed in terms of fraction of injected dose excreted per hour and plotted versus hours. The best fitting equation was found by least squares to be $0.343 t^{-3/2}$. Figure 9 shows the excretion measurements plotted together with the 95 percent confidence limit of the power function. The outermost confidence limits correspond to the error in a single measurement, while the innermost limits are those for an average measurement. Note that there is a large error associated with a single measurement. The range is wide; a factor of 10 defines the ratio of the upper to the lower limit.

Integrating the excretion equation from time t to infinity yields $0.14 t^{-1/2}$ (days), the equation for retention in the body. An interesting point for concern arises when we compare this power function estimate with the measured retention. We define measured retention in the body as the difference between the amount excreted and the amount injected. Figure 10 shows the graph of the measured retention for the patients plotted versus the time they expired, together with the power function estimate. Also plotted on this graph is the percent of injected dose in kidneys and bones of the patients. It can be seen that the power function estimate of retention agrees more closely with the organ burdens than with the measured retention values. The greatest discrepancy occurs

Figure 6

THE MODEL:



THE DIFFERENTIAL EQUATIONS:

BLOOD

$$\frac{dS_1}{dt} = \lambda_2 S_2 - \lambda_1 S_1$$

BONES

$$\frac{dS_2}{dt} = f \lambda_1 S_1 - \lambda_2 S_2$$

KIDNEY

$$\frac{dS_3}{dt} = \phi_1(1-f)\lambda_1 S_1 - \lambda_3 S_3$$

URINE

$$\frac{dS_4}{dt} = \phi_2(1-f)\lambda_1 S_1 + \lambda_3 S_3$$

THE INTEGRATED EQUATIONS:

BLOOD

$$S_1(t) = \frac{I}{\mu_2 - \mu_1} \left[(\mu_2 - \lambda_1) e^{-\mu_1 t} + (\lambda_1 - \mu_1) e^{-\mu_2 t} \right]$$

BONES

$$S_2(t) = \frac{f \lambda_1 I}{\mu_2 - \mu_1} \left[e^{-\mu_1 t} - e^{-\mu_2 t} \right]$$

KIDNEY

$$S_3(t) = \frac{\phi_1(1-f)\lambda_1 I}{\mu_2 - \mu_1} \left[\frac{\mu_2 - \lambda_1}{\lambda_3 - \mu_1} e^{-\mu_1 t} + \frac{\lambda_1 - \mu_1}{\lambda_3 - \mu_2} e^{-\mu_2 t} + \frac{(\lambda_2 - \lambda_3)(\mu_2 - \mu_1)}{(\lambda_3 - \mu_1)(\lambda_3 - \mu_2)} e^{-\lambda_3 t} \right]$$

URINE

$$S_4(t) = I - \frac{(1-f)\lambda_1 I}{\mu_2 - \mu_1} \left[\frac{(\mu_2 - \lambda_1)(\lambda_3 - \phi_2 \mu_1)}{\mu_1(\lambda_3 - \mu_1)} e^{-\mu_1 t} + \frac{(\lambda_1 - \mu_1)(\lambda_3 - \phi_2 \mu_2)}{\mu_2(\lambda_3 - \mu_2)} e^{-\mu_2 t} + \frac{\phi_1(\mu_2 - \mu_1)(\lambda_2 - \lambda_3)}{(\lambda_3 - \mu_1)(\lambda_3 - \mu_2)} e^{-\lambda_3 t} \right]$$

APPLICATION OF MODEL:

GIVEN AN EXCRETION EQUATION

$$\text{URINE} = I - \sum_1^3 a_i e^{-a_i t} \quad \text{WHERE} \quad \sum_1^3 a_i = I$$

THE ROOTS OF

$$x^2 - \sum_1^3 \left(\frac{1-f}{a_i} \right) x + \frac{\sum_1^3 a_i I}{\pi a_i} = 0$$

ARE $1/\lambda_2$ AND ϕ_2/λ_3 , WITH $\mu_1 < \lambda_3 < \mu_2$

$$\lambda_1 = \mu_1 + \mu_2 - \lambda_2$$

$$(1-f) = \frac{\mu_1 \mu_2}{\lambda_1 \lambda_2}$$

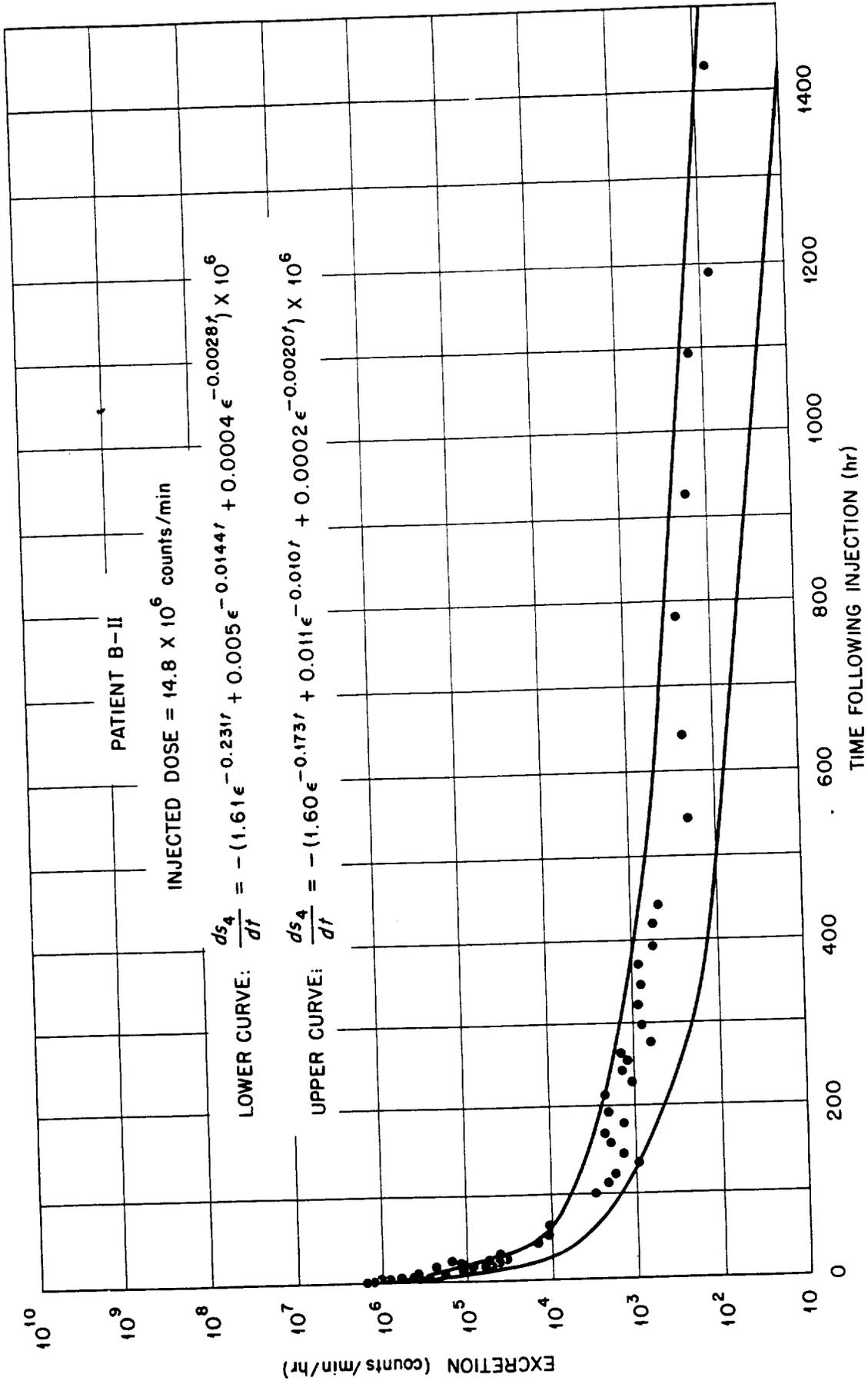


Figure 7

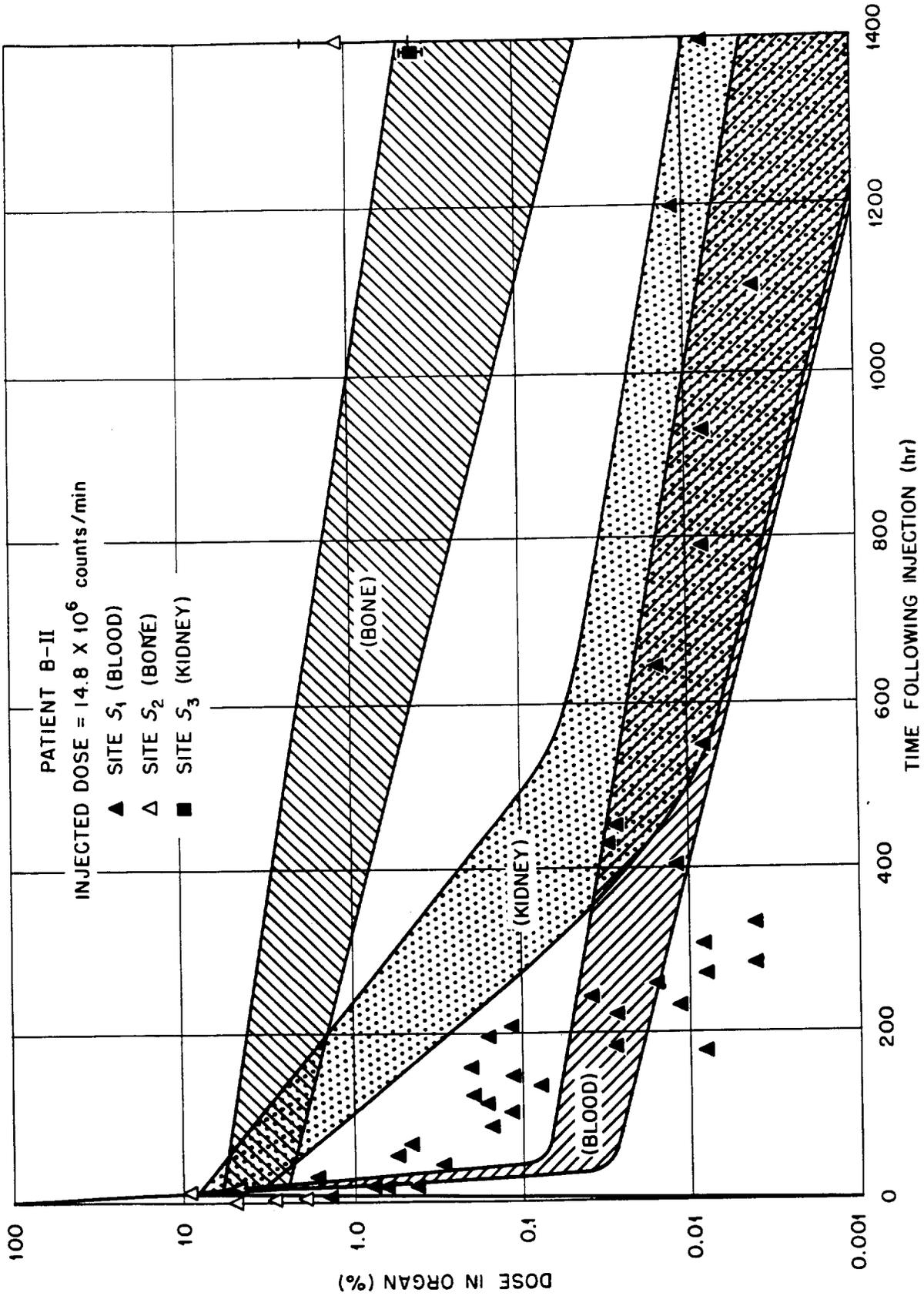


Figure 8

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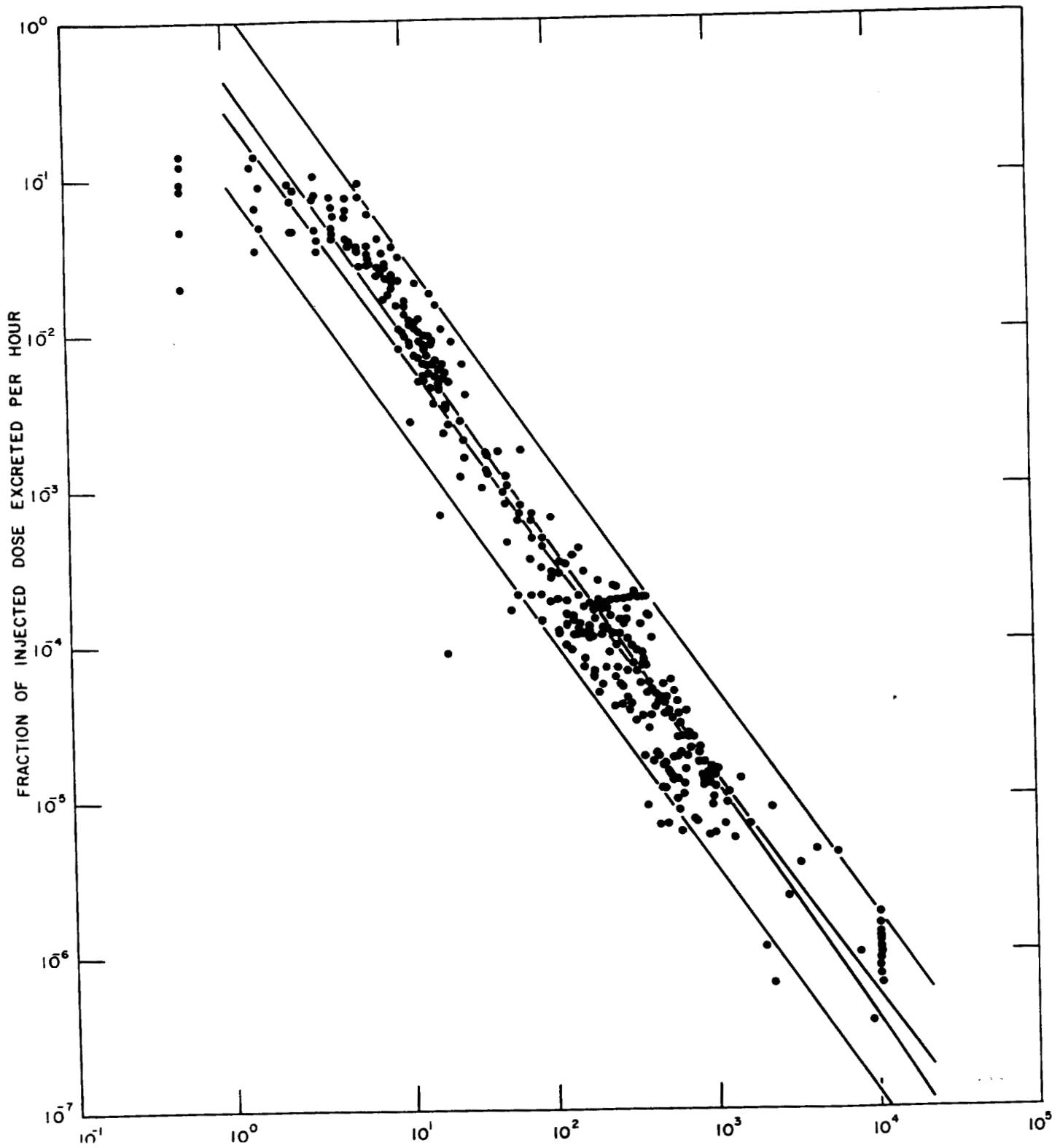


Figure 9. FRACTION OF INJECTED DOSE EXCRETED PER HOUR FOR 6 TERMINAL BRAIN TUMOR PATIENTS

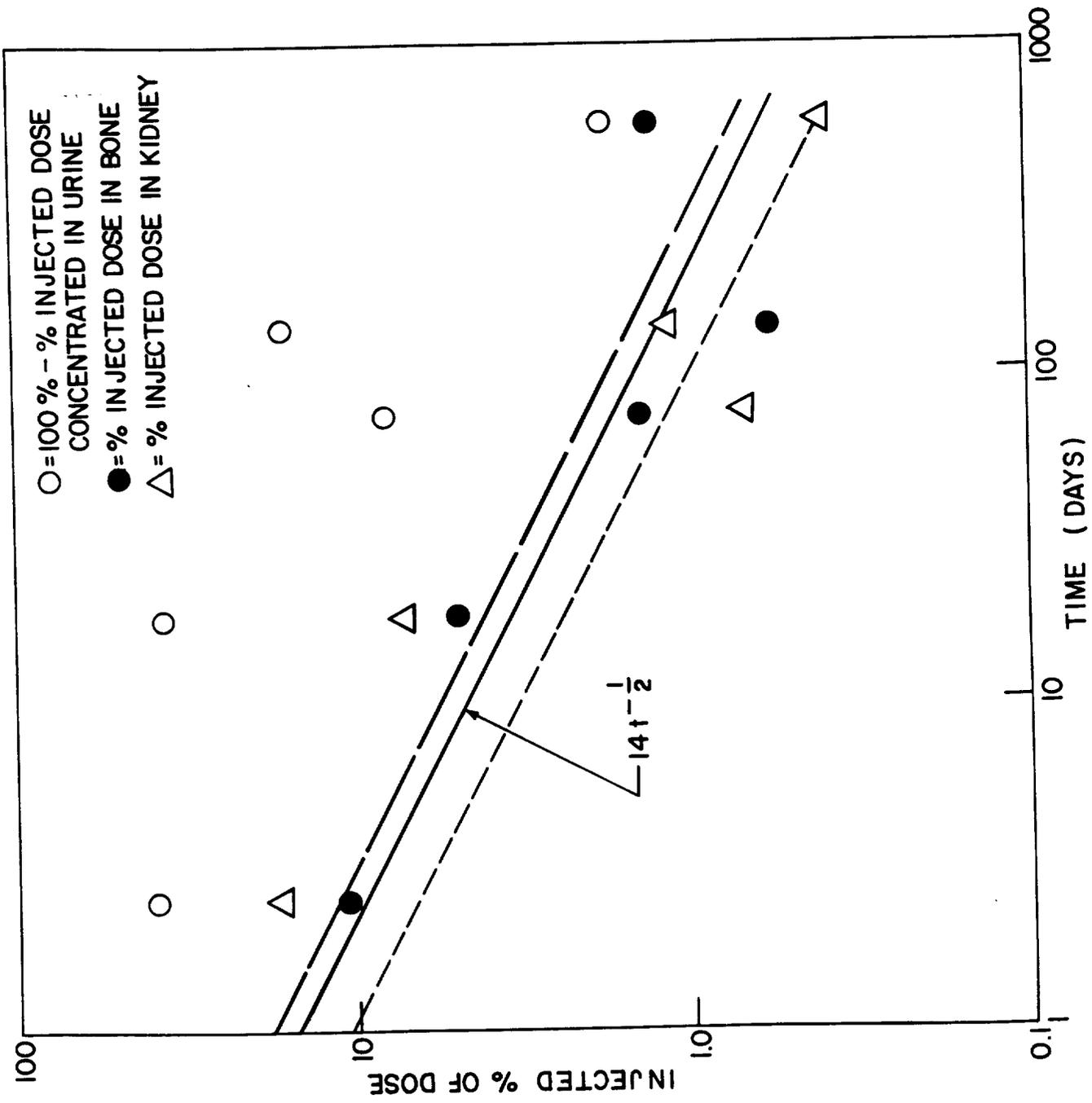


Figure 10. COMPARISON BETWEEN CALCULATED AND MEASURED BODY BURDEN AND ORGAN BURDEN

before 200 days have elapsed. At 2.5 days the measured value for Patient I is 36 percent while the estimated value is 10 percent; at 18 days the measured value is 39 percent, in poor agreement with the estimated value of ~ 4 percent; and so on. At 566 days, the best agreement is demonstrated. The measured retention here is 1.8 percent (Patient III), while the estimated value is ~ 0.6 percent. It is believed that the disparity is a result of the different elimination patterns shown by each patient, which in turn can be correlated with the size of the dose injected.

Since the power function estimates the burdens of kidneys and bones with little disparity, it may be used for calculations of MPC's via the method of Norris, et al.¹ Figure 11 shows some tentative MPC values for air and urine. On the left side MPC's for air appear and to the right is the value for urine. The equations for retention in the critical organ, $R(t)$ for a single injection and excretion from the body for a single injection appear at the top of Figure 11. To convert these into continued injection, one multiplies the equations by the differential time, integrates from $t = 1$ day to t days, adds to this the fraction in the organ at day 0, and multiplies the whole expression by the continuous inhalation level. This obtains qf_2 , the number of μc in the critical organ which delivers 0.3 rem/wk to it. Substituting for qf_2 the value 0.006 μc and solving for MPC at 10^4 days, we get $2 \times 10^{-4} \mu c/\text{day}$; and converting to inhalation exposure, we get $4 \times 10^{-11} \mu c/\text{cc}$, which agrees closely with the current value of $3 \times 10^{-11} \mu c/\text{cc}$.²

To calculate the permissible excretion level the same procedure is followed, yielding 355 d/m/day, which is higher than the currently employed value of 70 d/m/day. Thus, a factor of 5 is indicated.

In summary, we can say that

1. The critical organ for radiation insult from storage of enriched uranium is the kidney when exposure is to a soluble substance.
2. The disappearance of uranium from the body shows a slight dependence upon the amount injected into the bloodstream.
3. The urinary excretion data can be described using the power function law. Integration of this function yields the retention as a function of time. The calculated retention agrees more closely with the retention in the critical organ than with retention in the body.
4. A tentative MPC for exposure to soluble compounds is calculated to be $4 \times 10^{-11} \mu c/\text{cc}$ on the basis of the power function equation.
5. A tentative MPC for urine is calculated using the power function law. The calculated value is 355 d/m/day, a factor of 5 greater than the present value employed, thereby indicating a margin of safety for exposure to soluble compounds.

ACKNOWLEDGMENTS

We wish to acknowledge the technical assistance of N. L. Gillum and G. J. Dodson who performed numerous chemical analyses.

AIR

EQUATION FOR SINGLE INJECTION

$$R(t) = 0.14 t^{-1/2}$$

$$E(t) = 0.07 t^{-3/2}$$

EQUATION FOR CONTINUOUS INJECTION

$$\int_1^t R(t) dt = q = \text{MPC} [0.14 \int_1^t t^{-1/2} dt + 0.14]$$

$$q = \text{MPC} [0.28 (t^{1/2} - 1) + 0.14]$$

q = 0.006 μc FOR KIDNEY

$$\therefore \text{MPC} = \frac{0.006}{[0.28(t^{1/2} - 1) + 0.14]}$$

$$= 2 \times 10^{-4} \frac{\mu c}{\text{DAY}}$$

AT t = 10⁴ DAYS

$$\text{MPC}_0 = 4 \times 10^{-11} \frac{\mu c}{\text{cc}}$$

CURRENTLY ACCEPTED MPC₀ IS

$$3 \times 10^{-11} \mu c / \text{cc}$$

URINE

$$\int_1^t E(t) dt = \text{MPC} [0.07 \int_1^t t^{-3/2} dt + 0.69]$$

$$= \text{MPC} [0.83 - 0.14 t^{-1/2}]$$

$$= 2 \times 10^{-4} \frac{\mu c}{\text{DAY}} [0.83 - 0.14 t^{-1/2}]$$

AT t = 1

$$\text{EXCRETION} = 1.4 \times 10^{-4} \frac{\mu c}{\text{DAY}}, \text{ AT } t = 10^4$$

$$\text{EXCRETION} = 1.6 \times 10^{-4} \frac{\mu c}{\text{DAY}} = 355 \frac{\text{d/m}}{\text{DAY}}$$

Figure 11. TENTATIVE MPC VALUES

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