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THE DISTRIBUTION AND EXCRETION OF HEXAVALENT URANIUM IN MAN

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INTRODUCTION

This study was undertaken, first to determine the intravenous tolerance dose of fissionable uranium in man for its possible application to neutron capture therapy of brain tumors; and secondly, to obtain human data with which to describe the excretion of uranium in urine and its relation to distribution in the body. This information is needed to permit a more realistic evaluation of occupational exposures in enriched uranium processing and fabrication plants. The study was a cooperative undertaking by the Health Physics Division, Oak Ridge National Laboratory, and the Department of Neurosurgery, Massachusetts General Hospital.

Previous investigations by W. H. Sweet, and others pointed out the use of the neutron capturing isotope, B^{10}, in the radiation therapy of intracranial tumors.[1,2,3] Their results, suggestive of temporary retardation of tumor growth in eight out of twenty-one patients, indicated that further exploration of neutron capture therapy was warranted. After careful theoretical evaluation of the clinical use of fissionable uranium, they concluded that its possibilities in capture therapy were worthy of investigation.

Some of the questions that arise out of consideration of this possibility are: 1) Will a high differential concentration of uranium in the tumor be achieved following intravenous administration? 2) Will a high differential concentration in the tumor persist long enough to permit effective exposure to thermal neutrons? 3) What is the absolute concentration

1026086

of uranium in neoplastic brain tissue and in other tissues? 4) What is the highest possible dose of fissionable uranium which can be intravenously administered without seriously affecting the patient?

Uranium is known to be nephrotoxic, but the dose required to produce toxic manifestations in man is not known. Small animal data show that a striking species variation exists, e.g., the mouse tolerates 100 to 200 times more uranium than the rabbit. The initial objective of this study, therefore, was to investigate the toxicity of uranium in man with a view to determining the highest intravenous injection dose.

This investigation provided a unique opportunity to obtain uranium distribution and excretion data on humans for application to a mathematical method of evaluating industrial exposures. A specific problem of great interest to industrial workers is the possible radiological effect of chronic exposure to the enriched uranium-contaminated dusts, smokes and fumes ever present in production plants. Heretofore, these exposures have been characterized by the arbitrary and limited monitoring techniques presently available to industrial health groups. Such methods are incapable of detecting evidence of biological significance in the case of continuous, long-term, low-level exposure to insoluble radioactive aerosols. For example, the body burden can not be determined, with any degree of confidence, on the basis of airborne-uranium measurements; neither is it possible to estimate concentration in critical organs on the basis of excretion measurements until a definite relationship between distribution and excretion is established. Here was a chance to obtain information on which to construct and test part of the evaluation method, i.e., the relationship between distribution and excretion of uranium as it leaves the circulation.

Although the primary justification for these experimental injections of uranium in man grew out of its theoretical value in neutron capture therapy, only the distribution and excretion portion of the study will be included here. The toxicological findings will be published by other authors at a later date.

METHODS

Selection and Care of Patients

The six patients selected for this study were in the terminal phase of severe irreversible central nervous system disease. Virtually all had brain tumors of a most malignant type. The ages of the patients were 26, 34, 39, 47, 60 and 63 years, and, aside from the central nervous system disease, they were in generally good physical condition without definite evidence of other pathological processes.

At the time of injection all patients were in coma and receiving the usual hospital care consisting of frequent turning, skin care, gastric tube feedings, catheter drainage and frequent tracheal suction. Three of the patients had tracheotomies.

The patients who did not terminate during the two to three week period following injection were transferred to a nursing home where they could still be closely observed.

1026087

Administration of Uranium

Preparation of Injection Solution. Pure uranium oxide (U_3O_8) was converted to nitrate ($UO_2(NO_3)_2$) by dissolving the oxide in an excess of nitric acid and evaporating to dryness. The resulting nitrate crystals were dissolved in distilled water and twice evaporated to dryness to eliminate final traces of nitric acid. The crystals were then dissolved and diluted to volume with distilled water. The solution was assayed at this point colorimetrically and by alpha count. The desired quantity of nitrate was then removed, placed in a rubber sealed container and autoclaved for sterility. A 0.4M sodium acetate solution was prepared and autoclaved. Equal volumes of each were combined shortly before the beginning of each study and the desired quantity removed for injection. All administrations were given at a pH of from 5.5 to 6.0. Except in the case of Patient I, all injection solutions were similarly prepared. In this case the uranium nitrate was placed in physiological saline and adjusted to the proper pH with sodium hydroxide and hydrochloric acid.

Following the injection, the syringe employed in the administration was used to deliver a replicate volume of the injection solution to a flask for quantitative analysis. This procedure accounted for any volume errors as a result of inaccurate markings on the syringe.

Injection Procedure. The uranium was injected intravenously in all the patients. The procedure consisted of first starting an intravenous of normal saline in an antecubital vein. After careful inspection to preclude any possibility of extravasation, the uranium solution was injected over a period of 10 to 15 seconds through the rubber intravenous tubing. In the first patient this was done through a metal 3-way stopcock. However, a small amount of the solution was lost because of leakage from the stopcock. In the second patient a glass 3-way stopcock was employed, but during the injection the glass side arm broke resulting in the loss of a small, but significant, amount of the solution. Thereafter, the injections were made by inserting the syringe needle into the rubber I.V. tubing. In all cases the syringe was irrigated 4 or 5 times with saline from the I.V. bottle prior to its removal from the tubing.

Collection of Specimens

Blood specimens of 1 to 3 milliliters were taken by phlebotomy in the arm not used for the uranium injection. During the first 24 hours, hourly specimens were taken; then at 12 hour intervals for several weeks, then at 24 hour intervals and, following transfer from the hospital, at 1 to 3 week intervals until expiration.

For the determination of initial bone uptake several bone biopsies were taken from the anterior tibia employing a 1/2 inch trephine through a small skin incision.

The urine samples were collected from indwelling catheters. During the first 24 hours they were collected at hourly intervals, or more frequently if the output was great; thereafter at 12 hour intervals for 2 to 4 weeks and finally 12 hour samples at 1 to 4 week intervals.

1026088

All feces specimens were collected during the time the patient remained under close observation in the hospital.

During the period of collection of samples for uranium determination numerous blood and urine specimens were taken for measurement pertinent to indices of chemical toxicity.

At the time of writing, 5 of the 6 patients have expired and permission for autopsy has been obtained on 4 of these. Samples of all body tissues were taken for uranium determination.

Preparation and Analysis of Specimens

Urine. Three 20 milliliter aliquots were removed from each specimen, when possible, and 20 milliliters of concentrated nitric acid were added to each aliquot. These solutions were reduced to dryness on a steam bath and shipped to the Oak Ridge National Laboratory for analysis.

Upon arrival at the Laboratory 20 milliliters of a hydrochloric-nitric acid solution (1:3 proportions) were added to each specimen bottle and allowed to stand until all the residue was in solution. The resulting solution was carefully rinsed with 0.1N nitric acid into a 100 milliliter beaker and evaporated to dryness. This acid digestion was repeated five or more times until a white residue resulted at dryness. A final digestion with 20 ml of nitric acid for chloride destruction was carried out.

Following evaporation, the residue was dissolved in 0.1N nitric acid and diluted to volume. Triplicate aliquots were removed from each volumetric dilution for electrodeposition[4] of the uranium and subsequent alpha counting.

Blood. The blood specimens were prepared in the same manner as the urine with the exception of the final nitric acid digestion. At near dryness, the sample was removed from the steam bath. The small quantity of acid and residue remaining was dissolved in 20 milliliters of distilled water and triplicate aliquots were removed for electrodeposition and subsequent alpha counting.

Soft Tissue Specimens of Less than 2 Grams Wet Weight. Soft tissue specimens (biopsy or autopsy) were weighed and muffled in platinum crucibles at 600° C for 24 hours. The ash was dissolved in 0.1N nitric acid and the entire volume analyzed by electrodeposition and alpha counting.

Feces, Bone, and Tissue Specimens Greater than 2 Grams Wet Weight. All specimens were wet weighed and muffled in platinum crucibles at 600° C for approximately 24 hours. Additional time was required for several specimens of bone to insure complete organic destruction. The resulting ash was weighed and analyzed for uranium using the aluminum nitrate-diethyl ether extraction procedure with subsequent evaporation in a stainless steel planchet for alpha counting.

Mathematical Interpretation of Data

A mathematical model, similar in structure to that designed by Teorell[5] for studying the tissue distribution of intravenously administered drugs, was designed to represent the distribution and excretion of uranium

1026089

following intravenous administration.[6] Its design, shown in Figure 1, was based on a simple diagram constructed by W. F. Neuman.[7] The values of f, O and λ were then taken from available research data on animals.[8] Only a few terms are used to represent the complicated metabolic processes in the four major compartments, the major premise being that these physiological processes are simple first order reactions.

The test of this model involves only the measured excretion and deposition values obtained in the experiment. After determining the excretion equation and the values of each parameter, it is possible to calculate the concentrations in each compartment for a comparison with the observed deposition values.

RESULTS

Blood Disappearance

Hexavalent uranium leaves the blood stream very rapidly. The blood values obtained in this experiment at varying time intervals after administration are presented in Figure 2. On the average, 99% of the injected dose is removed from the circulation in a matter of 20 hours, assuming uniform distribution at injection (time zero) and a blood volume of 7.14% of body weight. Once reduced, the blood values remain relatively constant until time of expiration.

Urinary Excretion

Concurrent with the fall of the blood-uranium level large quantities of uranium appear in the urine. Most of the excretion takes place in the first twenty-four hours after administration; thereafter, ever decreasing quantities are excreted. Essentially all uranium is excreted in the urine, since less than one percent of the injected dose is found in the feces. Figure 3 shows the urine excretion data obtained in this study. These data are presented as log-log plots for the purpose of comparing the excretion rates on an identical time scale. It will be seen in all cases that the excretion rate is non-linear over the total period of observation.

Distribution in Tissue

The percent of injected dose per gram of tissue found in tibia biopsies during the first 40 hours after administration is shown in Table I. These data indicate that the accumulation of the injected uranium ranges from 2×10^{-4} to 23×10^{-4} percent of injected dose per gram, the average for the first 24 hours being 10.1×10^{-4} percent. This corresponds to an initial deposition of 6.0 percent of the injected dose in bone assuming an average patient skeletal weight of 6000 grams.

In contrast to this value of initial deposition in the skeleton, are the autopsy values shown in Figure 4. Here the average skeletal content, in terms of percent of injected dose per gram, is plotted as a function of time. The data show that the initial deposition in bone, estimated by extrapolation, is 23.9×10^{-4} percent of injected dose per gram, or 14 percent of the injected dose. This is suggestive of a

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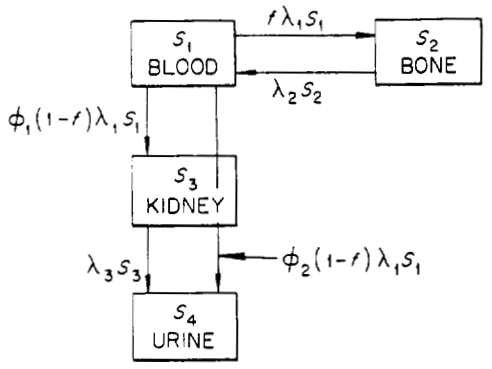
THE MODEL:



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

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

BONES

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

KIDNEY

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

URINE

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

APPLICATION OF MODEL:

GIVEN AN EXCRETION EQUATION

$$\text{URINE} = I - \Sigma_1^3 a_i \epsilon^{-\alpha_i t} \qquad \text{WHERE} \quad \Sigma_1^3 a_i = I$$

THE ROOTS OF

$$x^2 - \Sigma_1^3\left(\frac{1-\frac{a_i}{I}}{\alpha_i}\right)x + \frac{\Sigma_1^3 a_i \frac{a_i}{I}}{\pi\alpha_i} = 0$$

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

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

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

Fig. 1. A Model for the Distribution and Excretion of Hexavalent Uranium.

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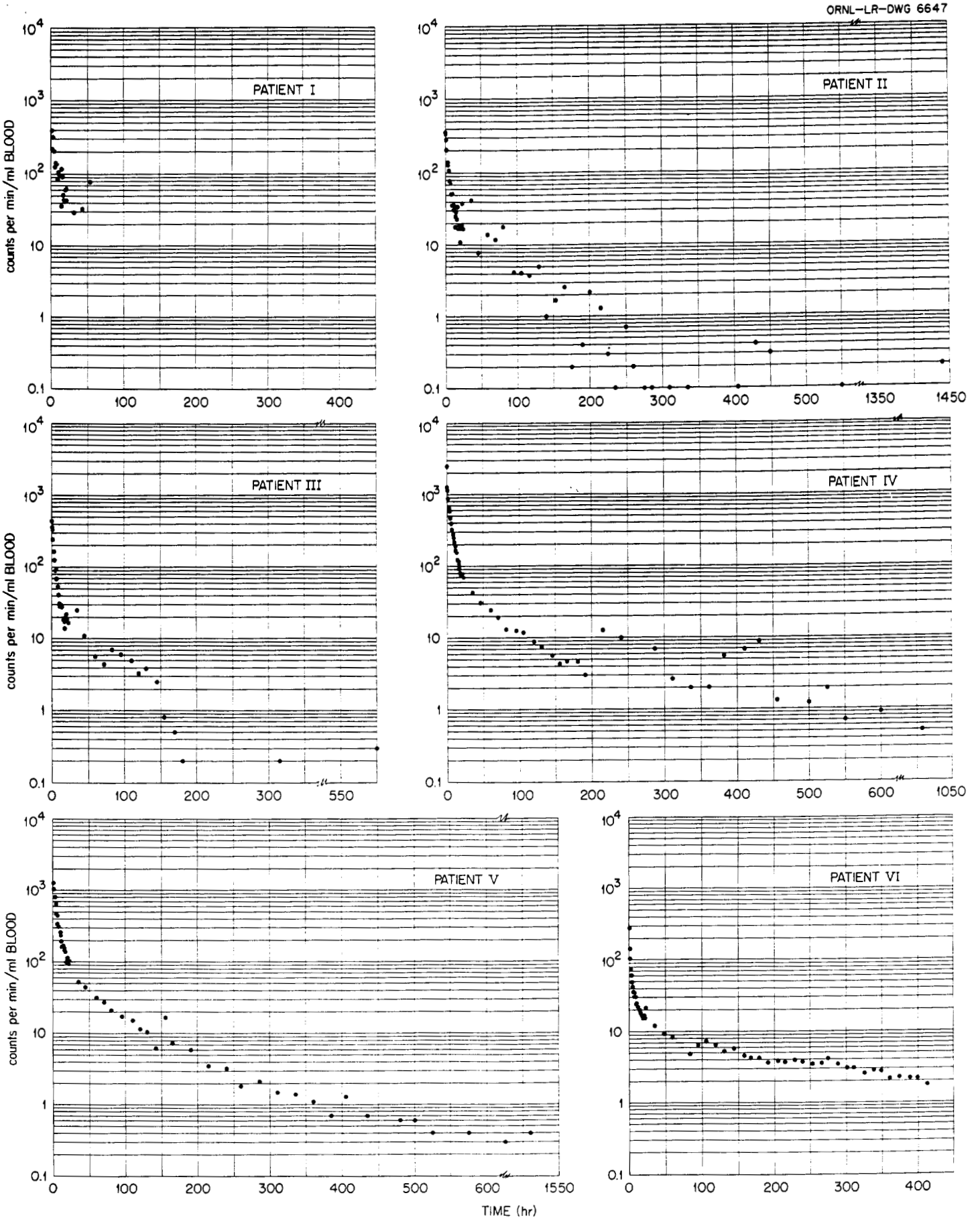

Fig. 2. Uranium Disappearance from Blood.

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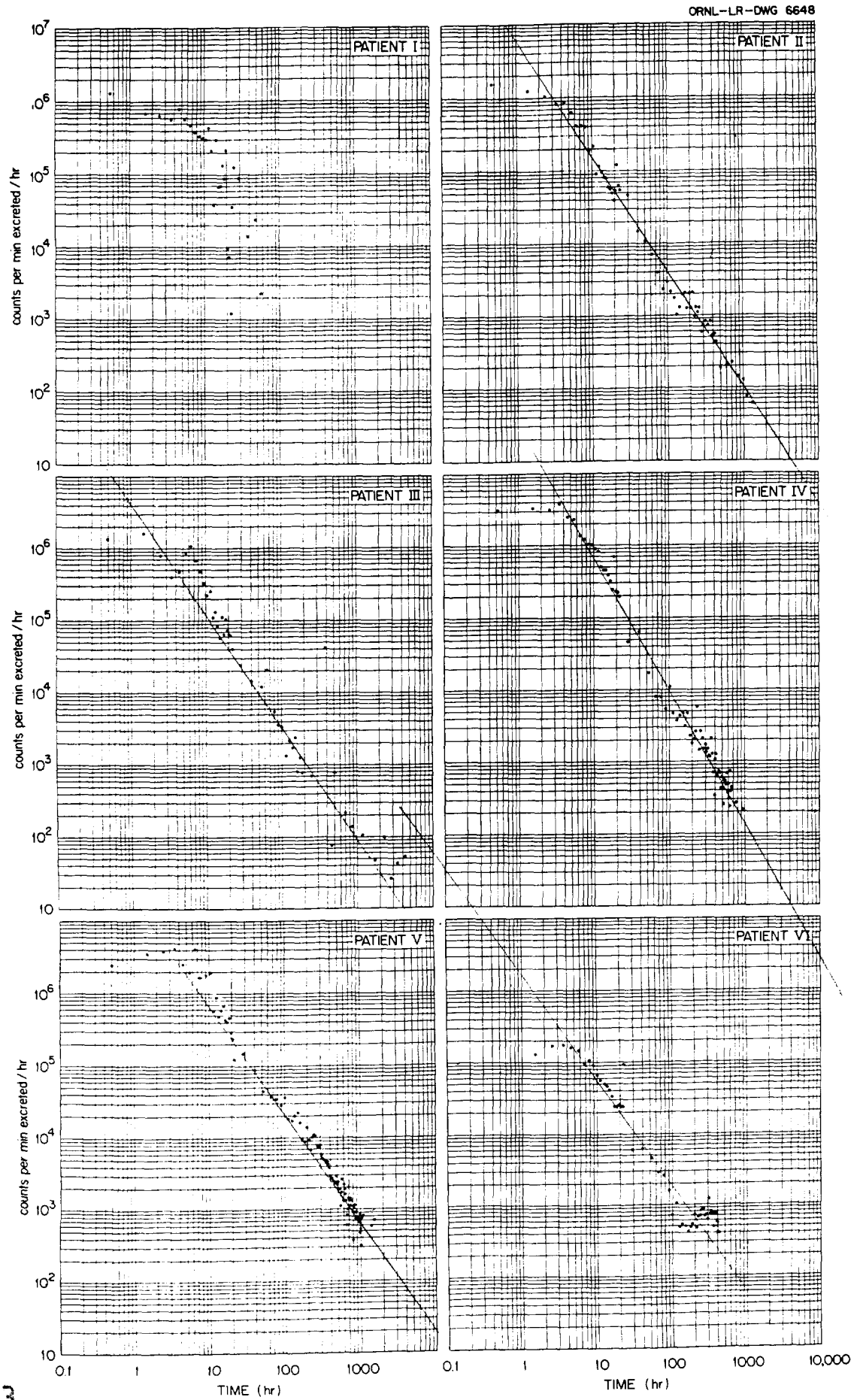

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Fig. 3. Urinary Excretion of Uranium.

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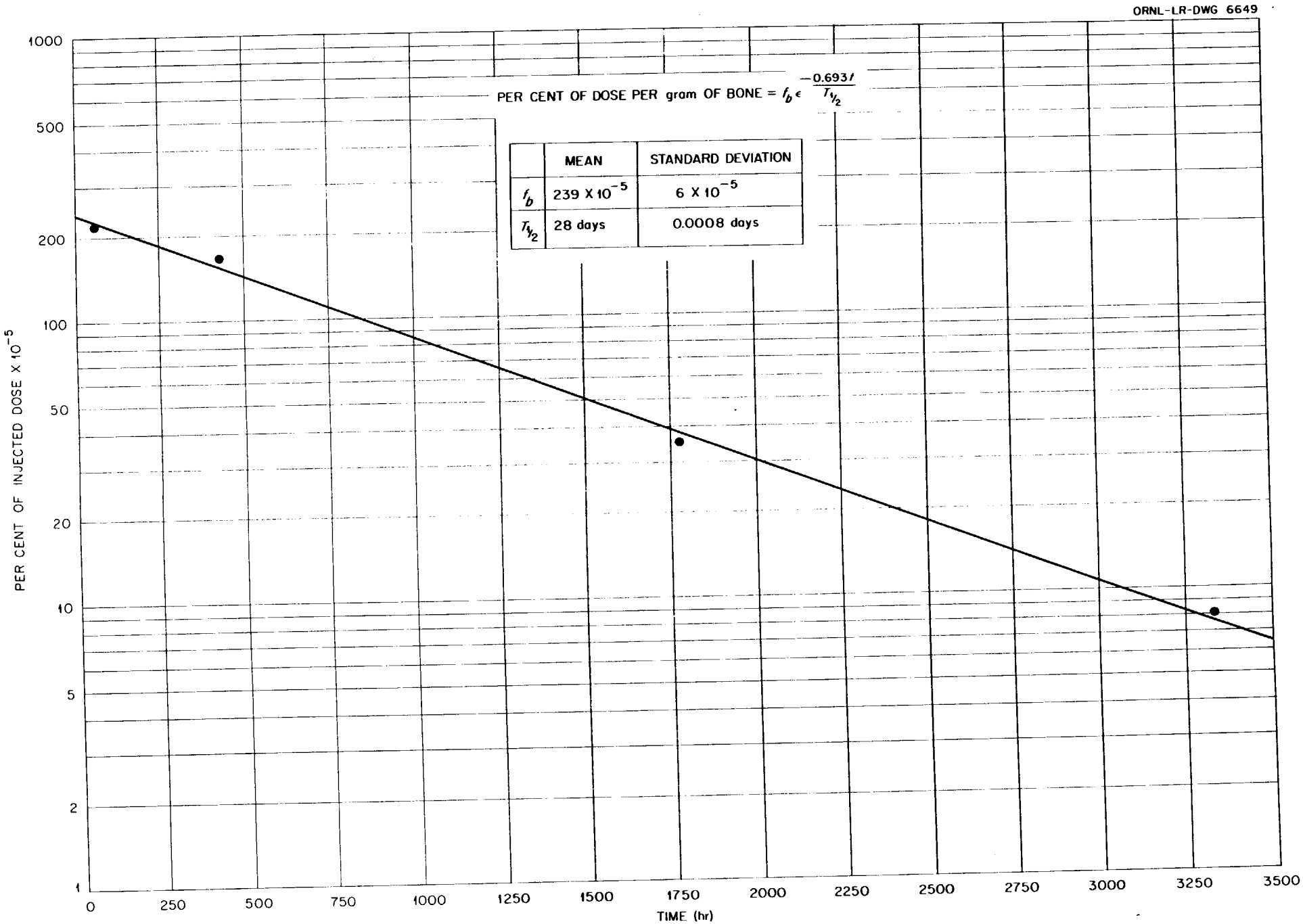

Fig. 4. Per Cent of Injected Dose per Gram of Bone (Wet Weight) at Autopsy.

Table I

Uranium Content of Bone Biopsy Samples in Percent of Injected Dose Per Gram x 10^{-4}

Patient No.	I	II	III	IV	V	VI
0-24 hours	8.7	11.2	12.9	10.8	8.0	8.8
	7.9	6.7	3.3		6.3	9.3
	23.4	4.4	2.0		5.9	
	16.2	15.9				
	8.2					
	13.4					
	17.9					
24-48 hours	7.0				2.2	
	15.1					

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skeletal build-up which peaks somewhere between 24 and 60 hours. However it must be remembered that biopsy samples may not be representative of skeletal distribution since they are very small and essentially compact bone, while the autopsy specimens are larger and include portions of all bone structures.

The kidney findings at autopsy are shown in Figure 5. Extrapolating these data to time zero indicates an initial deposition of 16 percent of the injected dose. The uranium is mobilized from the kidney with a 16 day half-life accompanied by a leveling off at approximately 1 percent.

A typical gross autoradiogram of the kidney, Figure 6, shows uranium non-uniformly distributed and concentrated primarily in the cortical structures. Figure 7, a microscopic autoradiogram of a kidney section from Patient VI, illustrates in detail, a typical site of deposition. Here the uranium is observed to be deposited within or upon epithelial cells of a proximal convoluted tubule.

The autopsy values of all tissues analyzed for uranium are listed in Table II. They are tabulated in terms of percent of injected dose per gram, because it was impossible to obtain weights on all the organs and tissues sampled. Thus, there is no other basis upon which to adequately compare these values. However, if one assumes the weight values of standard man[9] to convert these values to percent of injected dose per organ or per tissue, it is evident that all soft tissues, excluding kidney, contain approximately 20 percent at 60 hours after injection and less than 1 percent at 1500 hours. This is unlike the results obtained in small animal experiments, where the soft tissue content fell to 1 to 2 percent of the injected dose concurrent with the fall in blood uranium.[10] This difference is markedly evident when the soft tissue concentration is related to the blood disappearance curve, as will be shown later.

DISCUSSION

Estimating the Injection Dose for Patients I and II

As described previously, injection solution replicates were collected following administration. These replicates were analyzed in a manner identical with the analysis of urine and blood specimens.

In the case of Patients I and II, injection incidents prevented administration of the predetermined dose. It was necessary, therefore, to estimate the injected dose. This was accomplished in the following manner: the excretion curves of Patients III and IV were plotted; the first part of each curve, being linear, was fitted with an exponential term; this single component, when integrated, represented .54348 and .53476 of the measured dose, respectively. The same procedure was followed with the excretion curves of Patients I and II. Dividing the area under their curves by the average of the values from Patients III and IV, .53908, it was possible to estimate their injected dose.

Comparison with Research Animal Data

The fractions of injected dose initially deposited in soft and hard tissue obtained in this study are in good agreement with those obtained

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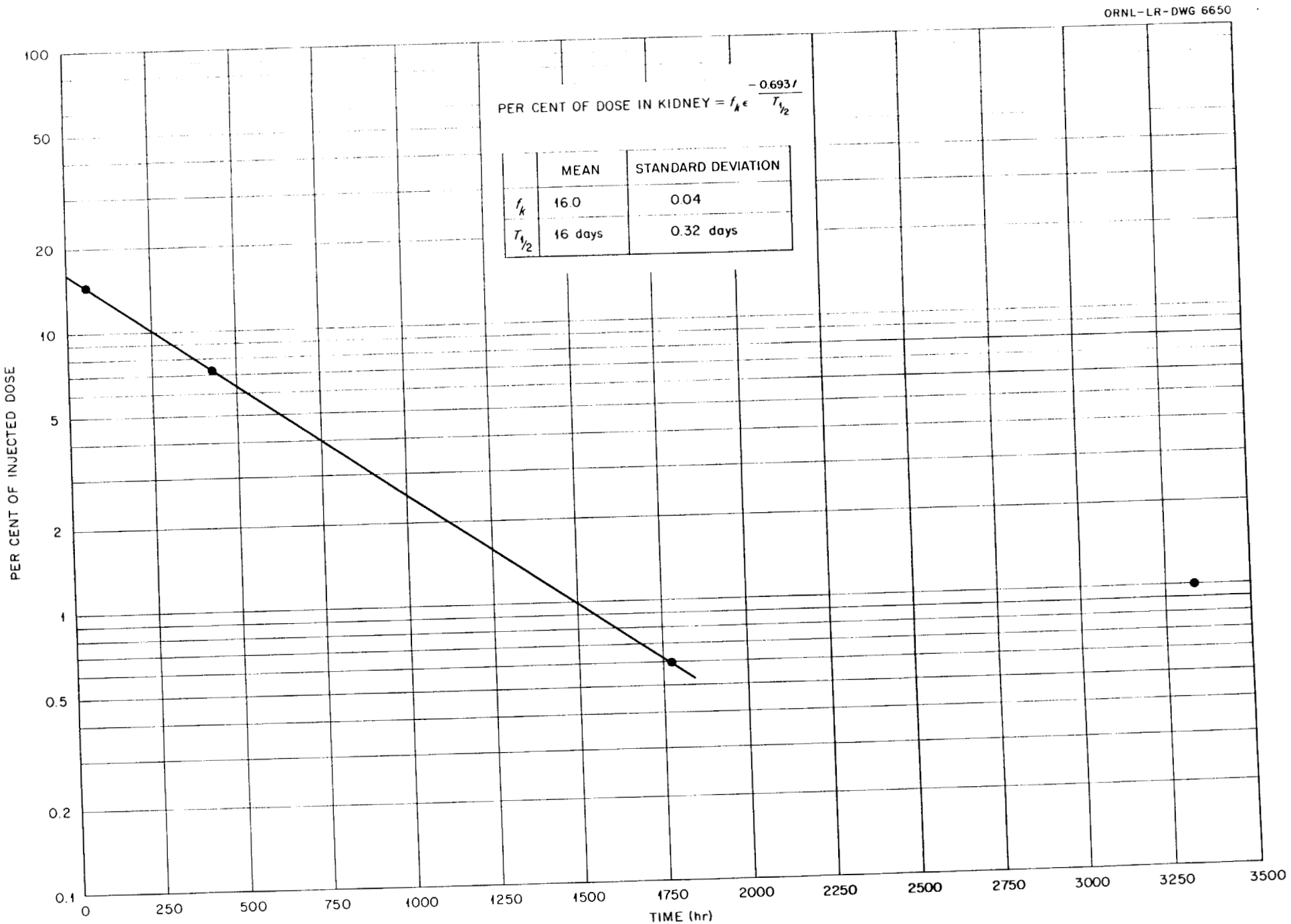

Fig. 5. Per Cent of Injected Dose in Kidney at Autopsy.

Fig. 6. Gross Autoradiogram of Kidney Showing Distribution of Uranium.

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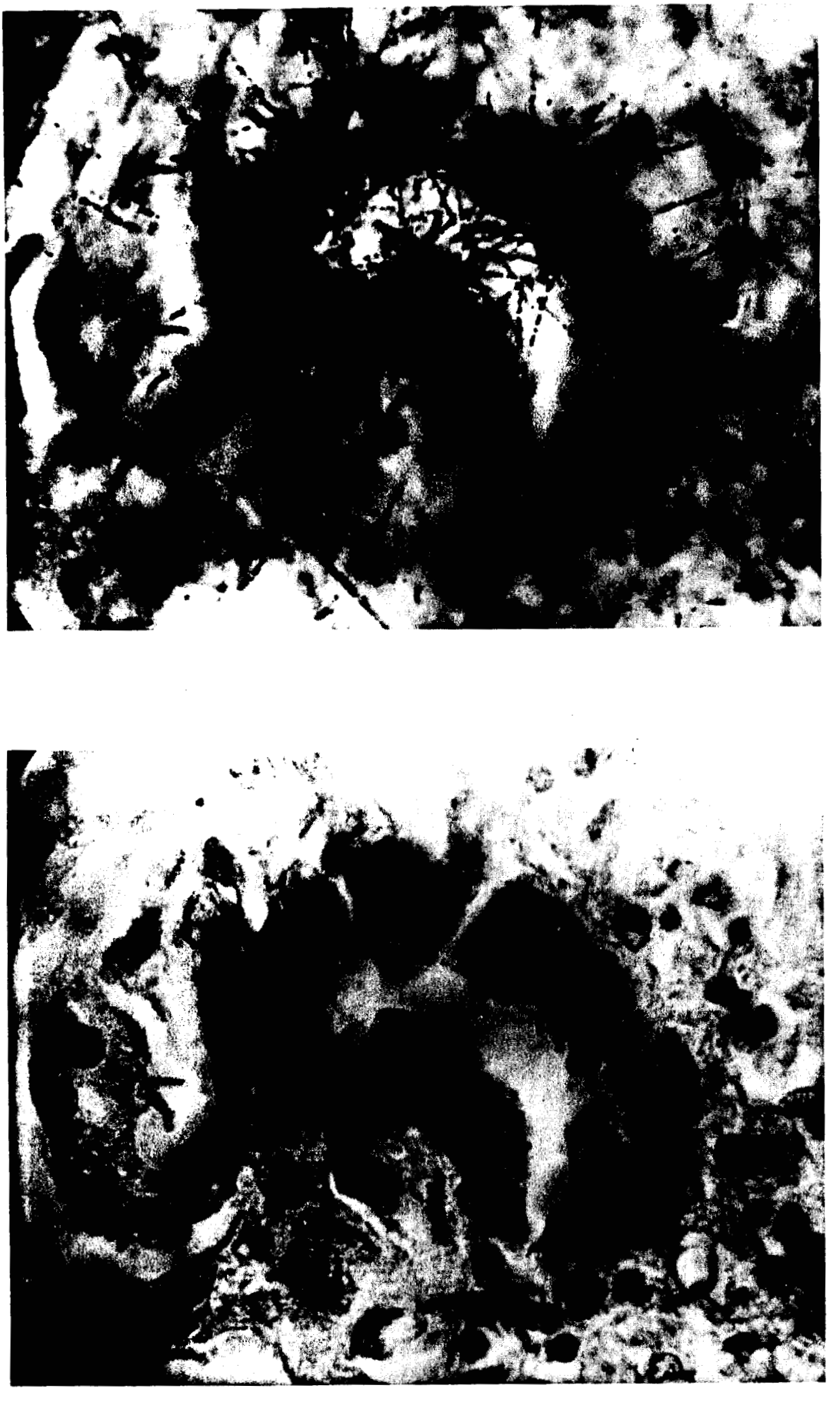

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Fig. 7 Microscopic Autoradiogram of Kidney Showing Uranium in or upon Epithelial Cells of a Proximal Convoluted Tubule.

Table II

Autopsy Results in Percent of Injected Dose
Per Gram x 10^{-4}

Patient No.	I	II	V	VI
Post Injection Time	60 hours	1775 hours	3335 hours	430 hours
Adrenal Gland	11.1	1.6	0.6	6.0
Aorta	7.1		0.01	7.1
Bladder	2.2	0.1	0.09	
Brain			0.05	13.8
Brain (Frontal lobe)	270.8	0.2		
Brain (Parietal lobe)	28.2			
Brain (Temporal lobe)		0.1		
Cartilage			0.1	
Cartilage (Rib)		0.9		
Cartilage (Tracheal)				3.5
Fat (Subcutaneous)	0.6			0.6
Fat (from skin)				8.7
Femur (II & V bone from shaft) (I & VI bone from distal end)	5.8	0.5	0.6	4.4
Gall Bladder	4.8		0.2	13.7
Heart	2.0	0.1	0.2	0.7
Intestine (small)	2.1	0.3	0.1	1.8
Kidney	554.0	22.1	39.3	239.9
Liver	10.4	1.4	0.9	6.5
Lung	4.7	0.3	0.2	3.6
Lung (Necrotic)	23.9			
Marrow (Bone)		0.1	0.2	
Muscle	0.4	0.3	0.09	1.0
Muscle (Psoas)				0.3
Pancreas	96.0	1.2	0.08	1.1
Prostate		0.2	0.2	1.6
Rib	19.7	2.6	0.9	42.1
Skin	3.0	0.2	0.1	1.7
Skull	7.9	11.9	1.9	
Spleen	18.8	3.6	0.5	7.7
Sternum			0.5	
Stomach	3.2	0.1	0.05	0.8
Testis		2.1	0.5	2.9
Thyroid		0.1	0.07	1.5
Tumor (Tissue from edge)	24.8	0.6	0.4	
Tumor (Viable)		0.6		
Vertebrae (Lumbar)		1.8		
Vertebrae (Thoracic)	53.8			

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in animal experiments. For example, Neuman states that from 5-20% of the injected dose in rats concentrates in bone.[11] Two independent estimates of these fractions in percent of injected dose determined by the analyses of biopsy and autopsy bone samples in this study gave values of 6% (± 3%, one standard deviation) and 14 ± .04%, respectively. The half life in the bone, however, differs by a factor of 4, i.e., 28 days for man while that for rats is reported to be 100 days.[12] The bone half life was determined from a plot of the autopsy results shown in Figure 4. Rat kidney initially contains 1/5 of the dose and has a half life of 4-6 days.[13] A plot of the percent of injected dose found in the kidneys of these patients at autopsy gives the fraction initially deposited as 16 ± .04% and a half life of 16 ± 0.32 days. This graph is shown in Figure 5.

These patients excreted from 49 to 84 percent of the injected dose in the urine during the first 24 hours as shown in Table III. Neuman cites excretion values covering the same time interval of 50 percent in mice, 60 percent in rats, 70 percent in dogs, and 73 percent in humans. In this study, which covered periods of observation ranging from 60 hours to 7 months, 61 to 98 percent of the injected uranium was recovered in the urine.

Previous animal work has demonstrated considerable variations in bone deposition with age, activity and diet. Also, deposition of uranium in the kidney has been shown to be markedly affected by the acid-base balance. It is apparent that the metabolic state of these patients would differ from that of healthy subjects. None of the patients showed the salt loss or retention occasionally noted following brain damage, but their bed-ridden condition indicated a state of negative calcium and nitrogen metabolism. No doubt these factors, and perhaps others, played an important role in some of the variations noted in these patients. For example, it might be inferred that the effect of a negative calcium balance would hasten the removal of uranium from the skeleton.

In general, considering factors of 2 to 4 as being small, the data obtained in this study are in good agreement with those obtained in small animal research.

Preliminary Application of the Model

The ultimate purpose of the model is to evaluate individual excretion curves in terms of distribution. By fitting a plot of excretion data with a sum of three exponential terms and equating this to the theoretical excretion equation, it is possible to estimate the amounts of uranium in principal sites of deposition. This requires analytical curve fitting methods to obtain the best fit of the excretion data.

An attempt has been made to obtain the best fitting excretion equation for each of the patients involved in this study. Two analytical methods[14,15] have been tried without success and other methods are being investigated at this time.

However, in order to illustrate the application of the model, a tentative schema employing the distribution and excretion measurements of all patients can be used. First, the data in Table III are plotted. Then a free hand curve is drawn and the equation of the curve is determined

Table III

Percent of Dose Excreted in Urine

Patient No.	24 hours	48 hours	Last Sample	Time of Last Sample
I	59	61	61	57 hours
II	78	84	92	1437 hours
III	84	88	98*	4823 hours
IV	77	81	85	1008 hours
V	67	72	84	1511 hours
VI	49	53	63	425 hours

* - Last sample analyzed, patient has not expired.

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graphically. This curve and its equation are shown in Figure 8a. The unknown parameters of distribution can then be determined in the manner shown in Figure 1. When these parameters are substituted into the integrated equations for blood, bone and kidney, the uranium content in these sites can be calculated. The resulting curves, together with related biopsy and autopsy values, are shown in Figures 8b, 8c and 8d.

While the calculated amounts of uranium in bone and kidney are in good agreement with the observed values, the difference between blood and soft tissue evident in Figure 8d is striking. This suggests a significant fixation of uranium in soft tissues (other than kidney) not found in small animals.

It must be pointed out, however, that final conclusions cannot be drawn because this application does not represent the final test of the model.

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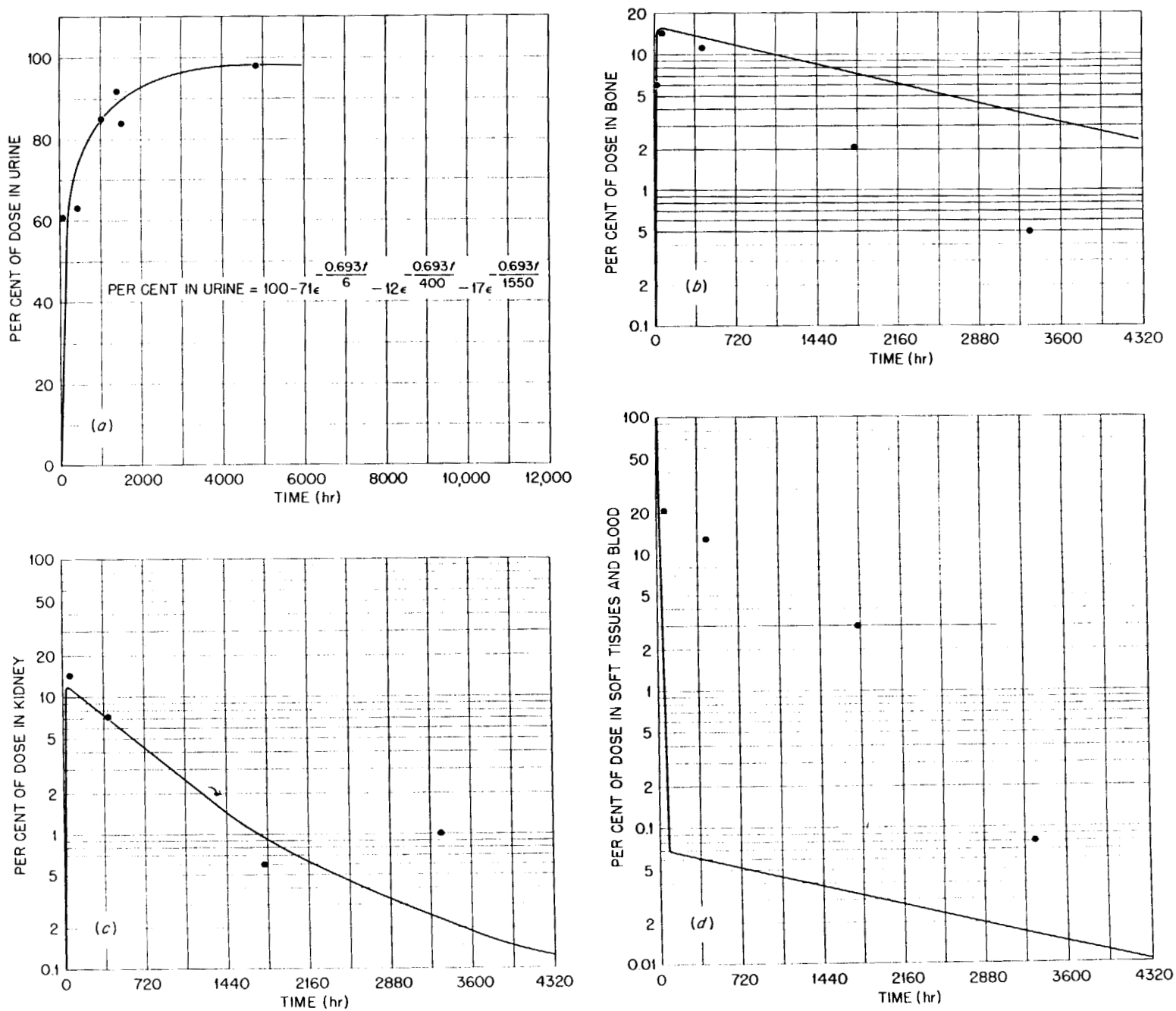

Fig. 8. Comparison Between Observed and Estimated Organ Contents.

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1026105