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A STUDY OF THE DISTRIBUTION AND EXCRETION OF URANIUM IN MAN

AN INTERIM REPORT

S. R. Bernard
E. G. Struxness

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AN INTERIM REPORT

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INTRODUCTION

1.1 Purpose of this Report

This report fulfills two purposes. It defines the problems with which this project is concerned and tells of the progress made in the investigation of these problems.

1.2 Statement of the Problem

The problem is concerned with the long-term radiological effect that enriched uranium may have upon production employees who have inhaled dusts, mists and fumes of uranium in the processing and fabrication of this material. It has been found that a certain number of these production employees have enriched uranium stored in their bodies. These findings are based on extensive studies of the air they breathe and analyses of their excreta - urine and feces[1 - 7]. Samples of airborne uranium taken in the vicinity of their work show that variable concentrations exist. Also, it has been found that the median particle size of these aerosols are in the range of likely penetration and retention in the lung. Samples of urine reveal high and variable concentrations of uranium and, when the employee is reassigned to work in other than uranium processing areas, these concentrations will drop to about one-half in a period of one month; from then on they decrease more slowly over longer periods of time[8]. All these data point to the conclusion that enriched uranium is stored in the bodies of these employees and is being slowly eliminated.

There is a possibility that long-term biological effects may occur since enriched uranium is radioactive and long-term storage of radioactive substances

in the body is known to produce serious and deleterious effects. The severity of these effects depends upon the absorbed radiation dose in the organs and tissues. There are no sensitive biological indicators yet which can serve to forewarn of the effects of radiation overexposure. Only the biological effect reveals itself and that, unfortunately, does not appear until it is too late to do anything about it.

This effect may be said to be a shortening of life span brought about by alterations in the normal metabolic processes induced by radiation. The alterations in metabolic processes are not understood; for that matter, neither are the fundamental mechanisms in normal metabolic processes. It is believed by some investigators that an adequate understanding of these processes is needed before an adequate explanation of these alterations can be made[9].

Figure 1 illustrates some of the altered metabolic processes. Here, radium was the source of radiation. This material gained entrance by ingestion into the body of two watch-dial painters. Both have died; one, 12 years after the beginning of employment and the other, 17 years later. Their ages at death were 32 and 48 years. Similar occurrences have been found among other radium workers.

The above effects can be reproduced in the laboratory by having small animals ingest or inhale radium and other radioactive materials. Such experiments have demonstrated the fact that altered metabolic processes become more pronounced if the total absorbed tissue dose increases. Since the total absorbed tissue dose is a physical index of the biological effect, it is clear that this must be measured and limited in order to prevent a reoccurrence of the experience in the radium industry.

A preliminary estimate of the total absorbed tissue dose in a few Y-12 employees has been made. This was accomplished by cumulating the amount of uranium excreted, then determining the corresponding absorbed tissue dose. Some uncertainty exists in the method of converting cumulative uranium into units of internal radiation exposure. Also, the extraneous contamination of urine samples raises the estimate of internal exposure. More information on the distribution and excretion of uranium is needed to validate this method of estimating internal radiation dose. Moreover, efforts must be made to collect urine samples that are known to be free of contamination from external sources.

1.3 History of the Project

An arrangement between the Y-12 Health Physics Department and the Department of Neurosurgery at Massachusetts General Hospital was established with the assistance of Doctor Harold C. Hodge of the Atomic Energy Project at the University of Rochester. Doctor Hodge was familiar with the activities of both groups and encouraged the formation of a joint undertaking to obtain information bearing on the above problem. After preliminary discussions between representatives of the Y-12 Health Physics Department and Doctor William H. Sweet of Massachusetts General Hospital, a final agreement was reached at a meeting called by Y-12 Management. Representatives of Y-12 Management, Y-12 Health Physics Department, ORNL Health Physics Division, Massachusetts General Hospital, and the AEC Division of Biology and Medicine were present at the meeting.

It was agreed that the Y-12 Health Physics Department would prepare injection solutions and perform the analytical work associated with this joint effort. Massachusetts General Hospital agreed to select the patients, perform the injections, and care for the patients during the period of study. A preliminary estimate of the number of patients to be injected was made without much deliberation. It was decided that six post-operative patients would receive various doses of uranyl nitrate hexahydrate, two pre-operative patients would receive the highest possible dose of uranyl nitrate hexahydrate, and that a similar scheme would be followed with injections of uranium tetrachloride.

The object of the post-operative studies was to determine the permissible intravenous administration dose[10]. The pre-operative injections were to provide information on uptake of uranium in tumorous tissue. These objectives were of direct interest to Doctor Sweet in his investigations of uranium as a fissionable material useful in the neutron capture therapy of brain tumors. Health Physics interests would be served by obtaining the data on distribution and excretion of uranium in these patients.

No financial arrangements were made to cover the specific costs of this cooperative project. The expenses at Boston were to be borne by Massachusetts General Hospital within the framework of an existing contract and the cost of preparing injection solutions and analyzing tissues and body fluids was to be considered as an integral part of the Y-12 Health Physics program.

About a year after this cooperative arrangement was established, Y-12 Management requested Laboratory Management to assume administrative and technical responsibility for this project. Consequently, in April, 1954, the health physicists and technicians of the Y-12 Health Physics Department assigned to this project were transferred to the Health Physics Division of Oak Ridge National Laboratory.

Y-12 Management, however, recognizing its interest in this research, consented to provide financial support until such time as the uranium study was completed, or until other arrangements were made. This arrangement has continued to the present.

The first patient was injected late in 1953. Since that time ten additional patients have been injected in accordance with the original plan. All expired and many samples (biopsy and autopsy) have been collected and analyzed. This report covers the results of the first eight post-operative administrations. Patients I through VI received intravenous injections of hexavalent uranium (U(VI)) Patients VII and VIII were administered tetravalent uranium (U(IV)). These patients were injected under the care and supervision of Doctor William H. Sweet at the Massachusetts General and Veterans Administration Hospitals in Boston. All samples (control and experimental) were pre-digested in Boston and shipped to Oak Ridge for final analysis.

1.4 Objectives of the Project

This project, inappropriately named "Project Boston" because of its association with interested co-workers in Boston, has the following objectives: 1) to obtain human data on the distribution and excretion of enriched uranium; 2) to determine by experimentation with dogs, rats, and mice more precise data on the deposition and distribution that are impossible to obtain from human studies; 3) to determine the MPC (Maximum Permissible Concentration) value of enriched uranium for NBS Handbook 52; and 4) to develop a method for evaluating urinary excretion in terms of its distribution in the human body.

These objectives are directly concerned with the problem of human exposure to enriched uranium in production plants where this material is handled. When these objectives are reached, management should consider the possibility of extending this study to plutonium, thorium, and the critical fission products.

METHODS AND EXPERIMENTAL WORK

2.1 Selection and Care of Patients

The eight 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, 31, 34, 39, 47, 56, 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 but patients III and VII 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 tracehotomies.

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.

2.2 Administration of Uranium

Preparation of Hexavalent 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 0.4 M 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.

Preparation of Tetravalent Injection Solution. A special procedure was required to prepare the tetravalent uranium injection solution because of its instability over an extended period. Tetravalent uranium will slowly oxidize to hexavalent uranium in the presence of oxygen.

A 2 oz. bottle was washed, dried, degassed under partial vacuum, flushed with dry argon, and weighed. Pure uranium tetrachloride (UCl_4) crystals, obtained from the Stable Isotopes Division, were placed in the bottle. The bottle was then weighed to obtain the weight of the crystals after which it was sealed with a rubber seal, degassed to remove oxygen from the interstices of the crystals, and further flushed with dry argon.

A buffer solution of 0.2 M acetic acid and 0.2 M sodium acetate at a pH of 4.7 was prepared in a flask and refluxed for 24 hours. After refluxing was complete and during cooling, the flask was flushed with dry argon. A portion of the buffer solution was transferred to another 2 oz. bottle previously treated to remove oxygen. The bottle was sealed with a rubber seal and autoclaved for sterility. Both bottles, one containing UCl_4 crystals under argon atmosphere and the other containing the specially prepared acetate buffer, were transported to Boston by courier.

Immediately prior to injection, a measured volume of buffer solution was withdrawn into a syringe and injected through the rubber seal into the bottle containing the UCl_4 crystals. Following gentle shaking of the bottle and the syringe, the crystals dissolved. Then a measured volume of the injection solution was withdrawn into the syringe.

Injection Procedure. The uranium was injected intravenously in all the patients. The procedure consisted of first starting an intravenous 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.

Following the injection, the syring 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.

2.3 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.

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

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

2.4 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 0.1 N 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 0.1 N nitric acid and diluted to volume. Triplicate aliquots were removed from each volumetric dilution for electrodeposition of the uranium and subsequent alpha counting.

Electrodeposition and alpha counting procedure is given below:[11]

1. Place cleaned silver disc in cell, assemble, and pipette 20 ml of the proper oxalate-salt base solution into the cell. The cell then should stand five minutes to check for leaks. If leaks occur, the cell should be reassembled and checked again.

2. Pipette the desired sample aliquot into the cell. If the solution appears yellow or yellow-green, adjust to blue or blue-green with ammonium hydroxide.

3. Add distilled water to cell to give total volume of 65 ml.

4. Connect cell to power supply, turn on, and adjust the current to 2 amperes.

5. When the temperature reached 95° C, adjust the current to maintain 95° ± 2° C and electrodeposit for one hour.

6. At the end of one hour, disassemble the cell, dry silver disc (blotting only) and place in marked envelope for counting room.

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 disssolved 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 0.1 N 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[12].

RESULTS

3.1 Biopsy Findings

Blood - Uranium leaves the circulating blood stream rapidly. A log x log graph (Figure 2) of blood measurements shows that within six minutes the blood contains only 0.007 per cent of the injected uranium per ml of blood, a three-fold reduction in concentration if 5,000 cc of blood are assumed. Assuming that uranium penetrates the capillaries immediately after injection to gain entry into 5,000 cc of extracellular fluid (ECF) space, and the concentration in ECF equilibrates with that in blood (plasma), then the percent of injected dose/ml x 10^4 ml is a measure of the concentration in the body fluid spaces. The measured concentrations in blood describe smooth curves during the first five to ten hours after injection, but fluctuate later, as the concentrations decrease to low levels. A closer examination of these data reveals more flucturation at shorter intervals after injection when low doses are administered (patients I, II and III) then when high doses are administered (patients IV, V, VI, VII and VIII). This point is more clearly shown in Figure 3.

Bone - Uranium deposits in bone shortly after injection. Biopsy samples of bone taken at one-half hour following injection contained 7.6 per cent of the injected dose per 7,000 grams of bone. In Table I, the percent of injected dose per 7,000 grams of bone (biopsy samples) are listed for each patient. The averages range from 0.5 to 9.1 per cent. Patients VII and VIII, who were administered UCl_4, show the lowest (0.9%) average deposit of uranium in bone.

Urine Excretion - There is a rapid clearance of uranium into urine, depending upon the valence and the mass of uranium injected. Table II shows the percent of injected dose accumulated in urine in the first 24-hours. Note Patients I - VI excrete an average of 69 per cent of the injected uranium while Patients VII and VIII excrete only 18.5 per cent. A log x log graph of the excretion rates appears in Figure 4. The percent of injected dose excreted per hour correlates, in the first four hours, with the mass of uranium injected. Excretion rates rise to a maximum at $\sim$3 1/2 hours when the larger doses of U(VI) and U(IV) are injected. This rise is distinct for the high doses (50 mgms - VI, VII and VIII), less distinct for the intermediate doses (15 mgms - IV and V), and not apparent for low doses (4 mgms - I, II, and III). After the maximum has been achieved the levels of U(VI) begin to decline and follow a linear path. Some variation occurs, occasional high and low samples accompanying the decline. It is interesting to note that these changes in excretion rates do not correlate with blood levels.

Tetravalent uranium excretion rates, after they reach the maximum, begin to follow the power function law. At 200 hours, they depart from the power function and decline more slowly. At 400 hours the pattern again seems to follow the power function.

Uranium Excretion in Feces - Negligible fractions of the injected doses are excreted in feces. This can be seen in Table III, where the percent of injected dose per sample of feces are listed. Figure 5 presents a graph of the counts per minute per gram of fecal ash, plotted as a function of time for Patients VII and VIII. Note that the counts/minute/gram from Patient VII rises to a maximum; in the case of Patient VIII, it is difficult to tell whether a maximum was achieved. However, the counts per minute per gram of ash decreases with time.

3.2 Autopsy Findings

The percent of injected uranium found in autopsy tissues are summarized in Table IV. Bones and reticulo-endothelial tissues, liver and spleen, contain the heavier deposits of U(IV) while bones and kidneys contain the major deposits of U(VI). The deposition of uranium in other tissues appears to be nil.

Deposition in Bone - Different samples of bone reflect different concentrations as seen in Table V. The samples of femur are lowest in concentration, while the vascular bone, rib, is highest in the early stages after injection and the skull concentration is highest at later stages. Figure 6 is a diagram of the uranium concentrations in a longitudinal plane sectioned from the distal end of the femur. The section, approximately one-fourth inch thick, was cut into smaller sections and each section analyzed for uranium. The numbers in each section are the concentrations in counts per minute per gram. In general, the concentrations decrease in the direction of the shaft.

Figure 7, a graph of all individual bone samples from Patients I, II, III, V and VI reveals a wide spread in concentrations. It is believed that the logarithmic mean concentrations, appearing in Table IV, are the best statistical measure for these samples.

Deposition in Kidney - A typical gross autoradiogram of the kidney, Figure 8, shows uranium distributed non-uniformly and concentrated primarily in the cortical structures. Figure 9, a microscopic autoradiogram of a kidney section from Patient VI, illustrates in detail, a typical site of deposition. Here, the uranium is deposited within or upon epithelial cells of a proximal convoluted tubule.

Deposition in Normal and Tumorous Brain Tissue - The concentrations of uranium found in tumorous brain (expressed as percent of injected dose per thousand grams) are higher than in normal brain tissue (Table VI).

3.3 Biological Half-Life in Bone and Kidney

It is important to know whether or not the current value for the biological half-life of uranium in bone (300 days) is less (or greater) than these data would indicate. It is found that the 300 day value is quite acceptable. In Figure 10, a semi-log graph of the percent of dose of U(VI) in bone is plotted with three other curves. Curve 1, obtained by the usual least square procedure, has a half-life of 200 days. Curve 2, which gives a better fit, was obtained in this manner: 1) Plot the bone biopsy and bone autopsy data on semi-log graph paper as shown in Figure 11; 2) fit each plot by least squares with a single exponential term and compute the bone half-life of each patient; and 3) plot each patient's bone half-life as a function of expiration time. Since

the latter increases in proportion to $t^{4/5}$ (Figure 12), these data can be represented by the equation $C \exp\left(\frac{\lambda t}{t^{4/5}}\right) = C \exp(\lambda t^{1/5})$ and, by least squares, the values of C and λ can be calculated. Curve 3 is the best single exponential representation of the bone data because integration from t = 0 to t = 70 years yields the area beneath it which is identical to the area (in the same interval) beneath curve 2.

Since the percent of injected dose deposited in the kidney is not different from the deposition in bone then its best single exponential representation would also be curve 3. Thus, the biological half-life for kidney is 300 days, a factor of ten greater than the presently accepted value.

3.4 Chemical Toxicity Findings

An investigation of the chemical effects of uranium upon the kidney tubules was carried out by Doctor A. J. Luessenhop, et al., of the Massachusetts General Hospital and the results of this study are summarized briefly below.

The parlous clinical state of these patients was said to make the interpretation difficult. However, some definitive evidence was accumulated which showed that a minimal dose to produce a nephrotoxic syndrome was 0.1 mgm of U(VI) per kilogram of body weight. A general survey of these clinical findings is presented in Table VII. The evidence for tubular damage manifests itself in urinary catalase and protein excretion, a well known sensitive test for the toxic effect on the kidney tubules[12]. Other evidence for the effect is the appearance of cellular casts in the urine and, even though it is faintly suggested, the interference with the renal capacity for reabsorption of Na and Cl and the secretion of K. The pathological studies did not reveal any detectable change in the tubules.

3.5 Best Fitting Equations

Body and Organ Burdens - A direct measure of body burden was not made. However, the best estimate is believed to be the average of the total percent of injected dose found in autopsy tissues and 100 per cent minus percent of injected dose excreted in urine. The best fitting power function equation $0.60\ t^{-1/2}$, was obtained by minimizing the weighted square residuals of the body burden estimates where the weights were taken to be inversely proportional to the variances. A plot of this equation together with the body and organ burden in kidney and bones appears in Figure 13.

The equation for organ burden in kidney is $0.20\ t^{-1/2}$, and it is the same as the organ burden in bone. This equation was determined by computing the average of the ratio of the burden in the organ to the burden in the body, as given by $0.60\ t^{-1/2}$. The lowest ratio was rejected from each calculation.

Urinary Excretion - The best fitting power function equation for the excretion rates of Patients I - VI is $34.3\ \%/\text{hr}\ t^{-3/2}$ (t in units of hours) (Figure 4). Excretion rates measured in the first 10 hours were omitted from the least squares fit. The best fitting equation for each patient's rate measurements is shown in Figure 14. Here, too, the excretion measurements of the first 10 hours were omitted. These excretion rates are approximated closely by the power function. Also, the parameters for the equation have a considerable range - exponents range from 2.31 to 1.36 while the coefficients range from 381.3 %/hr to 22.9 %/hr.

3.6 Kinetic Studies of Distribution and Excretion

A simple mathematical analysis of the dynamic process of U(VI) distribution and excretion is possible with the linear model shown in Figure 15. This model is based on small animal distribution and excretion data found in the literature[12]. It permits an estimate of the amounts of uranium in deposition sites as a function of time. The procedure for its application is to fit the excretion data with three exponential terms and to determine the parameters of the distribution.

Figure 16 shows the results of its application to the distribution and excretion of one of the Boston patients[13]. Two curves band the excretion measurements to include the error in estimating the parameters. When these sets of parameters are manipulated as dictated by the linear model, the percent of injected dose may be estimated for the organs, Figure 17. Note that the model underestimates the percent of injected dose in the kidneys, but that it estimates bone and blood content reasonably well.

The model is being modified presently to give a closer approximation of these experimental results. It appears that better agreement will be obtained by incorporating a mechanism to simulate the formation of diffusible and non-diffusible complexes in the blood and including a pathway from kidney back to blood to simulate resorption in the tubules. These modifications are under study[14].

DISCUSSION

4.1 Evaluation of Maximum Permissible Concentrations in the Body, Air and Urine.

The autopsy findings confirm the present MPC values recommended by the National Committee on Radiological Protection and the International Commission on Radiation Protection. Although the data show kidney as the critical organ rather than bone, the over-all change in q (the MPC in the body) is not significant. q, calculated on the basis of these data, is .02 μc, which differs from the present value, 0.04 μc, by a factor of 2. q was calculated with the usual equation and f_2 was set equal to 1/3 (see Table IV and Figure 13).

The current $MPC)_a$ (= 1×10^{-11} μc/cc) applicable to the case of exposure to soluble uranium compounds in air is low by a factor of two when compared with the $MPC)_a$ calculated on the basis of these data. Both the power function law and the exponential law were used to make the calculation

$$MPC)_a \left[\begin{array}{ll} = \dfrac{3.5 \times 10^{-8}\, q f_2}{Tfa\,(1 - \epsilon^{\frac{-693\,t}{T}})} & = 2.3 \times 10^{-11}\ \mu c/cc \\[2ex] = \dfrac{5 \times 10^{-8}\, q}{fa' \int_0^t .6\, d\tau\, (t - \tau)^{-1/2}} & = 1.7 \times 10^{-11}\ \mu c/cc \end{array} \right.$$

where q = .02 μc, f_2 = 1/3, T = 300 days, fa = $(.25 + f_1)f_2$ = .025, f_2 = .11, fa′ = .25 and t = τ = 2.6×10^4 days (70 years).

The Maximum Permissible Excretion level $MPC)_u$ computed with the power function differs from that calculated with the exponential law by a factor of ten:

$$MPC)_u \left[\begin{array}{l} = 2 \times 10^7 \text{ fa } MPC)_a \left(1 - \epsilon^{\frac{-.693\,t}{T}}\right) = 1 \times 10^{-5} \ \mu c/day \ (22 \text{ d/m/day}) \\ \\ = 2 \times 10^7 \text{ fa}' MPC)_a \left(1 - .6\, t^{-1/2}\right) = 1 \times 10^{-4} \ \mu c/day \ (222 \text{ d/m/day}) \end{array} \right.$$

The current $MPC)_u$ (70 d/m/day) is 1/3 the higher value and three times the lower value.

4.2 Estimating Body Burden from Urinary Excretion Data

Instantaneous Body Burden (Injection Dose) - 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.

Injection incidents in Patients I and II prevented administration of the predetermined dose. Therefore, it was necessary to estimate the injection 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 injection dose.

This method of estimating injection doses can be applied to practical problems of industrial exposure. Only a few excretion measurements immediately following the exposure incident are required. In equation form, the estimated injection dose is given by

$$I_{est} = \begin{pmatrix} \text{Initial} \\ \text{rate of} \\ \text{excretion} \end{pmatrix} \begin{pmatrix} \text{Half-life} \\ \text{in} \\ \text{blood} \end{pmatrix} \times 2$$

As an example, Figure 18 shows the estimated injection doses of six Rochester patients made in this manner. The poorest estimate, an error of 58 per cent, is shown in the case of the sixth Rochester patient. This error can be reduced to 26 per cent if the first urinary excretion measurement is eliminated from the calculation.

The method cannot be applied accurately to the excretion data of Boston Patients V and VI because of the effect of dose upon the shape of the excretion curve. When the excretion rates exhibit a tendency to rise to a maximum the method yields an overestimate of the injection dose. The reasons for this are not understood.

Body Burden as a Function of Time - An untenable estimate of body burden is given when a material balance (amount in body = amount injected - amount excreted) is employed in conjunction with the power function equation. Such an estimate is not tenable because of an error in the measured excretion rates, or in the power function, or in both. This is shown in Table VIII where the percent of dose excreted at infinity was calculated by integrating the power function from

t = 24 hours to t = ∞ and adding the percent excreted in the first day. This calculation was performed with both the Rochester and Boston data for purposes of comparison. There is no essential difference between the percent excreted at infinity and the percent accumulated in the urine at the time of the last sample. Studies of the best fitting power function are under way to elucidate this finding.

Part of the difficulty in applying the power function to the excretion data stems from the fact that excretion is not measured over a long enough period, i.e., the best fitting power function is inadequate when applied to short term experiments. This argument may not be important when the data are examined from another viewpoint. Figure 19 presents a graph of excretion rate in fraction of injected dose excreted per hour plotted as a function of 1 - fraction of injected dose excreted in urine. The excretion curve of the third Boston patient is a straight line while the curves of all other patients bear resemblance to asymptotic functions. The straight line is evidence that the power function law is obeyed, proof of which comes from eliminating the time variable from the equation for body burden, ($q = at^{-b}$) and its derivative, which is the negative excretion rate, $dq/dt = -abt^{-(1 + b)}$. This yields

$$-dq/dt = \left(\frac{b}{a^{1/b}}\right) q^{(1 + 1/b)}$$

a non-linear differential equation. A plot of log (-dq/dt) versus log q should be a linear function if the power law is obeyed. Since there were no independent measures of the body burden and since 1 - fraction of injected dose excreted in urine may be in error, it cannot be concluded that the asymptotic curves mean that the power law was not obeyed.

A better method for estimating body burden from urinary excretion is suggested by these considerations. A graph of body burden versus excretion rate is shown in Figure 20. The straight line has the equation

$$(- dq/dt) = + .056\ q^3/I^2$$

where I is the injection dose. Actually the equation is for mere convenience. The application of this graph to the practical problem does not depend on any law for retention and excretion. With data from additional patients, this graph can be improved.

4.3 Estimating Cumulative Internal Radiation Exposure from Routine Urinary Excretion Measurements.

Current estimates of cumulative internal radiation exposure are based on the lung as the critical organ because the predominant exposures in Y-12 are due to airbonre, insoluble uranium compounds. There are, however, occasional inhalation exposures to high levels of soluble compounds which give rise to perturbed excretion levels. In these cases, the pattern of excretion resembles that of continuous administration upon which is superimposed the excretion of a single injection.

Figure 21 presents a typical case. This worker was exposed to a high airborne concentration of a soluble uranium compound. Here, the estimate of cumulative internal radiation exposure should be based on the kidney as the critical organ rather than the lung. If it is assumed that there is no appreciable hold-up of the soluble compound in the lung and the MPC for a continuous soluble exposure is 70 d/min/day, then the cumulative dose can be estimated as follows:

1) Determine I, the injection dose, by one of the following methods: (a) Multiply the amount excreted in the first 24 hours after exposure by 1/0.7; or (b) use the method discussed in section 4.2; or use the equation $I = (-\dot{q}/0.3)t^{3/2}$ where $-\dot{q}$ is the measured excretion rate in units of d/m/day or mrem/day and t is the time (in days) at which the measurement was made.

2) Determine q, the body burden in the equation, $q = .6\ I\ t^{-1/2}$.

3) Integrate these values for q until the steady state is reached and include these values into the cumulated unperturbed exposure record. Cumulated unperturbed exposure represents the contribution to the dose resulting from continuous absorption in the blood stream. It must be remembered that this method applies only to the case of a single exposure.

Another factor which affects the estimate of cumulative internal dose is that of contaminated urine specimens. Extraneous contamination can be introduced inadvertently by the employee or by the laboratory analyst. The following suggestions will help to minimize this problem:

1) Analyze the urine immediately after voiding by a direct method.

2) Analyze specimens in uncontaminated laboratories.

3) Avoid cross-contamination.

An immediate analysis is possible with a well type dip counter[15], but its limit of sensitivity is about ten times the $MPC)_u$. Therefore, this instrument could be used to "screen" the samples. Employees voiding uranium concentrations detectable with this counter should be required to submit additional samples for immediate analysis. After the levels drop to the limit of sensitivity of this instrument the employee could again submit samples at the regular frequency.

The highly contaminated samples should be analyzed separately from the low level samples thereby reducing the possibility of cross contamination.

Methods for analyzing larger volumes of urine are under development to improve the precision and to lower the limit of sensitivity. In the existing electroplating method, one of the unattractive features is the relatively high contamination potential. This is shown in Table IX. Note that, as the volume of blank urine increases, the amount of activity in the blank samples remains constant.

4.4 Comparison with Other Data

Small Animals - The results of this study of human distribution and excretion can be compared with the results of small animal experiments[12, 16]. The notable differences are:

1. Storage of U(VI) in the kidney of small animals was found to be insignificant in comparison to storage in the bone. The biological half-life for uranium in the kidney of rats is ~6 days. In these humans, averaged over a 70 year period, the biological half-life is approximately 300 days.

2. The disappearance of U(VI) and U(IV) from the blood stream of humans is slower. In studies with rats, 99 per cent disappears in as little as two hours. These human data reveal that 20 hours are required for blood clearance.

3. In the case of rats, 2/3 of the injected uranium is excreted in the urine in 24 hours. On the average, 70 per cent is excreted by these patients in the same period. It should be noted, however, that the rate of excretion depends on the total mass of injected uranium. For example, 50 per cent of the injected dose was excreted in the first 24 hours when 50 mgms were injected; 84 per cent was excreted in the first 24 hours following the administration of 4 mgms.

4. Small animals, when injected with tetravalent salts of uranium, excrete significant quantities (~40 per cent) of the injected dose in feces.

Humans excrete negligible amounts via the G.I. tract.

Rochester Patients - In general, there was very little, if any, difference exhibited in the urinary excretion of the Rochester patients[17]. This is surprising in view of the fact that their clinical states were different. None of the Rochester patients had maladies comparable in severity to the terminal Boston patients. There was a slight difference in experimental technique with respect to: (a) sample collection (Rochester patients voided at natural times whereas Boston patients were catheterized); and (b) level of injection dose (Rochester patients were administered smaller (0.4 - 4 mgms) doses of $UO_2(NO_3)_2 \cdot 6H_2O$).

The urinary excretion findings were similar in these respects: a) The best fitting power function, 57.2 %/hr $t^{-1.8}$ differed slightly from that of the Boston patients, viz., 34.3 %/hr $t^{-1.5}$; b) the amount of uranium excreted in the first 24 hours was essentially the same, 76 per cent compared with 69 per cent (Table VIII); and c) the percent of injected dose excreted at infinity was the same, 79 per cent compared with 85 per cent (Table VIII).

The fecal excretion of uranium in the Rochester subjects was negligible. This is in good agreement with the Boston patients.

Some subtle differences are indicated in Figure 19. The Rochester Curves are not as different from each other as are the Boston patient curves. In addition, the Rochester excretion rates initiate at higher values (Figure 21) than the Boston patients (Figure 3).

4.5 Future Work

The work is not complete. To evaluate the industrial inhalation exposure to enriched uranium more adequately, the future work should include the following studies:

1) Additional patients: More patients are needed to improve the validity of the findings on the eight patients reported.

2) The Influence of Mass of Injected Dose upon the Blood Disappearance and Excretion Rate: It is important to know what the effects are at low levels, i.e., can the distribution be altered, the disappearance from blood hastened.

3) Excretion Resulting from Multiple Injections.

4) Excretion Following Inhalation of Soluble and Insoluble Uranium Compounds. Studies of excretion following inhalation of metal fumes with dogs are under way. These studies are needed in the case of humans as well.

SUMMARY AND CONCLUSIONS

Human data on the distribution and excretion of enriched uranium, the product of a cooperative study by the Department of Neurosurgery, Massachusetts General Hospital, and the Health Physics Division, Oak Ridge National Laboratory, are presented. These data are evaluated for information with which to determine the internal radiation hazards of long-stored, enriched uranium in production workers. Eight terminal brain tumor patients were administered uranium compounds, six were injected with $UO_2(NO_3)_2 \cdot 6H_2O$, and two with UCl_4. Measurements were made of the uranium excretion in urine and feces, the disappearance of uranium from blood, the distribution of uranium in bone (biopsy and autopsy), and in many samples of tissue.

The findings in this investigation were:

1) The critical organ for radiation damage is the kidney rather than bone. The kidney burden was found to be the same as that of bone and the biological half-life in bone, 300 days, was found to be the same as that of the kidney.

2) The measured excretion rates for urine in Boston patients (a) can be approximated with a best fitting power function and (b) are slightly different from the excretion rates of patients injected at the University of Rochester.

3) An improved method for estimating body burden and cumulative internal radiation dose from urinary excretion is applied to the case of workers exposed to high airborne levels of soluble uranium compounds. Suggestions are made to minimize errors in this estimate.

4) The Maximum Permissible Concentrations in the body, in air, and in urine calculated with these data differed, by no more than a factor of 3, with the currently recommended values for exposure to soluble compounds of uranium.

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Table I

Uranium Content of Bone Biopsy Samples in Percent of Injected Dose per 7,000 Grams

Patient	I	II	III	IV	V	VI	VII	VIII
	6.1	7.8	9.0	7.6	5.6	6.2	0.5	1.4
	5.5	4.7	2.3		4.4	6.5		1.1
	16.3	3.1	1.4		4.1			
0 - 24 hrs	11.3	11.1						
	5.7							
	9.4							
	12.5							
24 - 48 hrs	4.9				1.5			
	10.6							
Average	9.1	6.5	4.2	7.6	3.9	6.4	0.5	1.3
			6.3				0.9	

Table II

Percent of Injected Dose Excreted in First 24-Hour Collection or Urine

Patient	I	II	III	IV	V	VI	VII	VIII
	59.4	78.0	83.8	77.2	66.5	49.1	20.0	16.9
Average				69.0				18.5

Table III

Percent of Injected Dose Excreted in Feces

Time (in days) of Sample	Patient I	II	IV	VII	VII
1		.0002	.0001		
2					.0006
3	.017				.0002
4			.0005	.0241	
5			.0088		.0003
6		.0003		.0117	.0038
7			.0022		
9			.0177		
10			.0168		.0005
11			.001		.0005
13				.0155	.0298
17				.0075	.0021
18				.0081	
19					.0015
20					.0001
21				.0031	
23				.0084	
24				.0044	
26				.0031	
31				.0048	
33				.0005	
38				.0041	
41				.0049	
43				.0010	
46				.0029	
48				.0001	
50				.0020	
51				.0013	
54				.0015	
56				.0015	
57				.0017	
59				.0016	
63				.0008	
64				.0035	
68				.0001	

Table IV

Per Cent of Injected Dose per Standard Man Organ or Tissue for Six Terminal Brain Tumor Patients

Patients I, VI, II, V and III Injected with $UO_2(NO_3)_2 \cdot 6H_2O$
Patient VIII Injected with UCl_4

Organ or Tissue	Sample Amount (g)	Patient Number I	VI	II	V	III	VIII
		Expiration Time (days)					
		2.5	18	74	139	566	21
Bone	7,000	10.0	4.9	1.4	0.6	1.3	14.4
Kidney	300	16.6	7.2	0.7	1.2	0.4	1.1
Muscle	30,000	1.2	2.1	0.9	0.3	0.06	0.4
Skin and subcutaneous tissue	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	
Blood	5,400	1.0	0.2	0.005	0.002	0.004	0.08
Stomach	250	0.08	0.02	0.003	0.001	0.001	
Small intestine	1,100	0.2	0.2	0.03	0.01	0.006	0.1
Liver	1,700	1.8	1.1	0.2	0.2	0.05	9.2
Brain	1,500						
Lungs	1,000	0.5	0.4	0.03	0.02	0.008	0.3
Heart	300	0.06	0.02	0.003	0.006	0.002	0.004
Spleen	300	0.6	0.2	0.1	0.02	0.006	5.6
Urinary Bladder	150	0.03		0.002	0.001	0.0003	0.06
Pancreas	70	0.7	0.008	0.008	0.0006	0.0004	
Testes	40		0.01	0.008	0.002	0.002	0.008
Thyroid Gland	20		0.003	0.0002	0.0001	0.0002	0.0009
Prostate Gland	20		0.003	0.0004	0.0004	0.0001	0.003
Adrenal Gland	20	0.02	0.01	0.003	0.001	0.0004	0.02
Miscellaneous tissues (blood vessels, cartilage, nerves, etc)	390	0.3	0.2	0.04	0.002	0.002	0.04
Total in Tissues		35	18	4	3	2	
Total Excreted in Urine		69	63	92	85	98	

Table V

Bone Autopsy Data - Per Cent of Injected Dose per 7,000 g

Patient No.*	Postinjection Time (days)	Sample					Mean
		Femur	Rib	Skull	Sternum	Vertebra	
		Injection: $UO_2(NO_3)_2 \cdot 6H_2O$					
I	2 1/2	4.1	13.8	5.5		37.7	14.0
VI	18	3.3	29.5				16.3
II	74	0.4	1.8	8.3	0.4	1.3	2.4
V	139	0.4	0.6	1.3			0.8
III	566	0.6	0.6	7.4	1.1	0.4	2.0
		Injection: UCl_4					
VIII	21	0.6	27.5			15.1	14.4

*No autopsy data obtained for patients IV and VII.

Table VI

Percent of Injected Dose per 1000 grams of Normal and Tumorous Brain Autopsy Tissue

	Injected with $UO_2(NO_3)_2 \cdot 6H_2O$					UCl_4
Patient	I	VI	II	V	III	VIII
Expiration Time (days)	2.5	18	74	139	566	21
Brain		1.4		.005	.005	.009
Frontal	27.1*		.02			
Temporal	2.8		.01			
Stem						.01
Tumor	2.5		.06	.04	.02	.14

* Believed to be contaminated.

Table VII

Summary of Clinical Findings on Patients I - V

Patient Clinical Findings	I	II	III	IV	V
I General					
Dermal changes					
Erythema	No changes				
Sweating	No changes				
Pulse	No changes				
Neurological changes	No changes				
Body Temperature	No changes				
Respiration Rate	No changes				
Heart	No changes				
Pulse	No changes				
EKG	No changes			Tachycardia	
Liver Function	Definite damage				
Cephalin Floculation		Elev. 1st day post inj.			
II Blood					
Pressure					
Glucose Tol.					
Hematology					
Reticulocytes					
Platelets					
Hemoglobin	Reduced				
Hematocrit	Reduced				
Sedimentation Rate	Markedly Elevated				
Leucocytes	Elevated	Normal			Elevated
Polymorpho Nucl. Cells		Normal	Elevated		
Serum Electrolytes					
Ph	No changes				
CO_2	No changes				
P	No changes			Increase	
Ca	No changes			Decrease	
Na	Decrease				No change
Cl	Decrease			No change	Decrease
K	Increase in first 5 days				
Total Protein	Normal	Below Normal			
Serum Globulin	No changes				
Alkaline Phosphatase					
Analase	Normal				

Table VII (continued)

Patient Clinical Findings	I	II	III	IV	V
III Urine					
Toxicity Tests					
Non-Profit Nitrogen	No change			Elev. post injection	No change
Catalase	too few determinations	Elev. post injection	Temp rise 1st day post inj.	Elevated post injection	
Protein					
Fluid Balance	no definite effect	Immediate increase post injection			
Specific gravity	Fluctuated in accordance with urine output				
pH					
Cl clearnace	No definite decrease below control values				
Urea "					
Endogenous Creatinine clearance					
Microscopic Analysis					
Erythrocytes	Abnormal Numbers				
Leucocytes					
Casts	Present pre-post injection	Fluctuated		Appeared post injection	
Glucose-Ketone Bodies	None present				

Table VIII

Percent of Injected Dose Excreted at Infinity for Rochester and Boston Patients

Patient Number*	Best Fitting Power Function	Percent of Injected Dose Excreted 1st Day	Percent of Injected Dose Excreted Last Sample	Percent of Injected Dose Excreted at Infinity	Time of Expiration**
B I	383.6 %/hr $t^{-2.31}$	59.4 %	69 %	63.9 %	2.5 d
R I	144.0 %/hr $t^{-2.15}$	82.3	86	85.5	141 hrs
B II	49.9 %/hr $t^{-1.56}$	78.0	92	92.8	74 d
R II	423.0 %/hr $t^{-2.50}$	84.7	87	87.1	142 hrs
B III	22.9 %/hr $t^{-1.35}$	83.8	98	104.9	566 d
R III	39.5 %/hr $t^{-1.80}$	69.2	72	73.1	214 hrs
B IV	117.3 %/hr $t^{-1.81}$	77.2	85	88.1	136 d
R IV	238.0 %/hr $t^{-2.09}$	66.6	72	73.4	404 hrs
B V	73.9 %/hr $t^{-1.58}$	66.5	85	86.6	139 d
R V	3792.0 %/hr $t^{-3.22}$	75.3	75	77.8	94 hrs
B VI	33.2 %/hr $t^{-1.36}$	49.1	63	72.0	18 d
R VI	96.2 %/hr $t^{-2.23}$	77.6	91	77.8	334 hrs
Averages B	113.5 %/hr $t^{-1.66}$	69.0	82	84.7	-
R	788.7 %/hr $t^{-2.23}$	76.0	81	79.2	-

* The prefix B and R correspond to Boston and Rochester patients, respectively.

** Rochester patients did not expire, hence the times listed correspond to the period of the experiment.

Table IX

Effect of Increased Sample Volume on the Amount of Uranium in Urine

Volume of Sample (cc)	Total Activity (c/hr)
2	14
	13
	17
	18
	12
	20
5	15
	15
	8
	10
	15
	20
10	19
	13
	21
	15
	10
	10
20	13
	12
	20
	10
	15
	18
50	12
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100	13
	12
	18
	13
	13
	20

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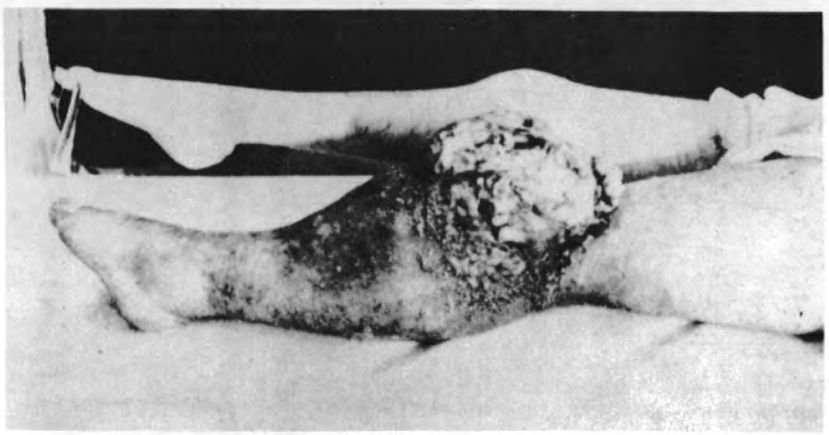
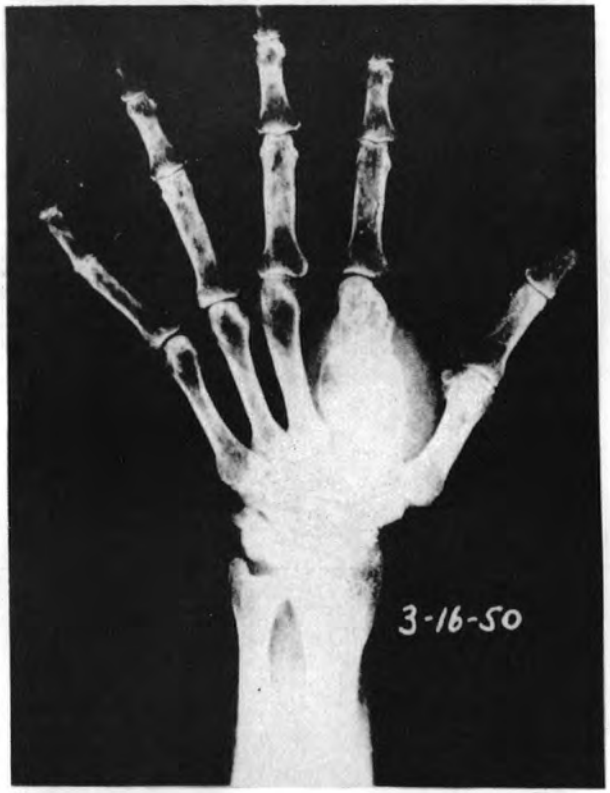


Case 9. Photograph taken after death (1945) showing large fungating and ulcerating osteogenic sarcoma arising in left tibia.

Case 19. (1936) This picture shows the large tumor of the mandible. There is ulceration of the lower part of the tumor mass. Reprinted from the Journal of Industrial Hygiene and Toxicology with permission of the publishers.



Case 25. Right hand (March, 1950). This roentgenogram shows marked extension of the lesion of the 2nd metacarpal bone. The entire shaft of the bone is now involved and the cystic nature of the new bone is more distinct.

FIGURE 1

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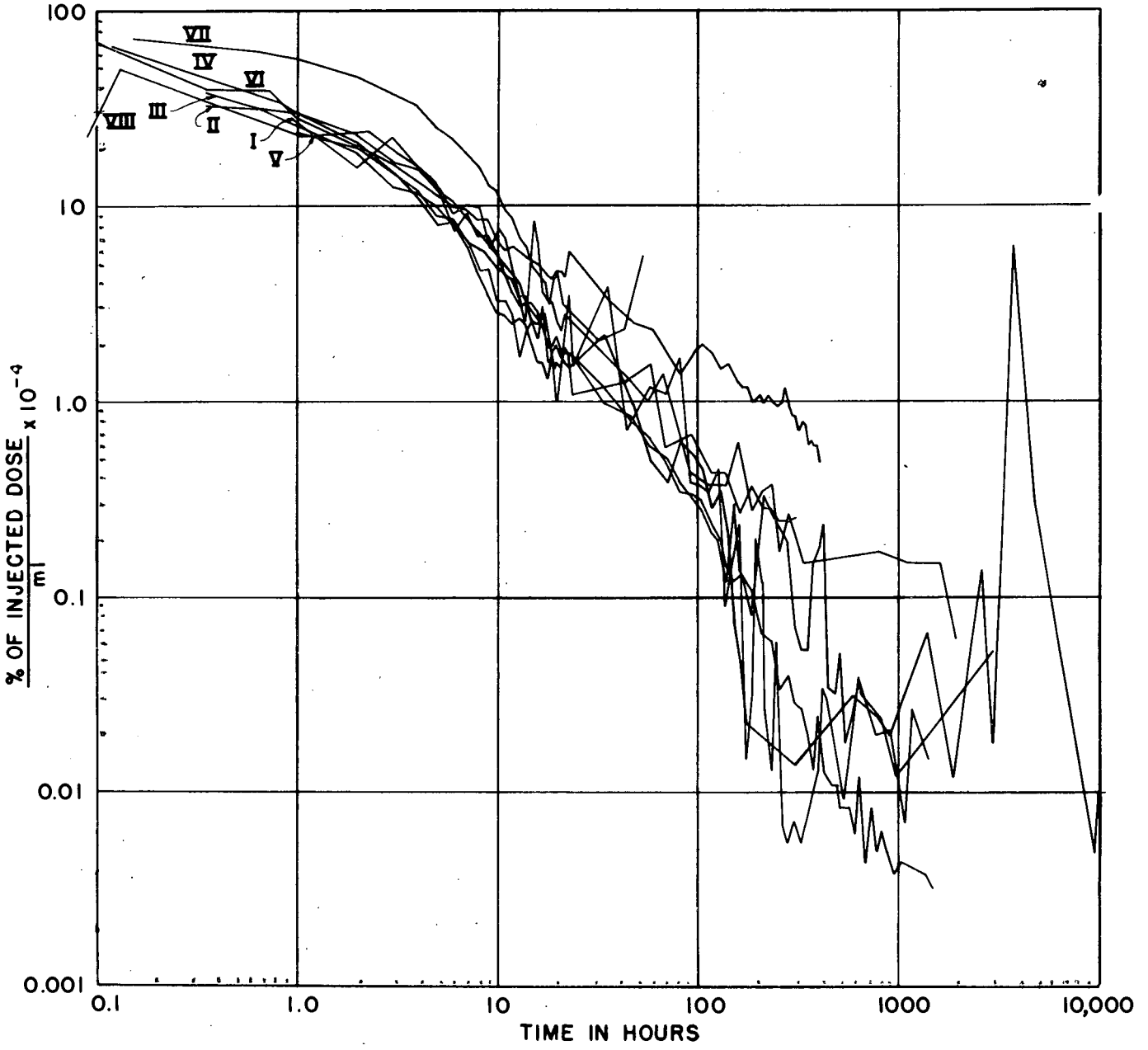

Fig. 2 DISAPPEARANCE OF URANIUM FROM BLOOD

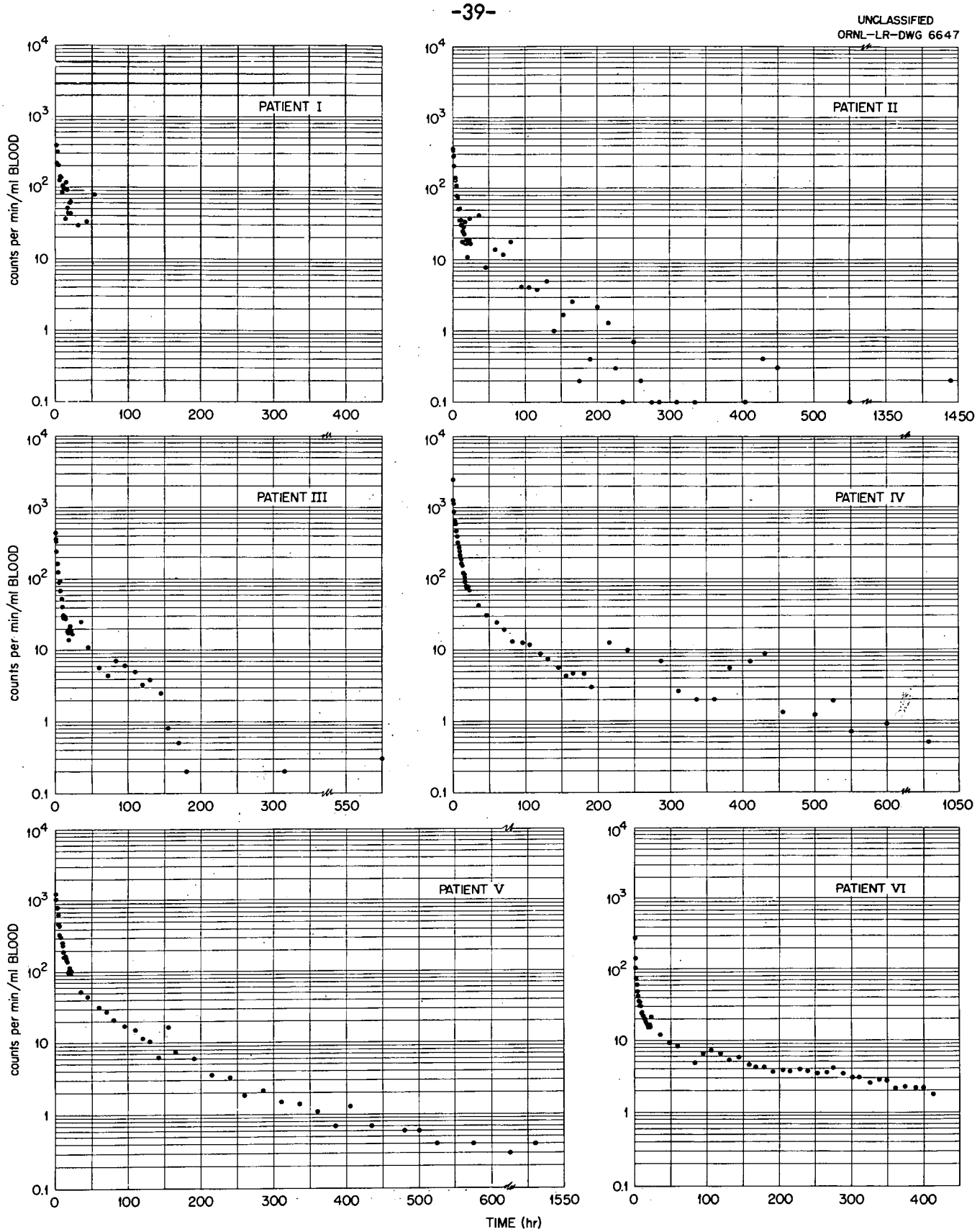

Fig. 3 URANIUM DISAPPEARANCE FROM BLOOD

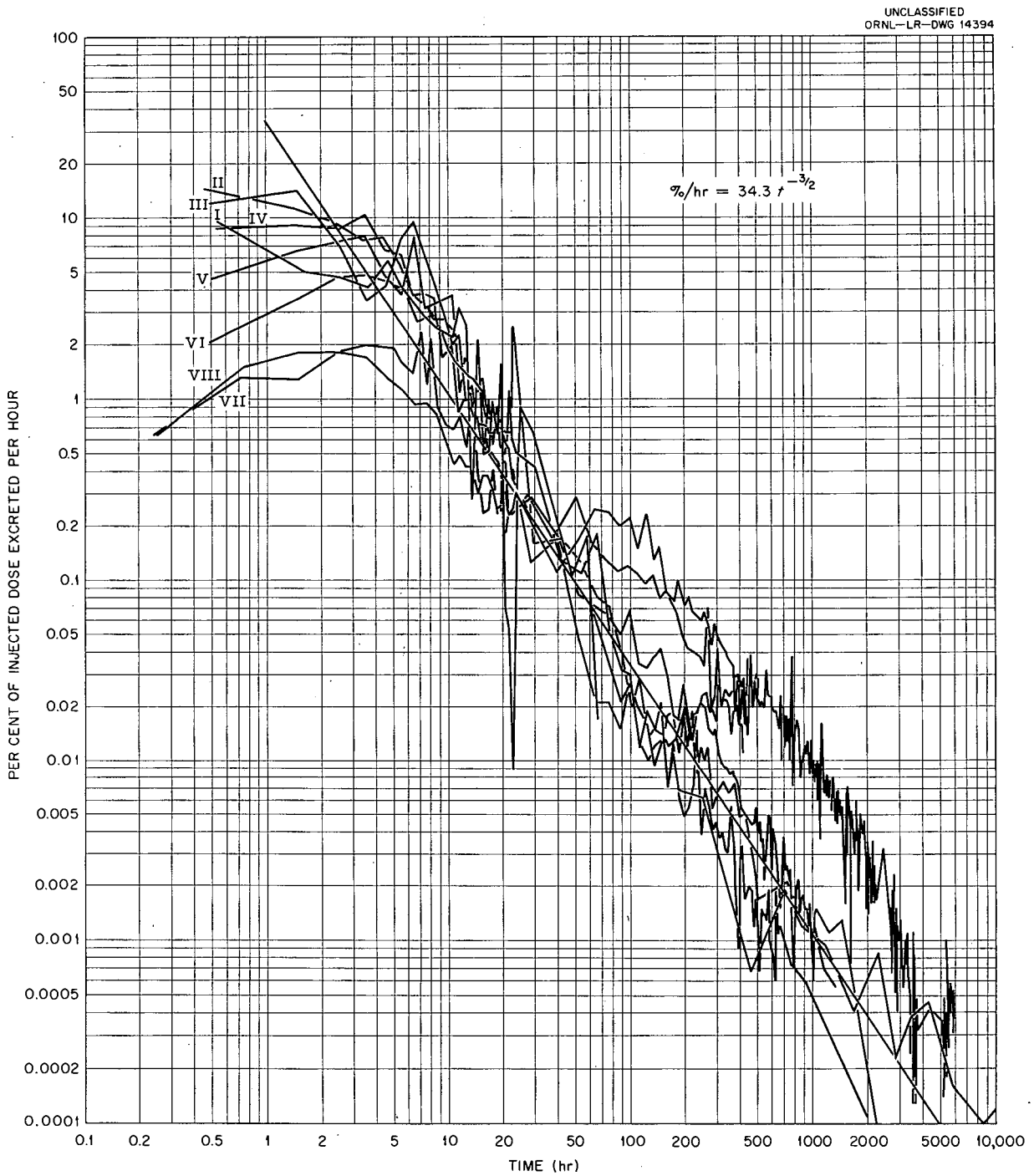

FIG. 4. URINARY RATE OF EXCRETION.

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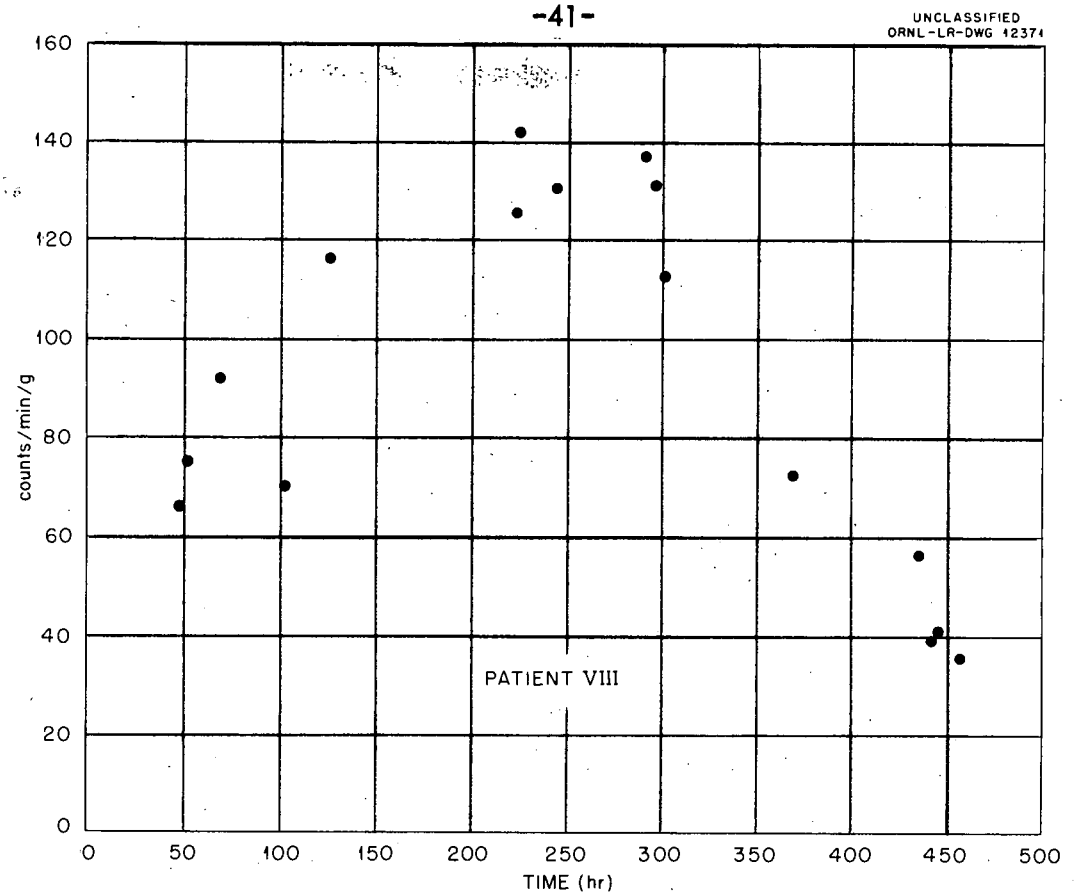


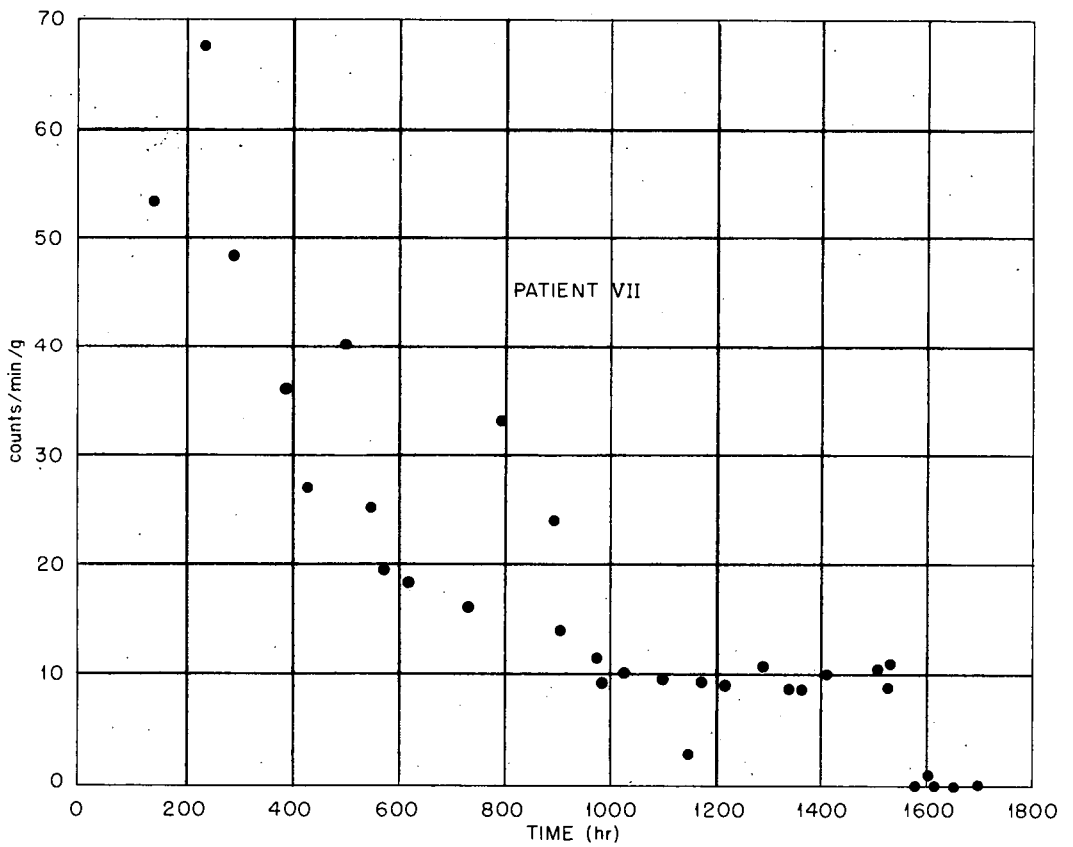


Fig. 5 URANIUM EXCRETION IN FECES

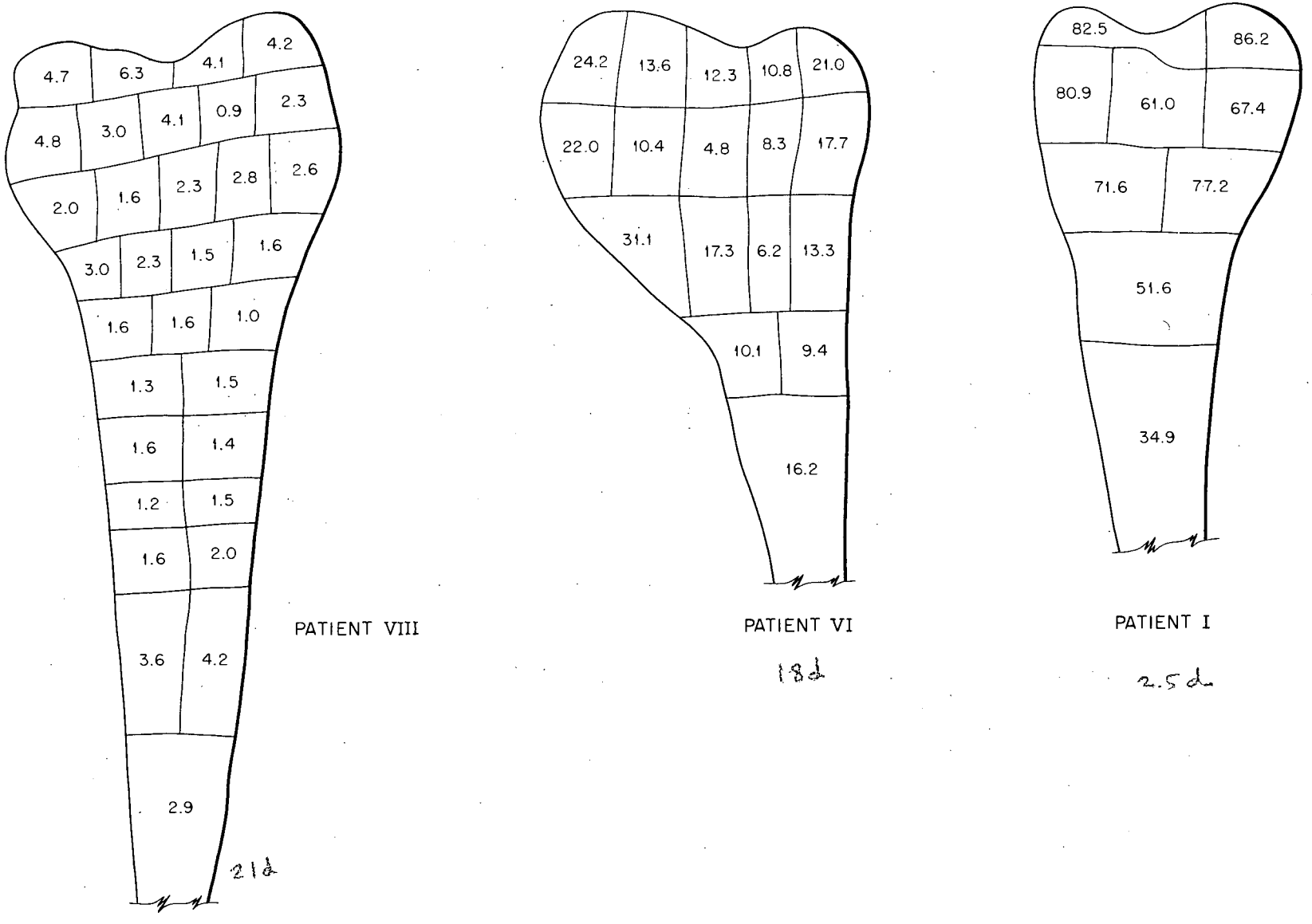


Fig. 6 DIAGRAM OF CONCENTRATION OF URANIUM IN LONGITUDINAL SECTION OF DISTAL END OF THE FEMUR
Numbers in each section represent counts /min/g.

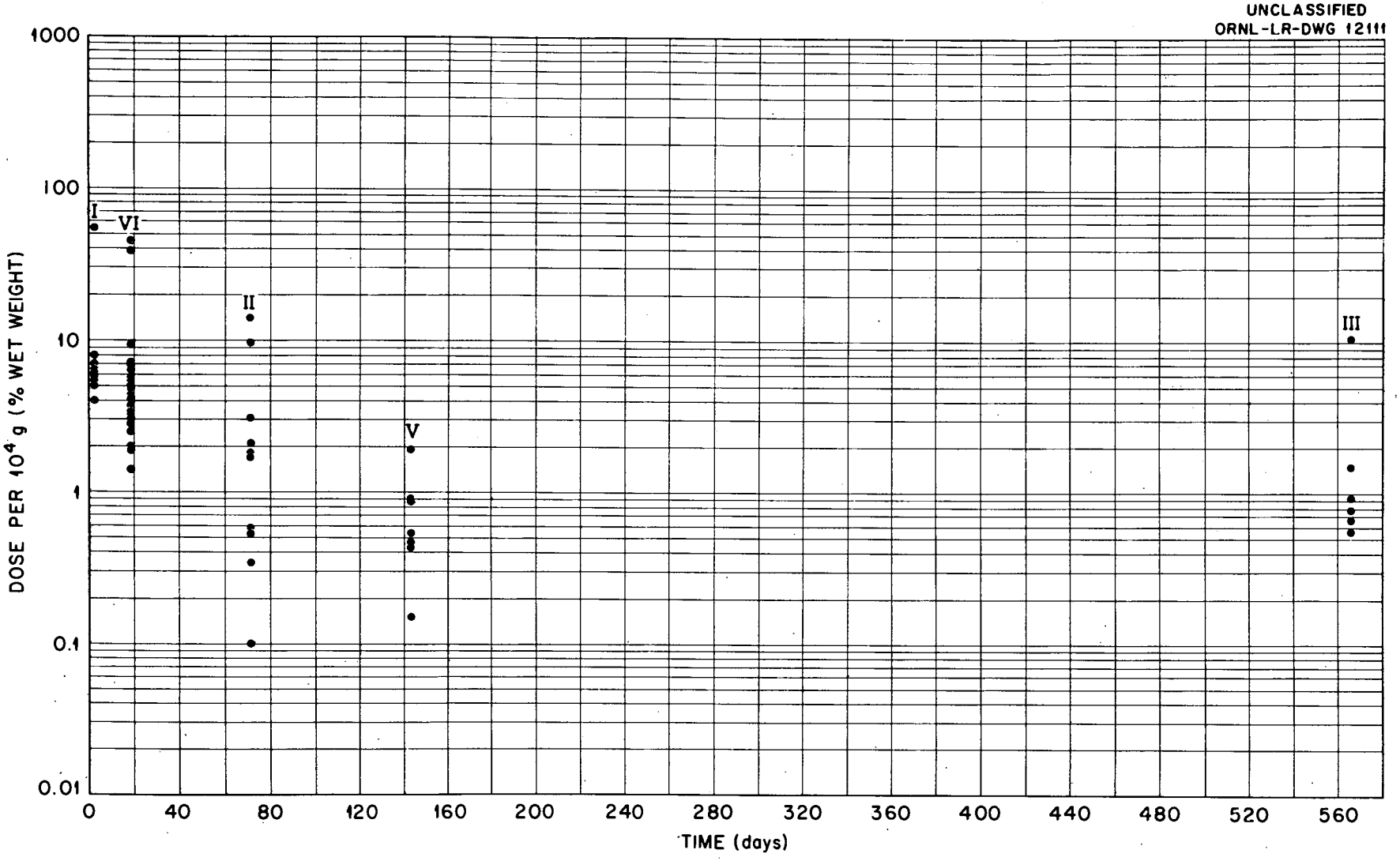
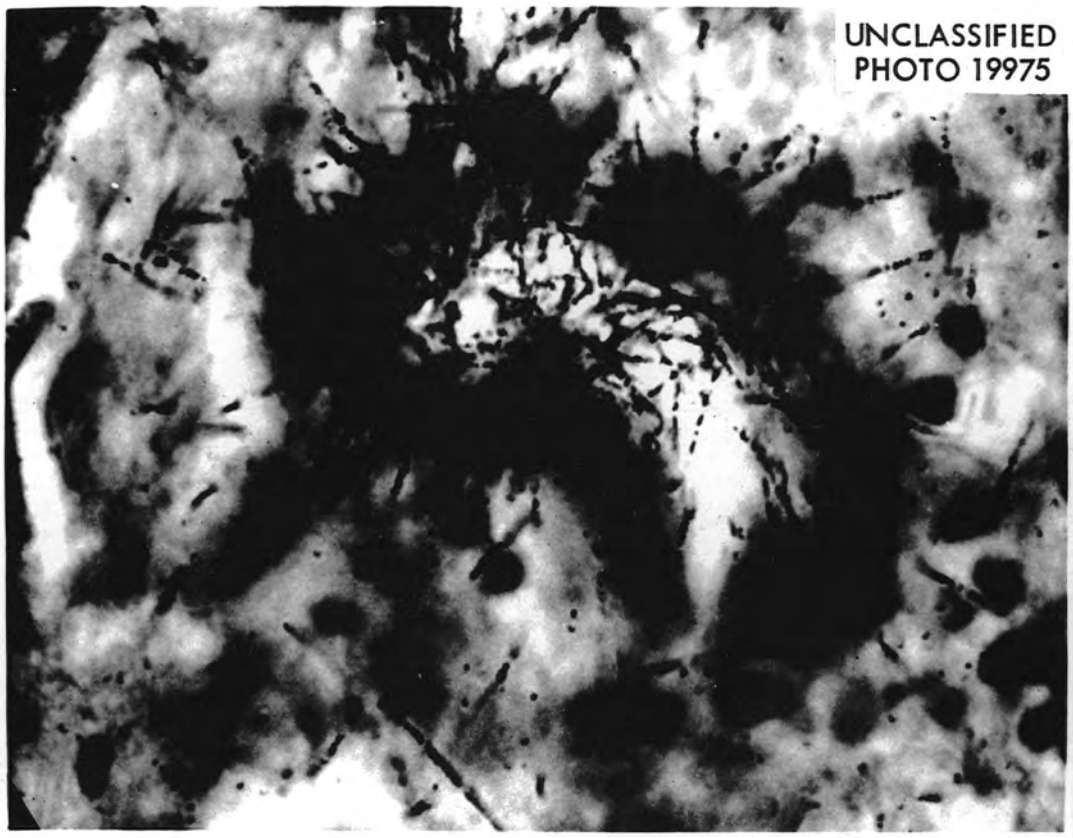


Fig. 7 CONCENTRATION OF URANIUM IN BONE

FIG. 8. GROSS AUTORADIOGRAM OF KIDNEY SHOWING DISTRIBUTION OF URANIUM.



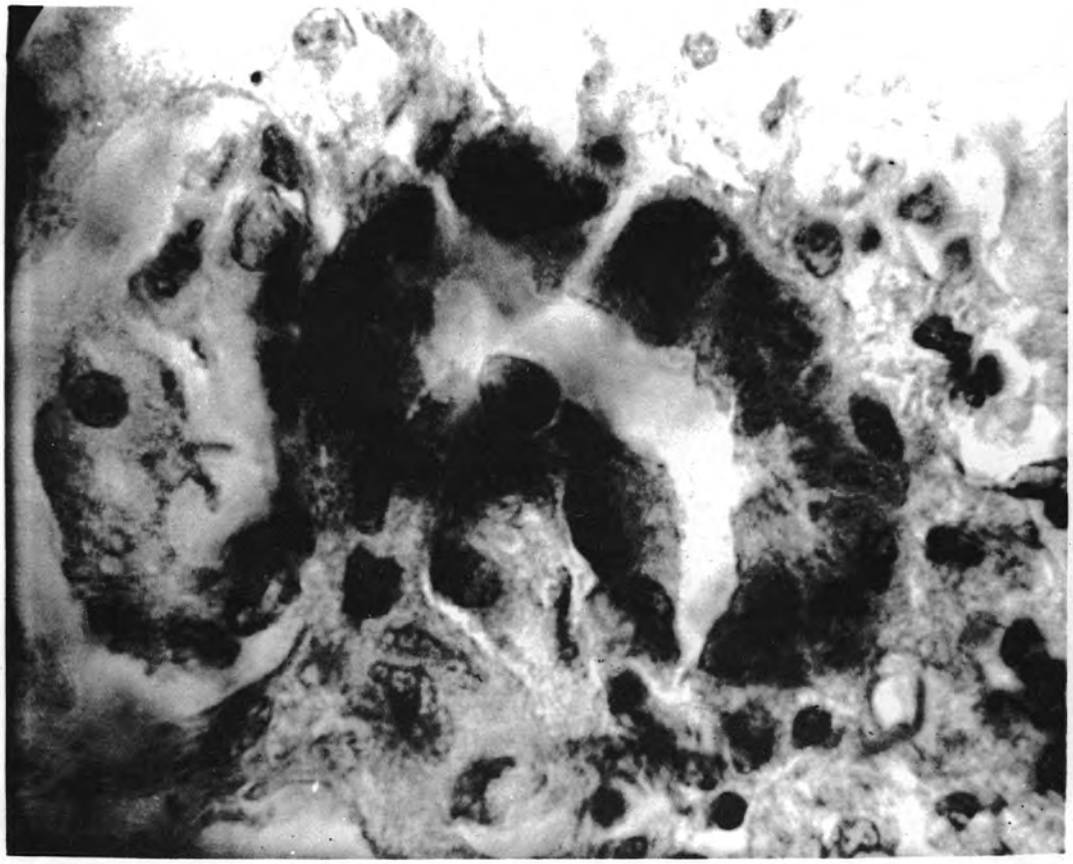


FIG. 9. MICROSCOPIC AUTORADIOGRAM OF KIDNEY SHOWING URANIUM IN OR UPON EPITHELIAL CELLS OF A PROXIMAL CONVOLUTED TUBULE.

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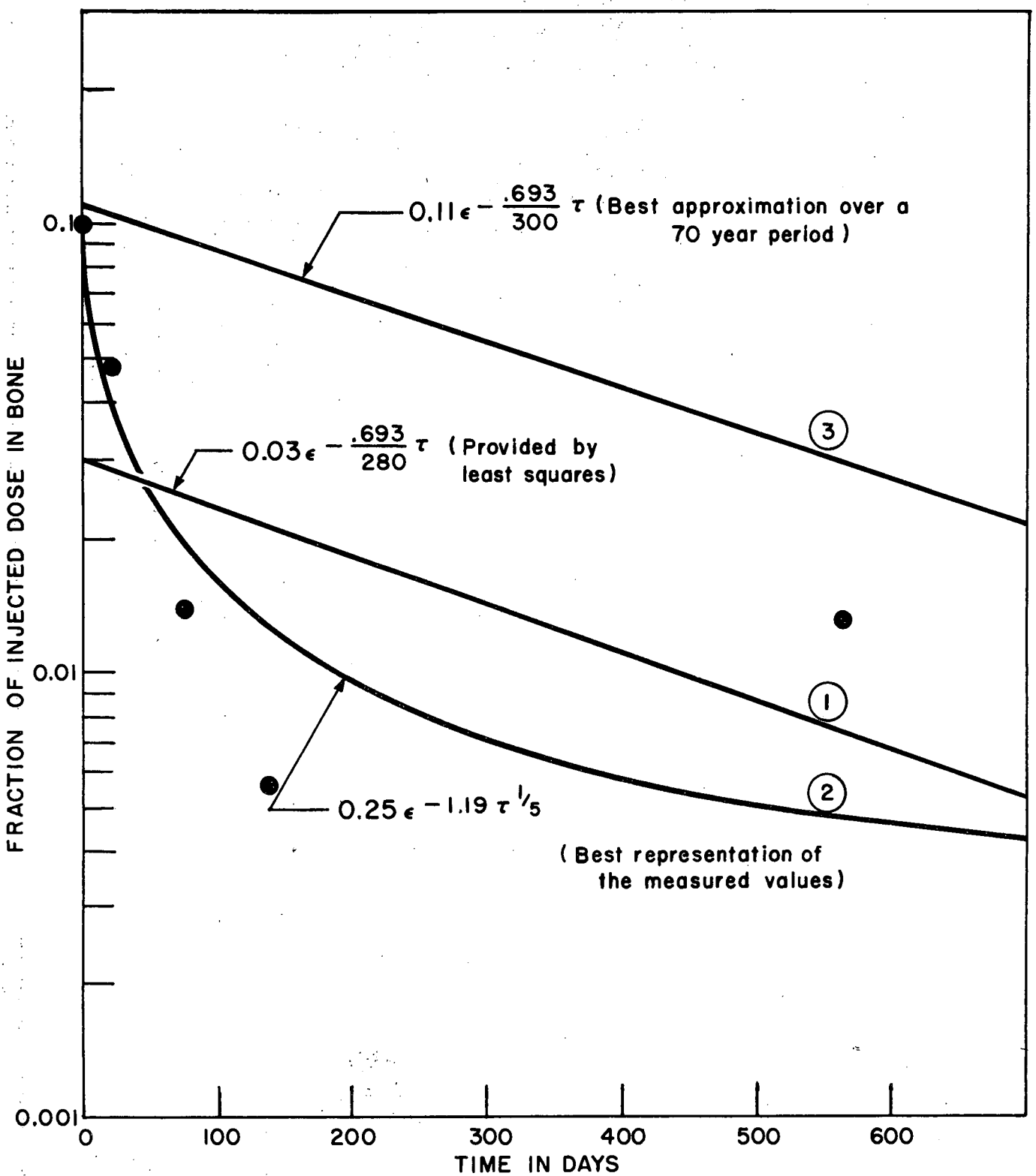

FIGURE 10, BIOLOGICAL HALF LIFE OF URANIUM IN BONE

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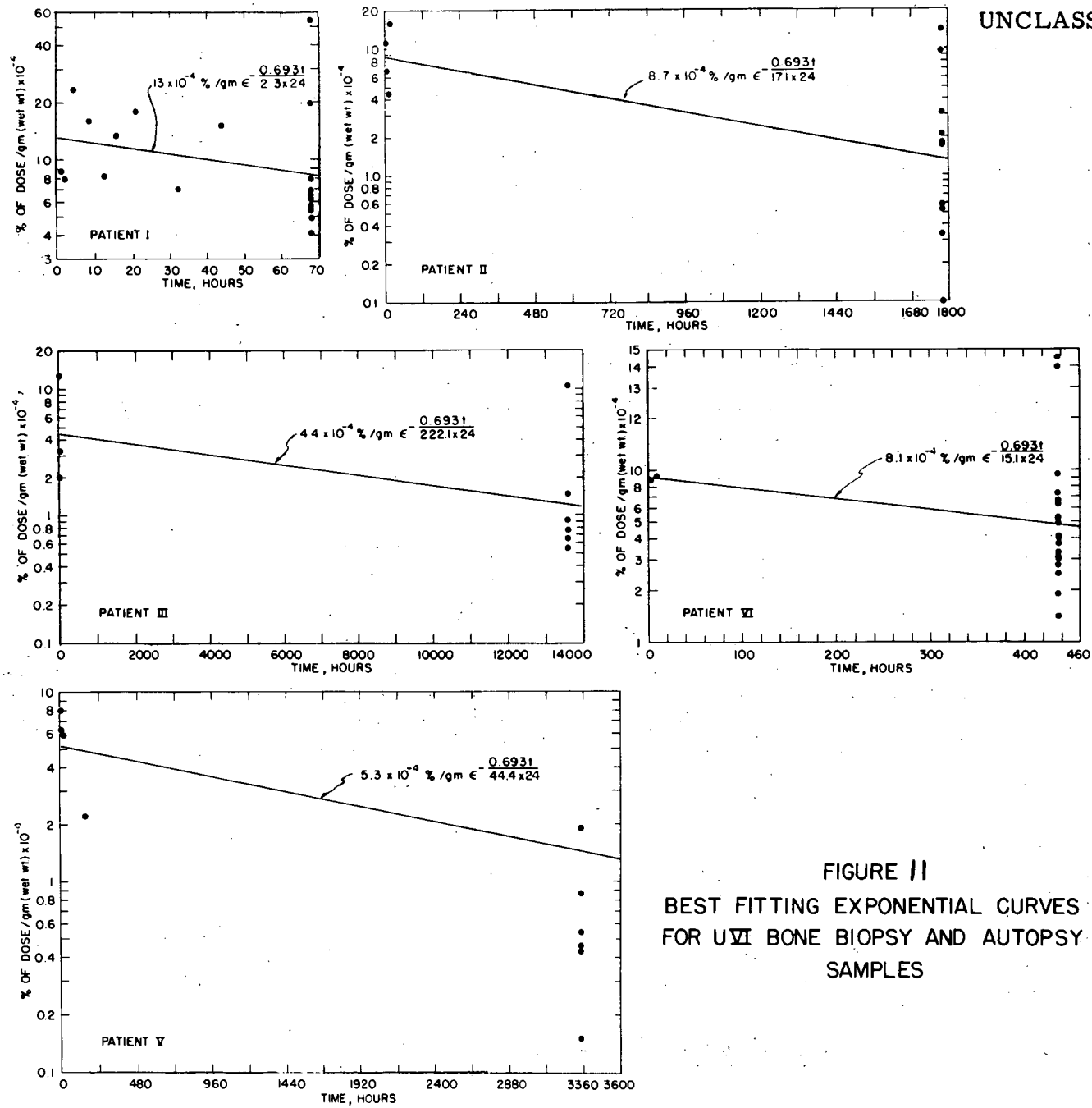

FIGURE 11
BEST FITTING EXPONENTIAL CURVES FOR UVI BONE BIOPSY AND AUTOPSY SAMPLES

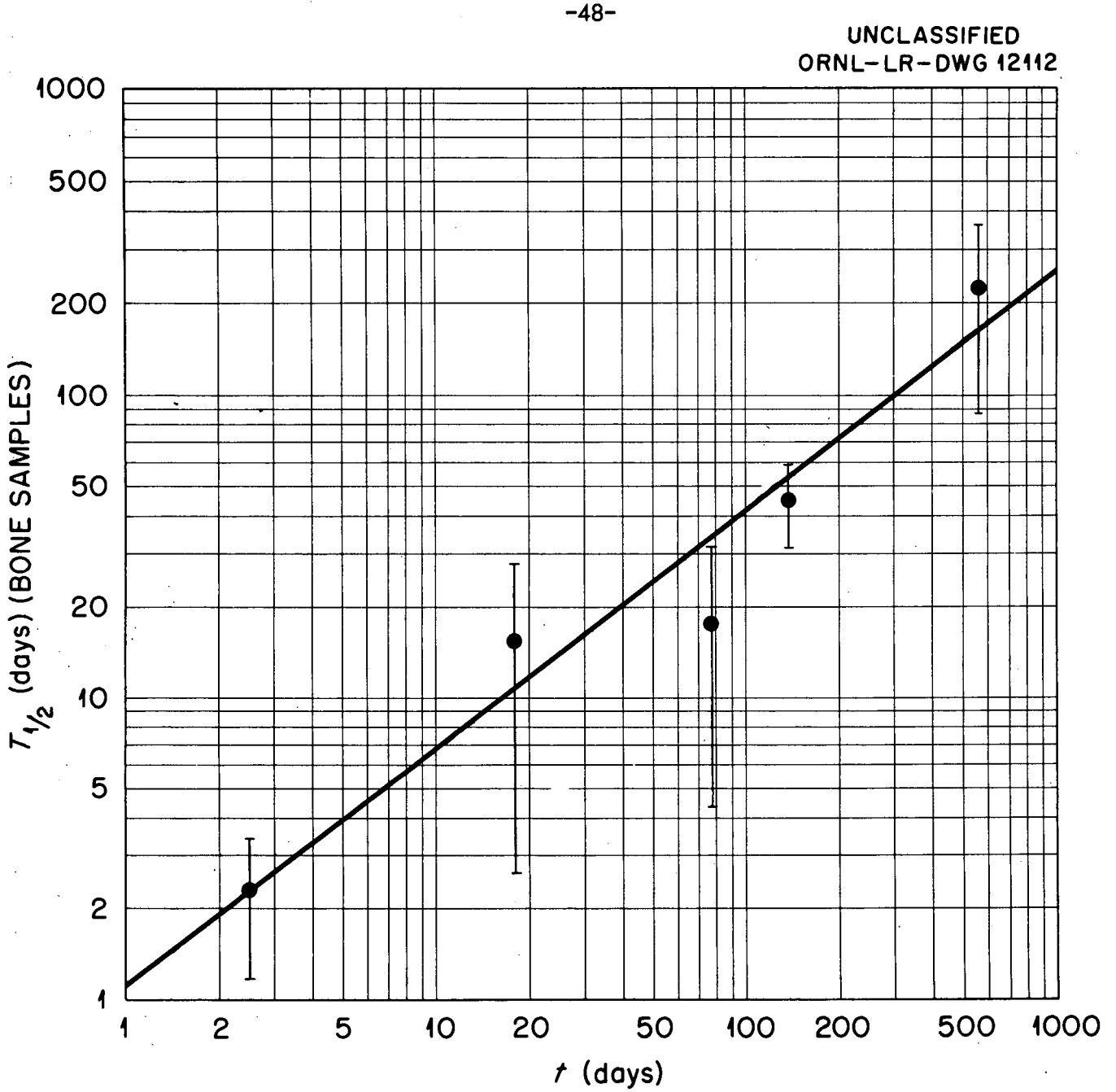

Fig. 12 BIOLOGICAL HALF-LIFE OF URANIUM IN BONE PLOTTED vs EXPIRATION TIME

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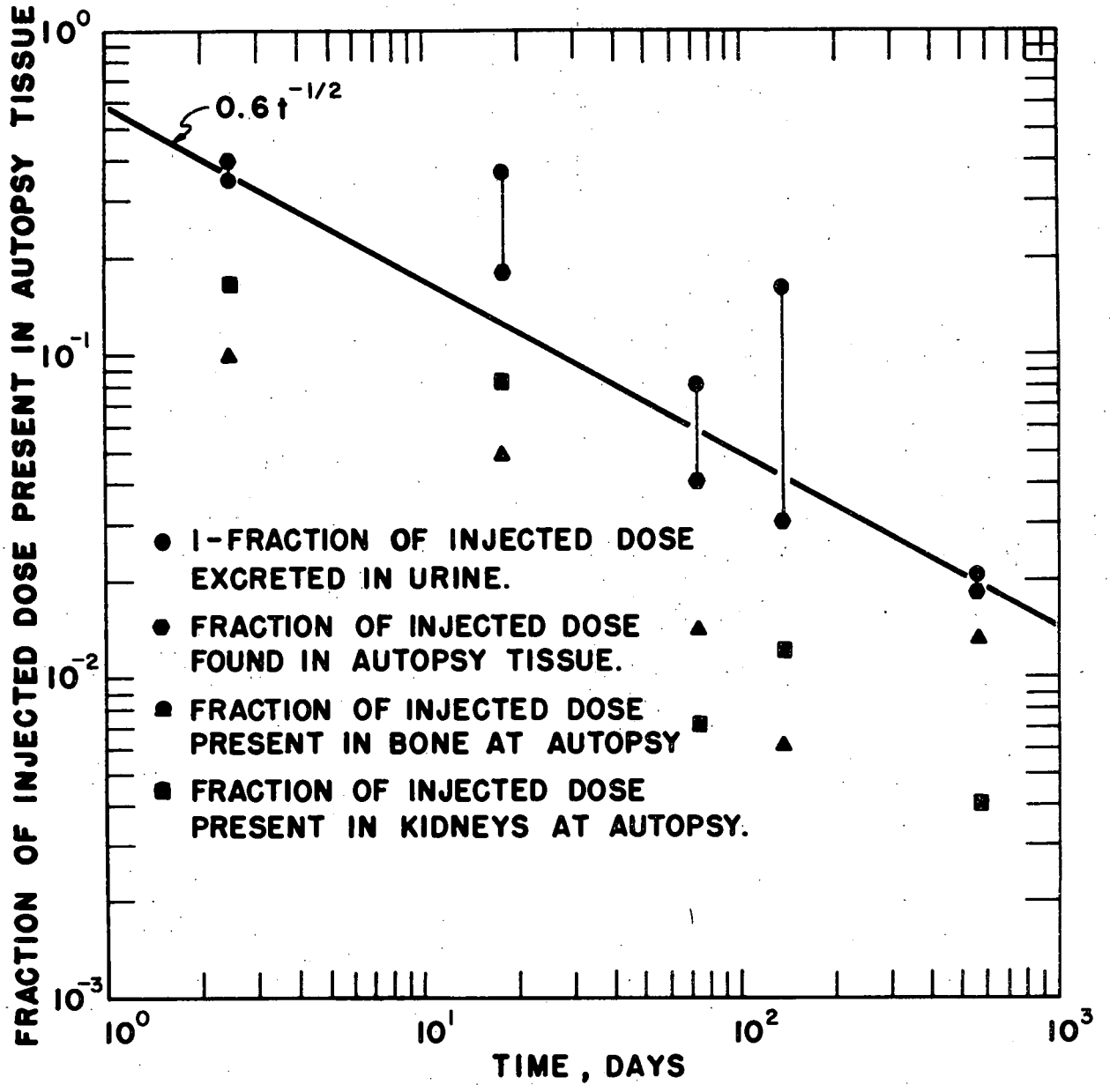

Fig. 13 URANIUM BURDEN IN ORGANS AND BODY

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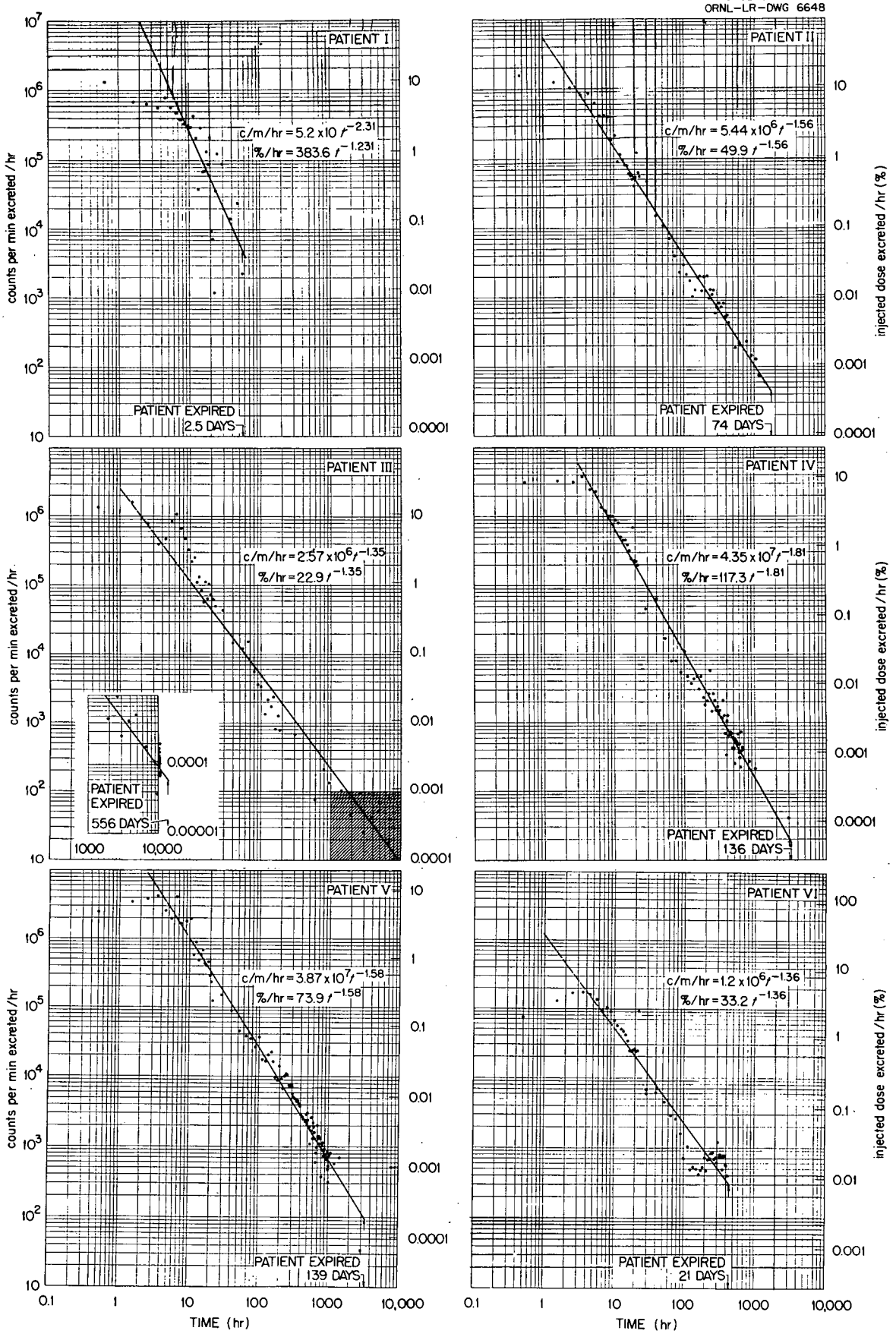

Fig. 14 POWER FUNCTION EXCRETION EQUATIONS

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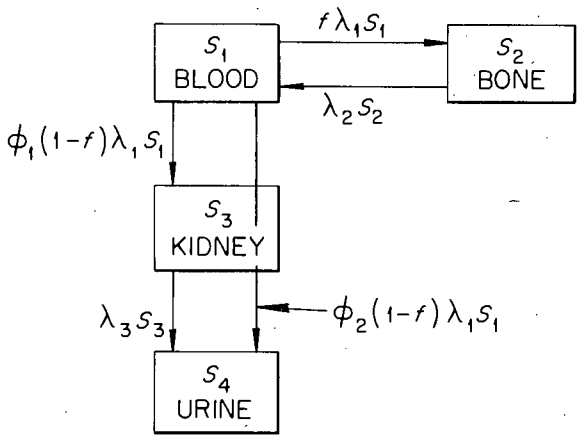
THE MODEL:



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

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

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. 15 MATHEMATICAL MODEL OF THE DISTRIBUTION OF URANIUM

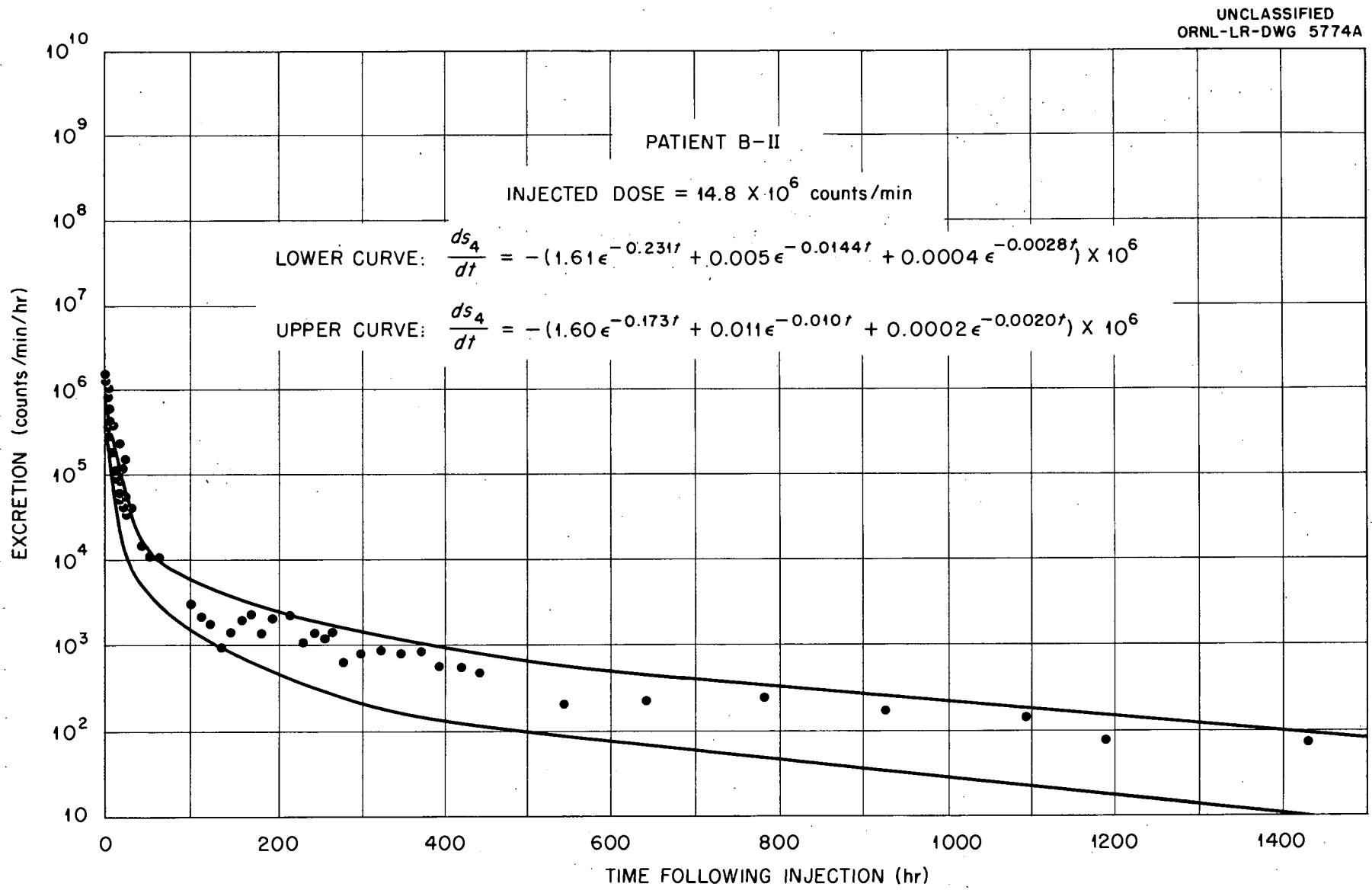


Fig. 16 URINARY EXCRETION RATE (PATIENT II) AND EXCRETION EQUATIONS

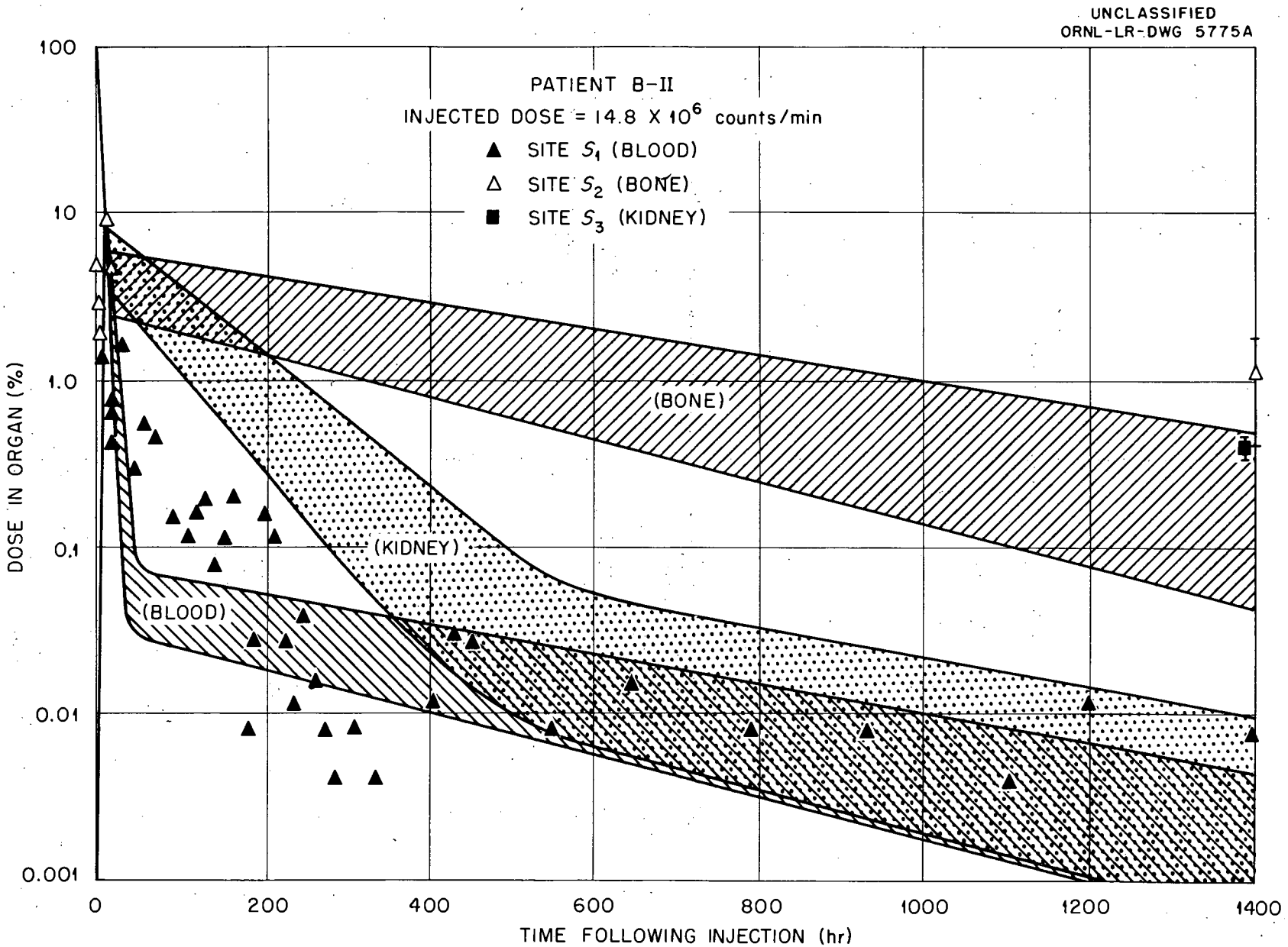


Fig. 17 ESTIMATED DEPOSITION OF URANIUM IN ORGANS

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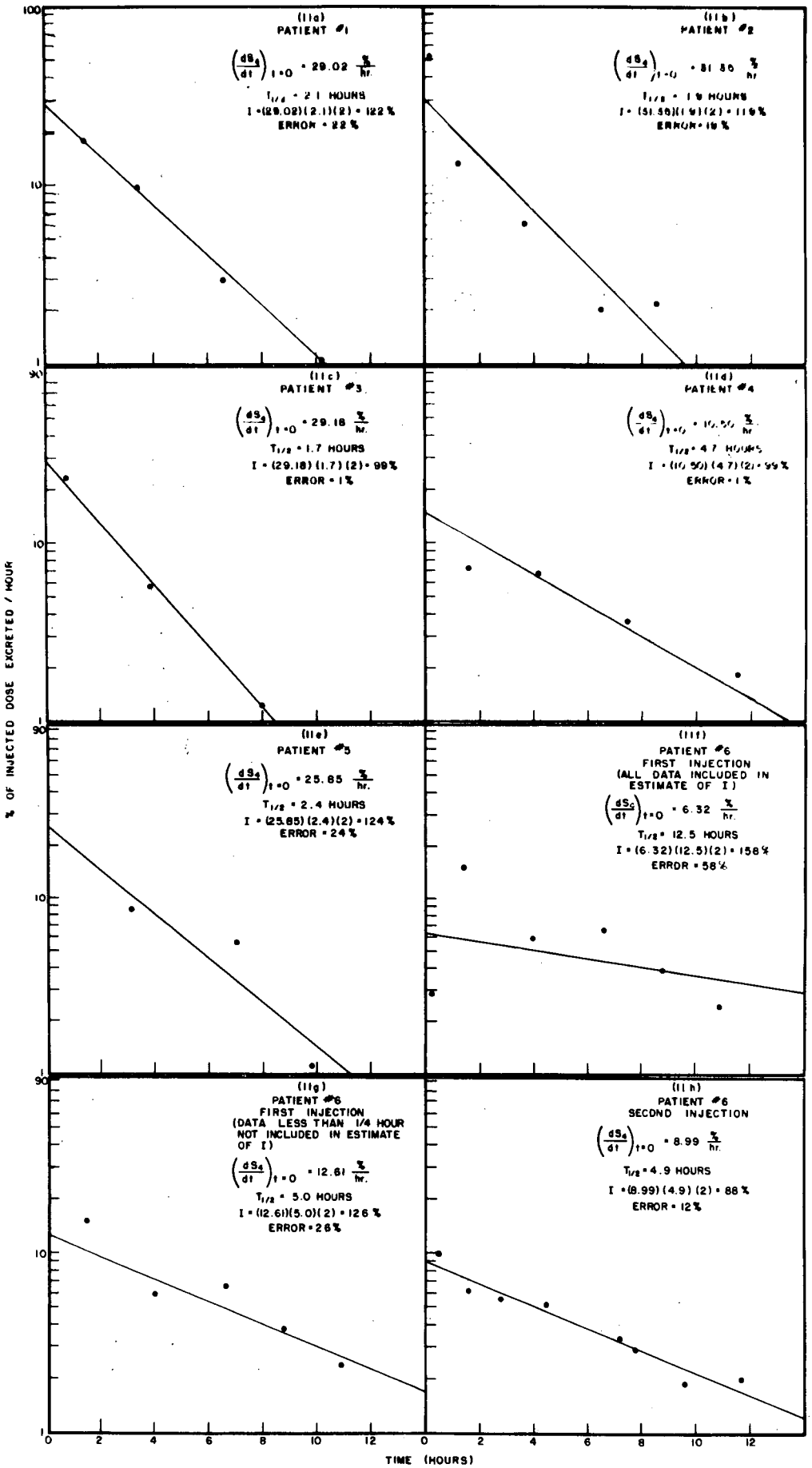

Fig. 18 METHOD OF ESTIMATING INJECTION DOSE FROM URINE DATA

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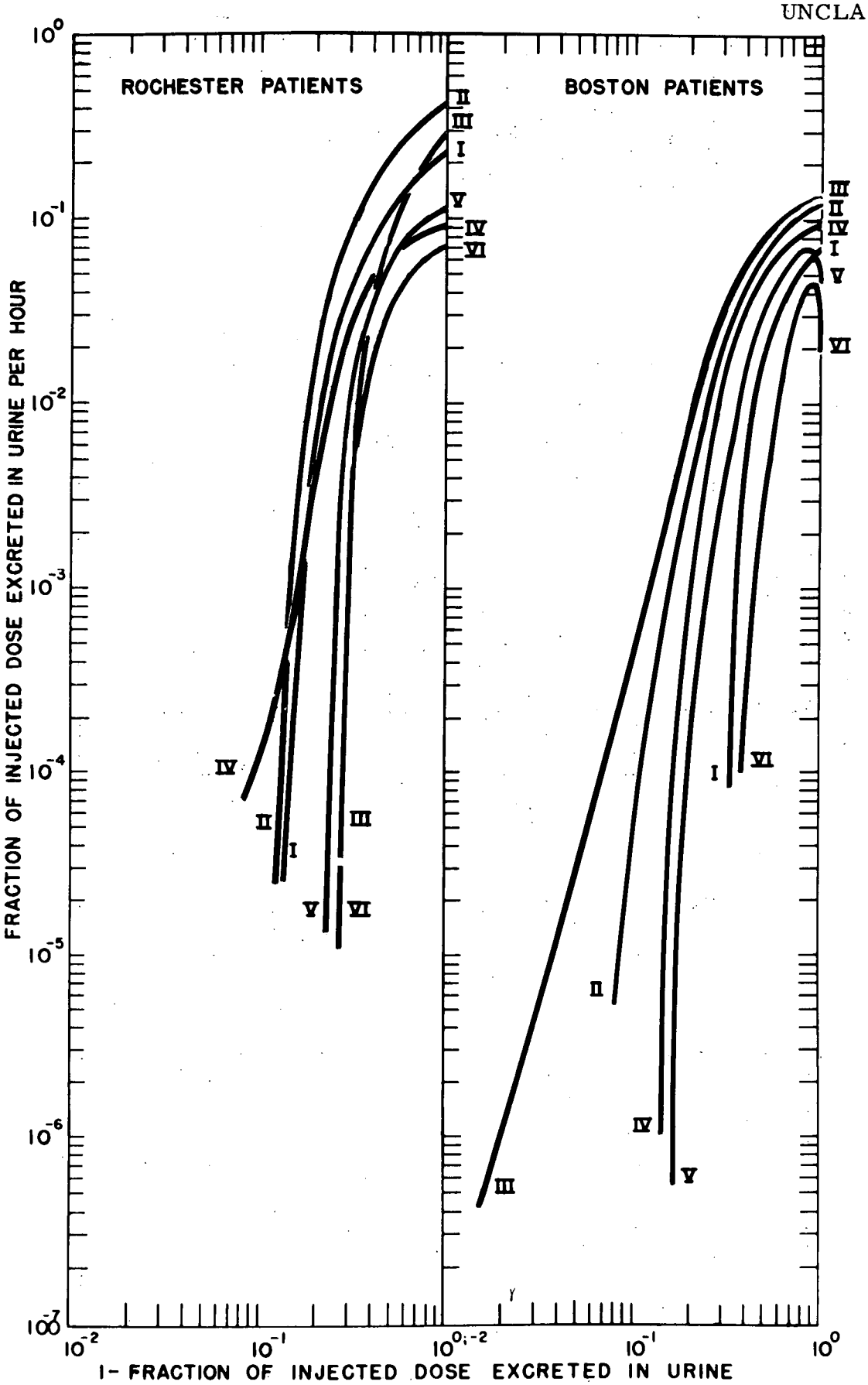

Fig. 19 URINARY EXCRETION RATE AS A FUNCTION OF 1-FRACTION OF INJECTED DOSE EXCRETED

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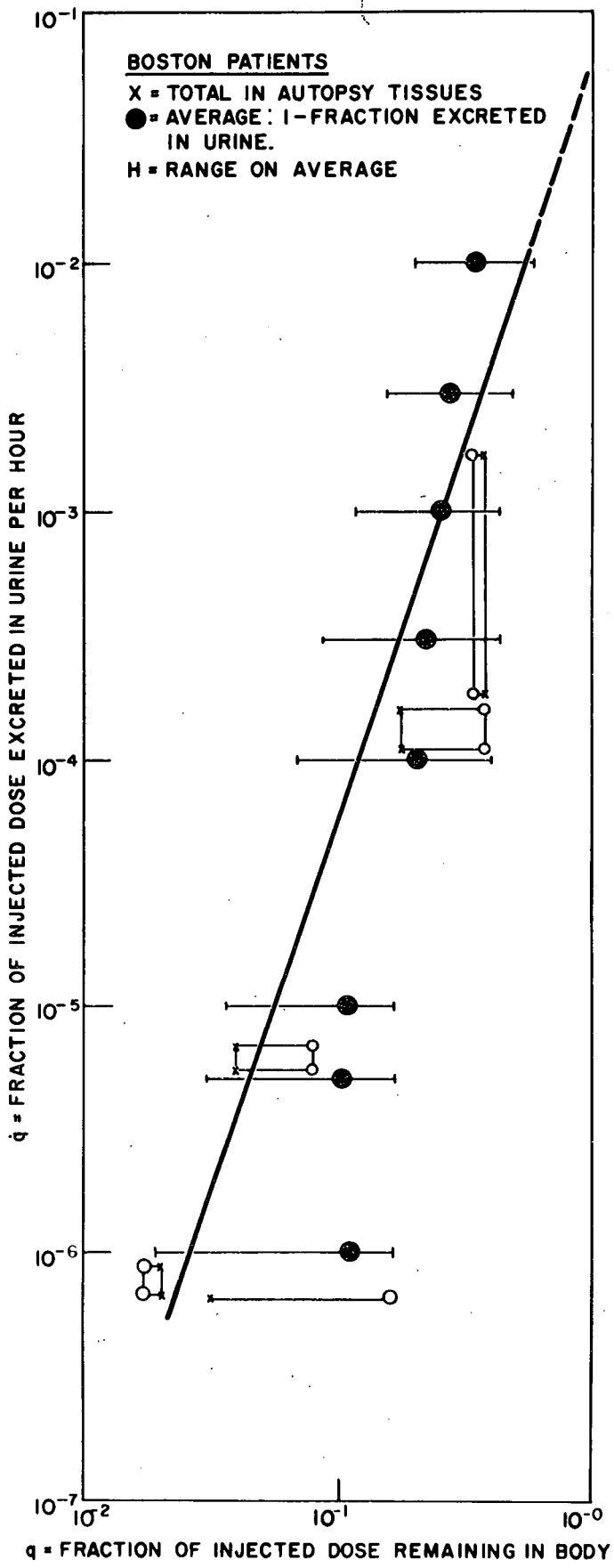
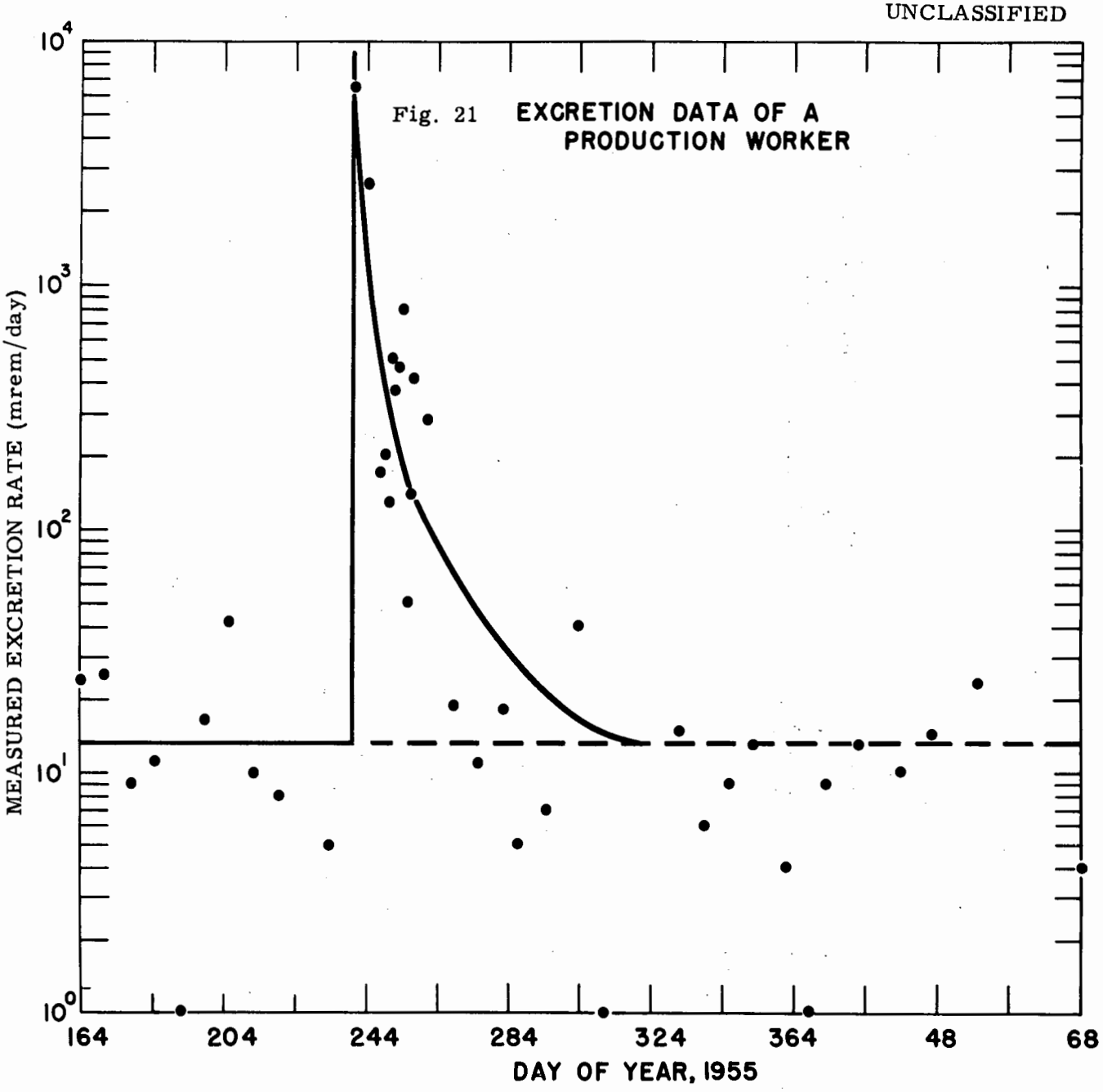


Fig. 20 RATE OF URINARY EXCRETION AS A FUNCTION OF BODY BURDEN

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