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A STUDY OF INDIVIDUAL VARIATION OF EXCRETION OF PLUTONIUM BY MAN AND OF ITS SIGNIFICANCE IN ESTIMATING THE SYSTEMIC BURDEN*

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Abstract

The excretion data of 15 terminal patients, reported by Langham,[1] who received ^{239}Pu by IV injection have been analyzed and studied in the context of the title. Power functions $bt^{-\beta}$ have been fitted to the urinary excretion data U(t) by minimizing (1) the sum of deviations and (2) the sum of percent deviations. This corresponds to minimizing the sums

$$\sum_t \left| U(t) - bt^{-\beta} \right| \qquad \text{and} \qquad \sum_t \left| 1 - \frac{U(t)}{bt^{-\beta}} \right|,$$

respectively. This minimization produces parameter values a and a which provide a best fit to an individual's data; and by pooling all the data, one obtains values of a and a for the group. The distribution of the data U(t) of an individual about his own curve of best fit and about the curve determined for the group is studied, and confidence limits P and p are determined so that the data U(t) only exceed $P\,bt^{-\beta}$ or fall below $p\,bt^{-\beta}$ on a preassigned percentage of days. For example, it appears from analysis of these data that an individual's daily excretion lies between 0.3 and 3 times the power function $bt^{-\beta}$ for the group about 90% of the time. Thus, if a plutonium worker's excretion on a certain day is higher than his previous trend by more than a factor of 3, one may conclude with a

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rather high degree of confidence, perhaps 90%, that he had a new intake to blood. If the employee's excretion is high on a certain day, but not by as much as a factor of 3, then one may conclude there is a chance of 10% or more that the excess represents only a temporary fluctuation and one need not postulate that a new intake has occurred.

The same type of analysis is used with the integral form of the power function, e.g.,

$$\int_{t-1}^{t} bx^{-\beta}\,dx = b\left[t^{1-\beta} - (t-1)^{1-\beta}\right]/(1-\beta)$$

in place of $bt^{-\beta}$. The use of these distributions in estimating body burdens is discussed and illustrated by examples.

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A number of computer codes have been described which interpret the urinalysis data of an employee to obtain an estimate of his intake of plutonium or, alternatively, his body burden.[2-6] All of these codes are based essentially on a model for excretion following a single intake to blood which predicts excretion in terms of a power function, i.e., fraction of a single intake (to blood) excreted t days postexposure is given as $b\,t^{-\beta}$. An employee's exposure plausibly may be considered to consist of a series of single exposures, and the computer codes define a series of intakes at various times which, according to the model, would suffice to some degree of approximation to account for the excretion pattern as measured.

Langham et al.[1] seem to have been the first to use this model for excretion of plutonium when they analyzed the data on some 15 terminal patients who were given ^{239}Pu complexed with citrate by IV injection. They also analyzed excretion data of employees and found that the excretion curves which described the trend of the patient data seemed to be in accord with the data on the employees. In this sense the model may be said to be supported by data out to five or more years postexposure.

Few attempts have been reported for taking statistical fluctuations of the excretion data into account in a systematic way. This paper is a preliminary analysis of the statistical day-to-day fluctuations of excretion data of the hospital patients reported by Langham et al.,[1] the different trends seen in the individual patients, and the different results found

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when the data are analyzed in terms of various models or methods of curve fitting. For brevity these three sources of difference might be referred to as "statistical fluctuations," "individual differences," and "differences in models." Finally, a code is described which allows one to explore to some extent the influence of each of these sources of variability on the estimated systemic burden, and the results of some of the cases studied are shown.

The Basic Model

The basic model for excretion of plutonium which has entered blood and its use in interpreting the urinalysis data of an employee have been described in reference 6. Briefly summarized, the excretion following a single unit intake of plutonium to blood is described by a function f(t) which represents the fraction of initial activity reaching blood at time 0 which is excreted on day t. Langham et al.[1] gave the relation

$$f(t) = b\,t^{-\beta} = 0.0023\,t^{-0.77} \qquad (1)$$

based on the study of the data on the terminal patients mentioned above. In this paper we retain the same essential idea, i.e., to represent excretion by a power function, but use different fitting procedures to obtain b and β.

If the function f is defined as above, t should be considered as a discrete variable, that is, t takes on values 1, 2, 3, ..., but f(t) is not defined for fractions of a day and hence does not define an instantaneous rate of excretion. Alternatively, one may define

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an instantaneous rate of excretion, and in that case the fraction of intake reaching blood at time 0 which is excreted on day t is given by the formula

$$f(t) = \int_{t-1}^{t} b\,\tau^{-\beta}\,d\tau = \frac{b}{1-\beta}\left[t^{1-\beta} - (t-1)^{1-\beta}\right]. \qquad (2)$$

In what follows, the function defined as a power function, that is, as in Eq. (1), will be denoted by f_d to indicate that it is a function fitted to the discrete points where $t = 1, 2, 3, \ldots$; whereas the excretion function defined by Eq. (2) will be denoted by f_c to indicate that it is defined in terms of a continuous rate function and represents the area under the graph of the power function representing the instantaneous rate of excretion. In either case the parameters b and β may be determined by fitting the appropriate function to the data on the hospital patients. In this paper the curve fitting is done in two ways. The first, represented by Eq. (3), minimizes the sub of absolute deviations of the formula about the sample urinary excretion values U_i; and the second curve-fitting procedure, represented by Eq. (4), minimizes the sum of percent deviations of the sample values about the trend curve defined by the function f. Either the point function f_d or the area function f_c may be determined by Eqs. (3) and (4). Thus four different models for excretion following a single intake are studied in the present paper. That is, a function f may be of either type f_d or of type f_c, and the curve fitting may be done my minimizing either the sum of absolute deviations or by minimizing the sum of percent deviations as indicated by Eqs. (3) and (4).

$$\sum_{i=1}^{n} |U_i - f(t_i)| = \text{Min} \tag{3}$$

$$\sum_{i=1}^{n} \left|\frac{U_i}{f(t_i)} - 1\right| = \text{Min.} \tag{4}$$

The curve-fitting procedures defined by Eqs. (3) and (4) have been applied to determine b and β for each of the 15 hospital patients, and the values of b and β determined in this way are shown in Tables I and II which are quoted from reference 6. It will be noted that there is a considerable spread of the values of b and β for different individuals, and this is to some extent a measure of the extent of individual variability among the patients of this group. Only the urinary data will be used in this paper, although the fecal data can be fitted by the same methods. All of the urinary excretion data of the patients may be pooled and the same minimization procedures applied to determine values of b and β which are in a sense representative for the group rather than for an individual patient. The excretion model determined for the group will be referred to in what follows as the "typical" excretion formula or excretion model. The values of b and β so determined are shown in Tables I and II.

Day-to-Day Fluctuations of Excretion Data

The excretion models determined in the preceding section only establish a trend of these data, and it is well known that there are wide fluctuations in the day-to-day excretion data. To establish some measure of the extent of this fluctuation, the distribution of the ratios $U_i/f(t_i)$ has been studied. When this ratio is less than 1, the sample value lies below the curve defining the trend of the data, and when it exceeds 1, the sample value is in excess of the trend curve. The cumulative curve for the distribution

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Table I. Urinary Excretion Formulas, $bt^{-\beta}$, for Fifteen Individuals (Obtained by minimizing the sum of the absolute deviations)

Patient	"Point Fit"		"Area Fit"	
	b	β	b	β
Hp-1	0.24	0.74	0.10	0.42
Hp-2	0.47	1.04	0.17	0.63
Hp-3	0.38	0.99	0.17	0.71
Hp-4	0.44	0.89	0.20	0.54
Hp-5	0.30	1.10	0.11	0.62
Hp-6	0.50	1.21	0.31	0.99
Hp-7	0.24	1.02	0.078	0.64
Hp-8	0.38	0.88	0.16	0.58
Hp-9	0.12	0.48	0.096	0.40
Hp-10	0.41	0.98	0.17	0.60
Hp-12	0.15	0.58	0.087	0.40
Chi-I	0.86	1.85	0.18	0.79
Chi-II	0.25	0.73	0.20	0.66
Chi-III	0.15	0.86	0.071	0.53
Cal-I	0.48	1.19	0.12	0.74
All the patients	0.32	0.93	0.15	0.65

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Table II. Urinary Excretion Formulas, $bt^{-\beta}$, for Fifteen Individuals (Obtained by minimizing the sum of the percent deviations)

Patient	"Point Fit" b	"Point Fit" β	"Area Fit" b	"Area Fit" β
Hp-1	0.28	0.82	0.18	0.65
Hp-2	0.66	1.21	0.17	0.63
Hp-3	0.57	1.20	0.16	0.72
Hp-4	0.44	0.89	0.19	0.56
Hp-5	0.18	0.79	0.11	0.62
Hp-6	0.50	1.21	0.31	0.99
Hp-7	0.48	1.26	0.089	0.75
Hp-8	0.32	0.81	0.23	0.73
Hp-9	0.12	0.47	0.096	0.40
Hp-10	0.73	1.22	0.16	0.72
Hp-12	0.15	0.57	0.12	0.52
Chi-I	0.11	0.61	0.099	0.57
Chi-II	0.17	0.62	0.16	0.60
Chi-III	0.15	0.83	0.083	0.45
Cal-I	0.26	0.88	0.13	0.72
All the patients	0.21	0.73	0.14	0.61

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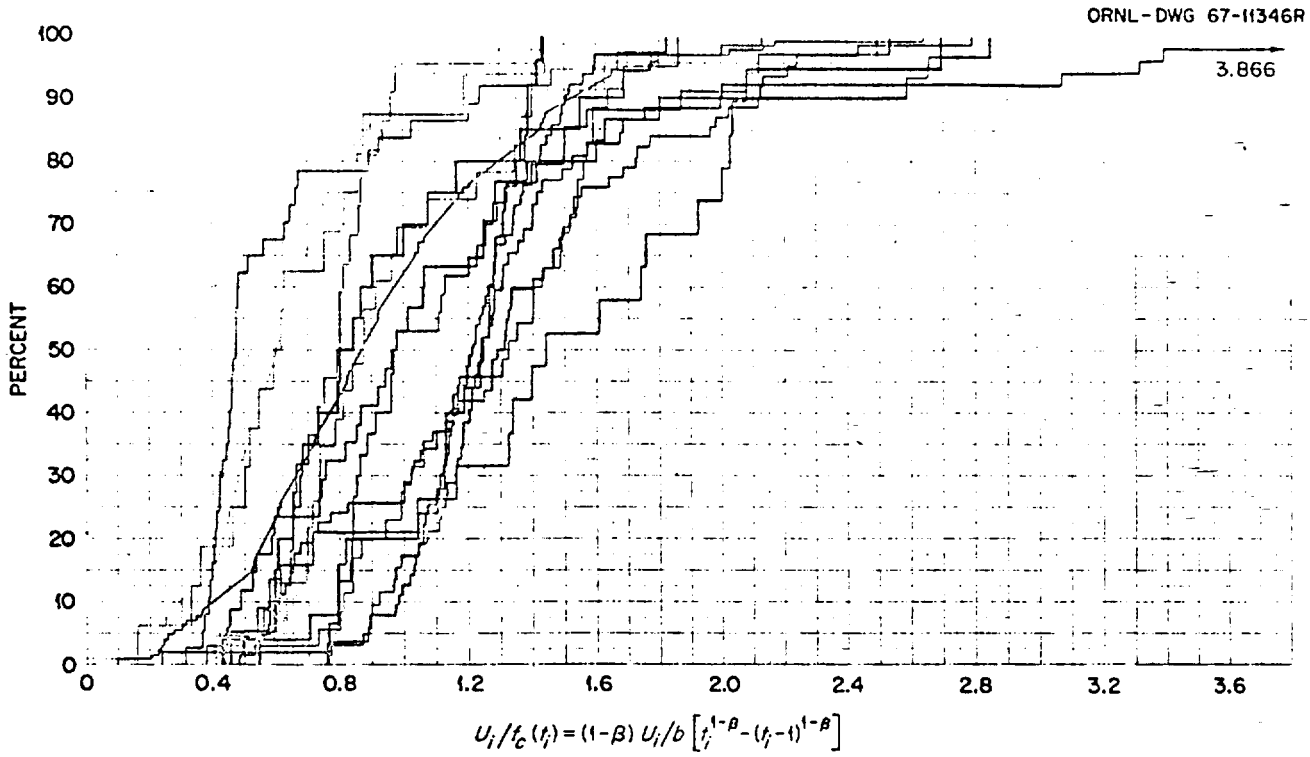
of these ratios has been determined in each case. This cumulative curve rises from the value 0 at the smallest value of the ratio and attains the value 1 for the largest value of the ratio in each individual case. Figure 1 shows a typical example of these curves for the 15 hospital patients. The excretion function f_c used here is that determined for the fluctuations around the typical excretion formula defined by Eq. (3) for the group. Figures 2, 3, and 4 show the similar data for other versions of the excretion model, but the individual curves have been omitted so that only the broad band containing all the individual curves is shown. From this band one can read off the extreme values of the ratio which would contain a specified percentage of the daily excretion values for each of the individuals. For example, using Fig. 1 it is apparent that for none of the patients was there more than 10% of the daily excretion data for which the ratio fell below 0.30 and for no patient were as many as 10% of the daily excretion values in excess of the number 2.59. Thus an 80% range for the ratio of the daily sample to the trend curve for the group is given by the range of ratios from 0.30 to 2.59. These distributions provide a measure of the extent of day-to-day fluctuations of an individual about his own trend curve or of an arbitrary individual of the group about the group trend curve. One may well hesitate to apply either of these measures of day-to-day fluctuations to employees whose individual trend curves are unknown and where there is little information on the extent of fluctuations of the group. Nevertheless, this is almost the totality of data of this kind that are available. One may mention, however, the study of Beach and Dolphin[7] who obtained distributions grossly similar to these based on employee data which were normalized in terms of their body burdens of plutonium.



Fluctuations of Daily Urinary Excretion Data of all Patients (Langham-1950) about the "Typical" Formula of Best Fit – "Area Fit" Formula Obtained by Minimizing the Sum of Absolute Deviations.

Fig. 1

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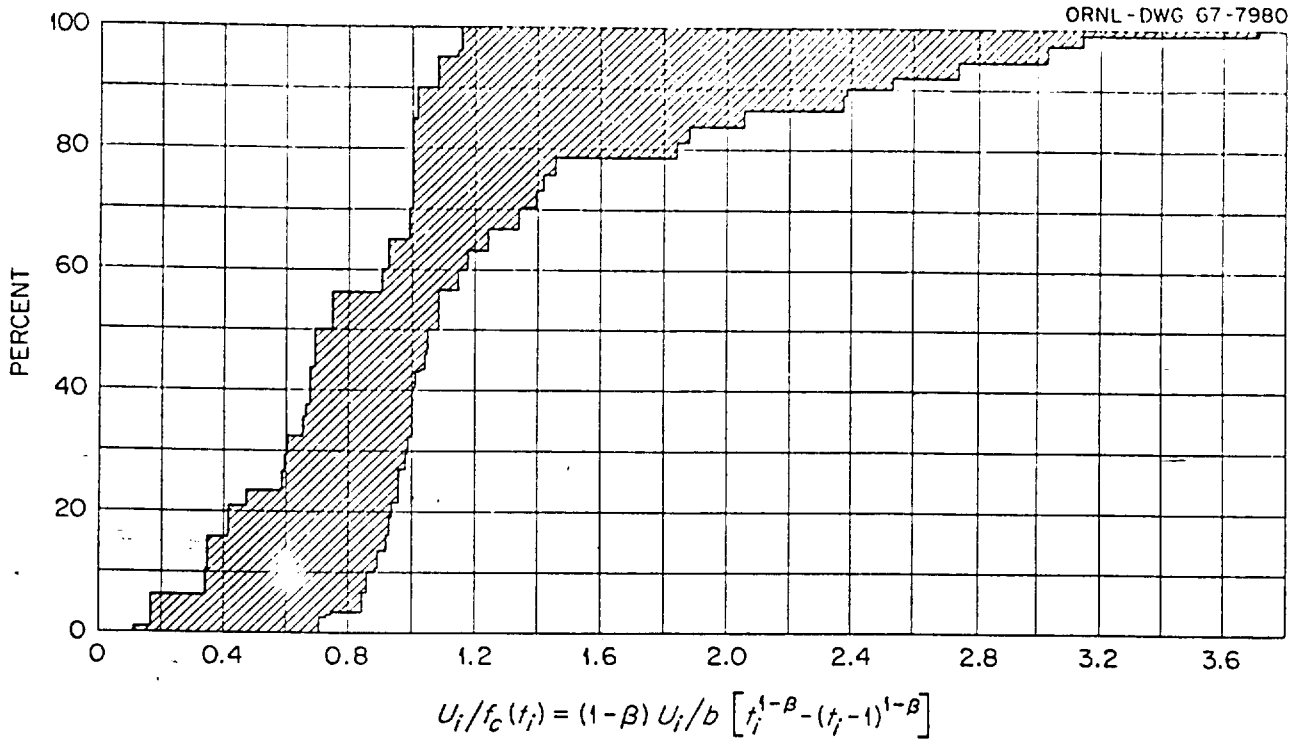

Fluctuations of Daily Urinary Excretion Data of all Patients (Langham-1950) about their Own Formula of Best Fit — "Area Fit" Formulas Obtained by Minimizing the Sum of Percent Deviations.

Fig. 2

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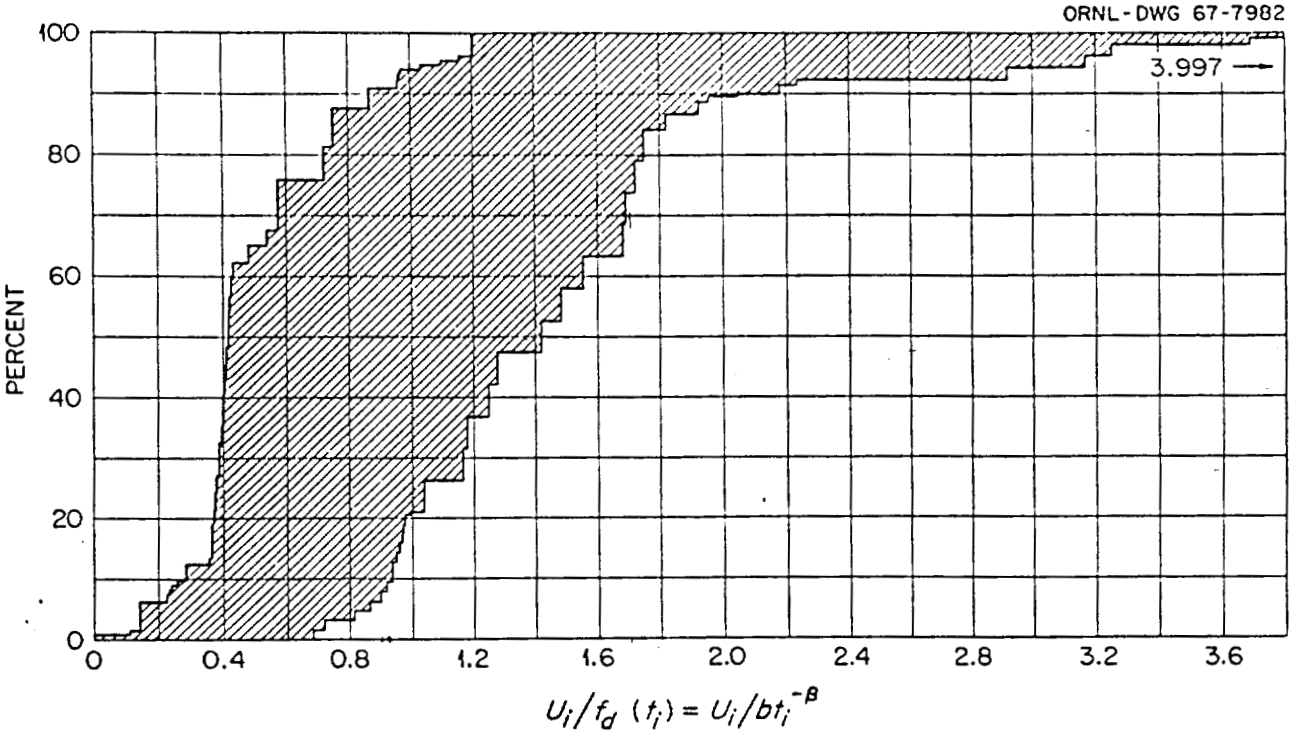

Fluctuations of Daily Urinary Excretion Data of all Patients (Langham-1950) about the "Typical" Formula of Best Fit – "Point Fit" Formula Obtained by Minimizing the Sum of Percent Deviations.

Fig. 3

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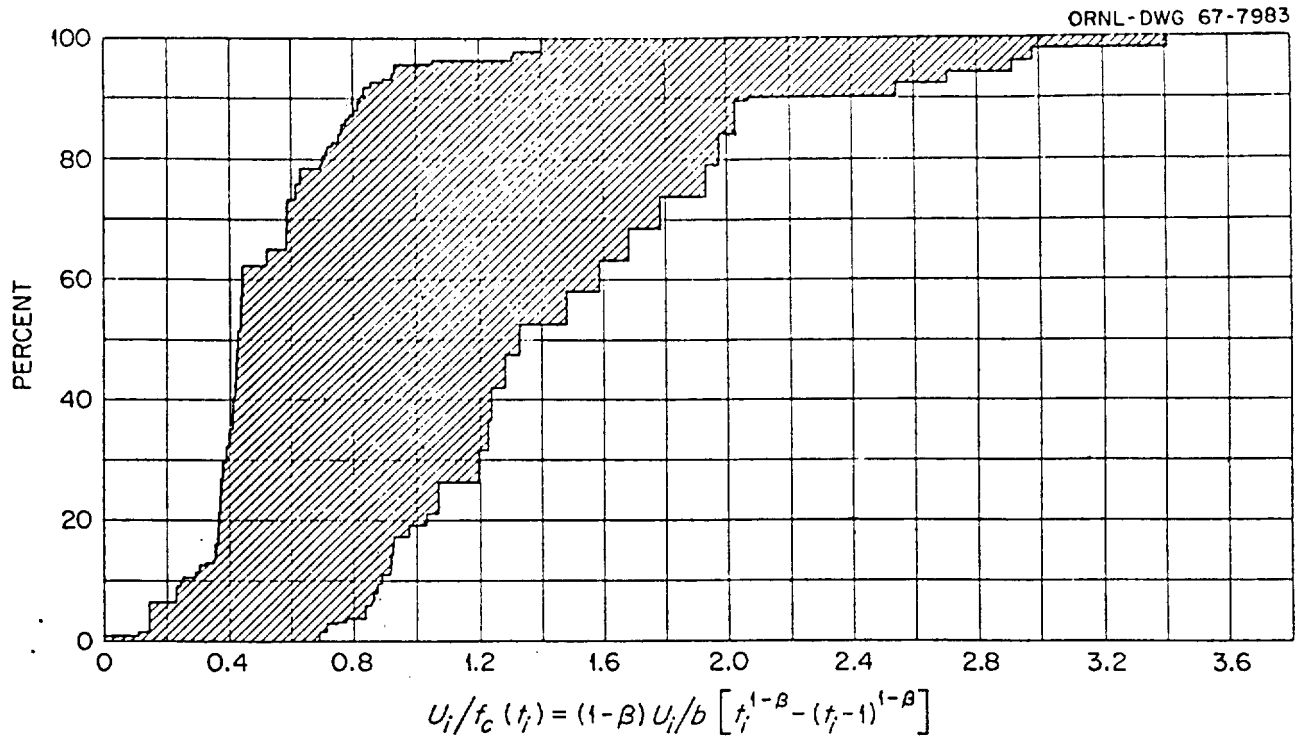

Fluctuations of Daily Urinary Excretion Data of all Patients (Langham-1950) about the "Typical" Formula of Best Fit -"Area Fit" Formula Obtained by Minimizing the Sum of Percent Deviations.

Fig. 4

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A Computer Code for Estimation of the Intake of Plutonium to Blood on the Basis of Excretion Data

The input for the code consists of the sample values U_i and the days t_i on which the sample was taken. It is assumed that each sample represents a 24-hr period of excretion. Essentially the design of the code is based on the supposition that an intake is potentially possible between each successive pair of sample values, and the code is designed to produce intakes which will reproduce the excretion data as nearly as possible on the basis of the model. Basically this is achieved in the following way. Assuming that the data on excretion are given by

$$U_i,\ t_i \qquad i = 1, 2, 3, \ldots n \tag{5}$$

one seeks to determine intake values

$$I_i \text{ on day } \tau_i \qquad i = 1, 2, 3, \ldots n. \tag{6}$$

Since the intakes to blood must be spaced between the sample values, one requires that

$$t_{i-1} < \tau_i \leqq t_i \qquad i = 1, 2, 3, \ldots n. \tag{7}$$

The first intake is determined as in Eq. (8) where the quantity $t_1 - \tau_1 + 1$ represents the number of days from the first intake on day τ_1 to the first sample day t_1. The convention has been made that intake is assumed to occur at the beginning of the day while the sample collection is only complete at the end of the day. There is a certain

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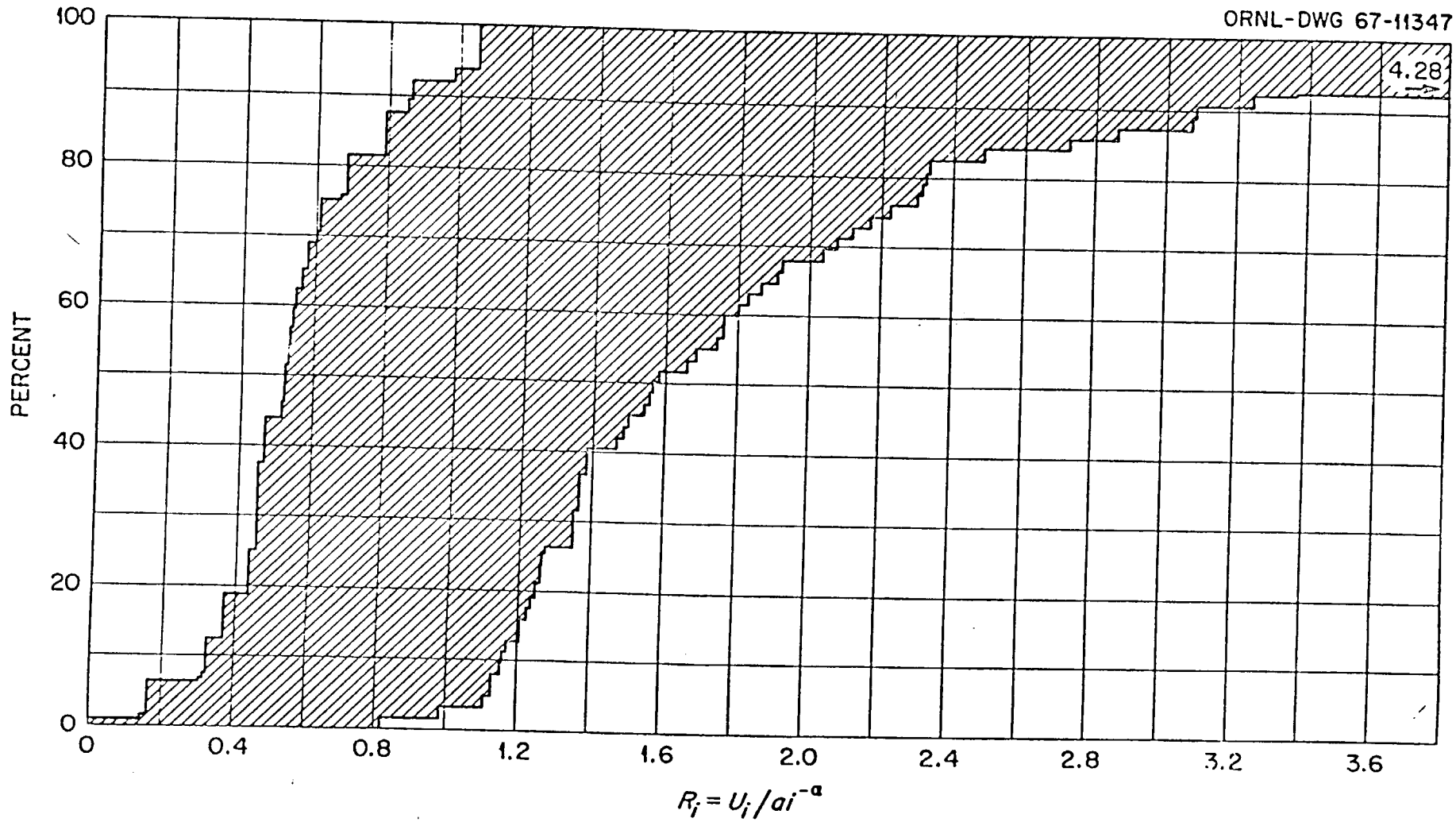

Fluctuations of Daily Urinary Excretion Data of all Patients (Langham - 1950) about the *Typical* Formula of Best Fit - "Point Fit" Formula Obtained by Minimizing the Sum of *Absolute* Deviations

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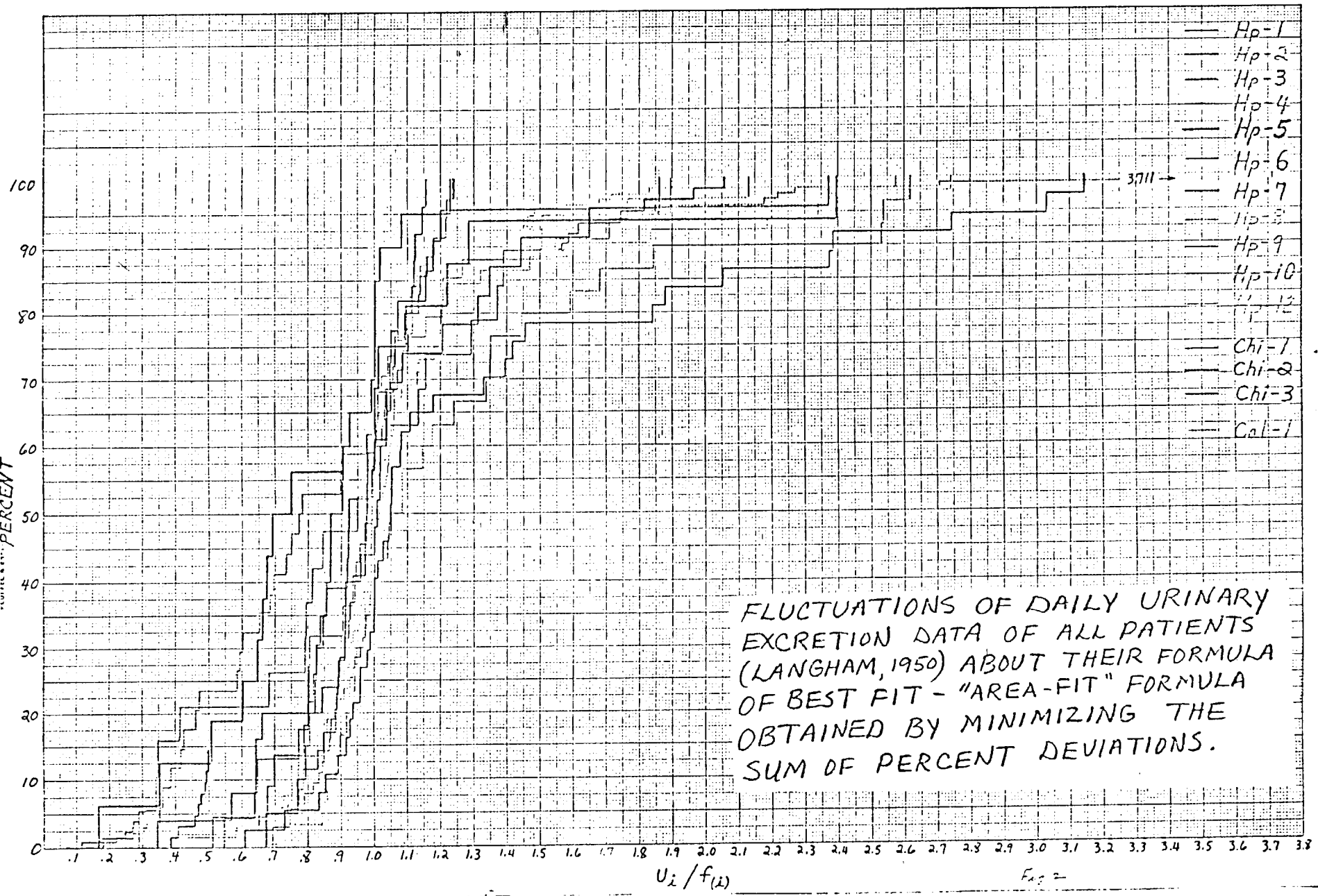

FLUCTUATIONS OF DAILY URINARY EXCRETION DATA OF ALL PATIENTS (LANGHAM, 1950) ABOUT THEIR FORMULA OF BEST FIT - "AREA-FIT" FORMULA OBTAINED BY MINIMIZING THE SUM OF PERCENT DEVIATIONS.

Fig 2

OWN FORMULA
"AREA-FIT"

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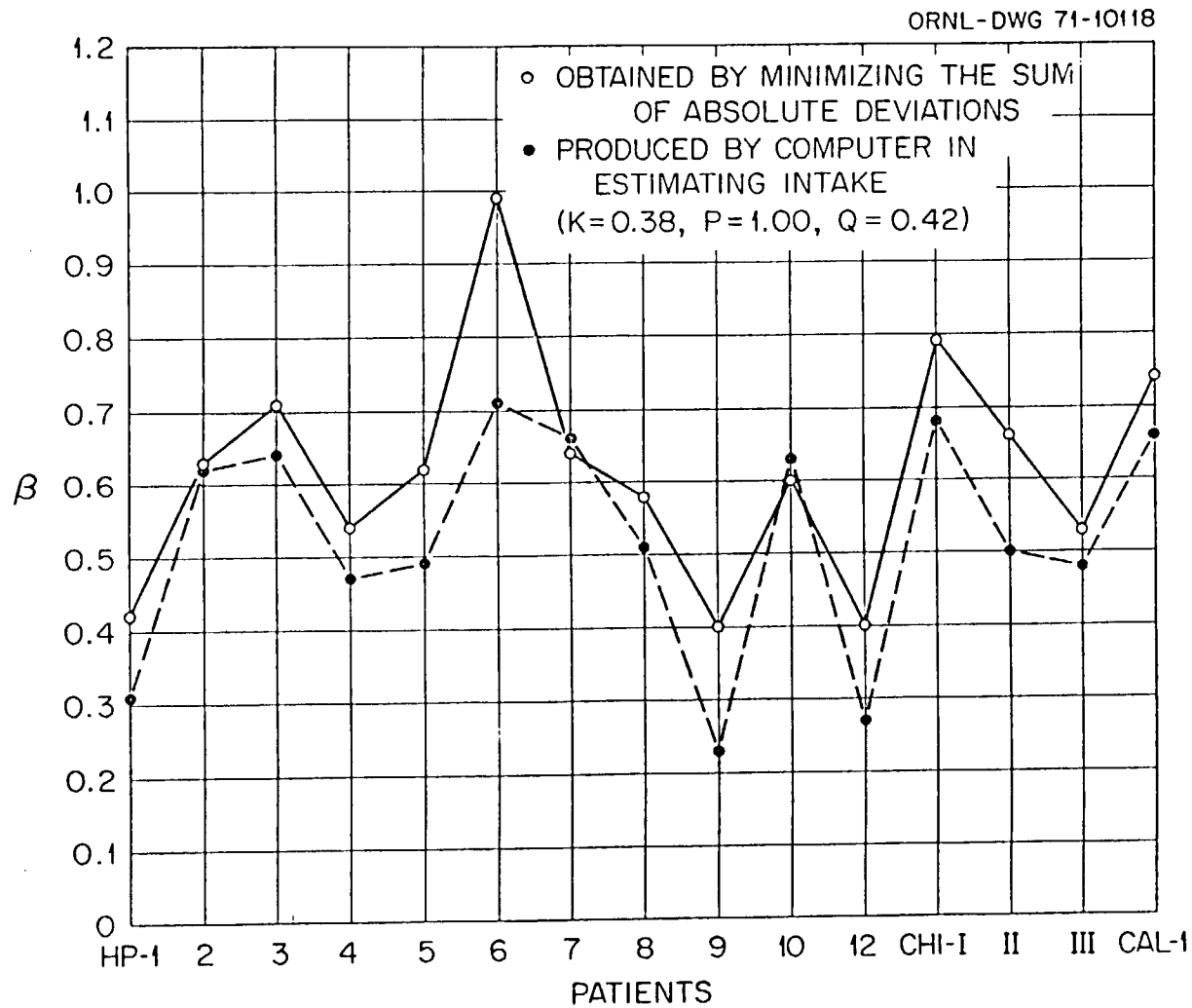

Exponents of Power Function $bt^{-\beta}$ for Excretion of Plutonium (Langham's Patients).

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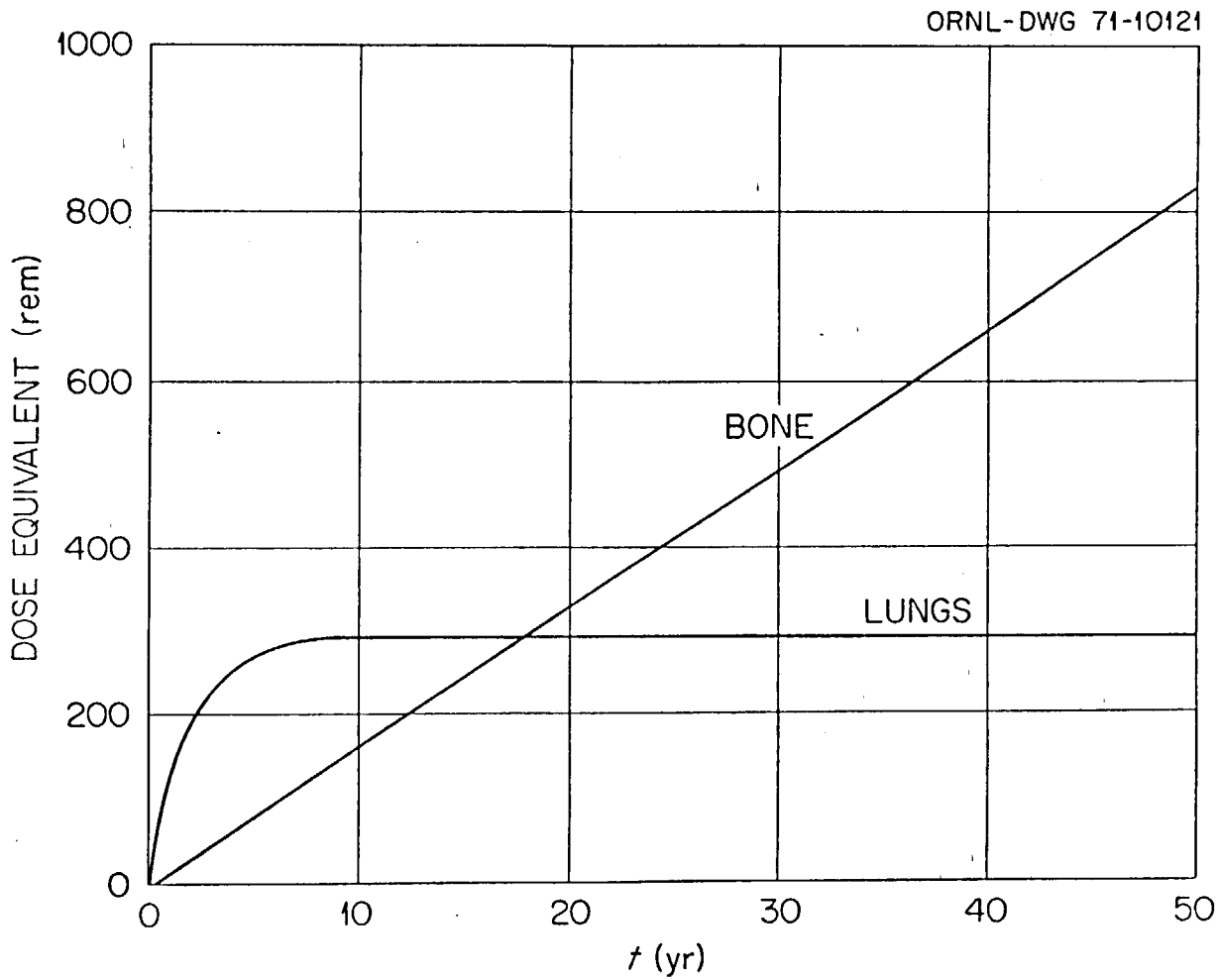

Accumulated Dose Equivalent to Lungs and Bone Following Inhalation of 1 μCi of ^{239}Pu. (Class Y Material, AMAD = 1 μm)

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degree of indeterminacy in Eq. (8) in that the function f may be any one of the functions as defined in Tables I and II and the variable τ_1 may be any day subject to the inequalities given by (7), that is, $0 < \tau_1 \leqq t_1$. Whatever the choice of the function f or of the day τ_1, the intake I_1 on day τ_1 will exactly reproduce the sample value U_1 according to the chosen model. In principle, the computer code then proceeds by induction. If intakes I_j have been defined for the first $i - 1$ cases, i.e., $j = 1, 2, \ldots, i - 1$, these intakes already account for some of the activity found in the sample on day t_i. This amount is represented by the sum in formula (9) which is then subtracted from U_i, so that only the remainder, i.e., the bracketed quantity, needs to be accounted for by the new intake I_i.

$$I_1 = U_1/f(t_1 - \tau_1 + 1) \tag{8}$$

$$I_i = \left[U_i - \sum_{j=1}^{i-1} I_j \, f\,(t_i - \tau_j + 1)\right] \Big/ f\,(t_i - \tau_i + 1) \tag{9}$$

One continues in this way to define successively the intakes I_i, and this would be a complete and rigorous solution to the problem if individuals exactly followed the trend formula defining f. Unfortunately, there are wide day-to-day fluctuations of the excretion data about the trend curve, and one cannot proceed in such a simple fashion as that indicated above. It may, for example, happen that the bracketed term in Eq. (9) may be negative, i.e., the previous intakes already more than account for the excretion as seen on day i. In this case no new intake is necessary, since an excess has already been accounted for according to the model. That this situation may occur is no cause for

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surprise since it may happen that the sample collected on day i is one which fell below the trend curve, that is, it was an unusually low output for that particular day. However, in such case, one need not seek for a positive intake, and one merely sets $I_i = 0$.

Likewise, it may happen that the numerator of formula (9) is not very large compared to U_i; that is, the previous intakes already account for most of U_i, or perhaps account for U_i within a fairly small factor. In this case one may be tempted to regard the excess as merely due to chance, i.e., as one of the high daily fluctuations. One may make this precise by using the distributions given in Figs. 1-4; that is, one may assign confidence limits within which the day-to-day fluctuations appear to lie with a certain degree of probability. Thus the values 0.30 and 2.59 specified earlier and based on Fig. (1) would be values such that, for that excretion model, in no patient did the ratio of the daily excretion to the trend formula lie outside this range in more than 20% of the cases. Using only the high value of 2.59, one may say that if an excess by more than this amount occurs, one has 90% confidence that there has been additional intake. One may then introduce into the code a test so that if the ratio satisfies the inequality (10) where P is chosen to represent the upper limit of daily fluctuations at the prescribed confidence level, then and only then does one postulate a new intake. Otherwise, if the ratio does not exceed P, one may postulate no additional intake but regard the excess represented by the bracket in formula (9) as being merely due to chance fluctuations.

$$U_i \Big/ \sum_{j=1}^{i-1} I_j \, f(t_i - \tau_j + 1) > P \qquad (10)$$

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The procedures mentioned above represent only a few of the possibilities which can be made a part of the code for estimation of systemic body burden or, alternatively, of intake to blood of plutonium. One may take the code as so designed, test it by using the excretion data of any or all of the hospital patients, and see with what degree of accuracy the code will predict the actual intake. This has been done for a number of the different models discussed above and at various confidence levels for the fluctuations, and the results are shown graphically in Figs. 5 and 6. Actually, no one of the models appears to be greatly superior to any one of the others, nor do the confidence levels tested thus far for taking account of daily fluctuations seem to make any great difference in the final estimate. In a few cases excessively high values of intake seem to be obtained. These are notably absent when the model uses the area formula, especially that where the absolute deviations are minimized. It appears that when no allowance is made for fluctuations the estimates tend to be high, and this is understandable because each high fluctuation may require some new intake to account for the excess. When allowance is made for fluctuations, this tendency is less pronounced. The cases tried here represent only a few of the many possibilities which may be tested, and various other ways of taking daily fluctuations into account are under study. It is hoped that this approach will eventually lead to a procedure which will not require that a new intake be prescribed for each high value that occurs since some of these may indeed be merely chance fluctuations of the data.

There remains one additional case in which the body burden is known, and that is the case reported by Foreman et al.[8] of a plutonium worker who was killed

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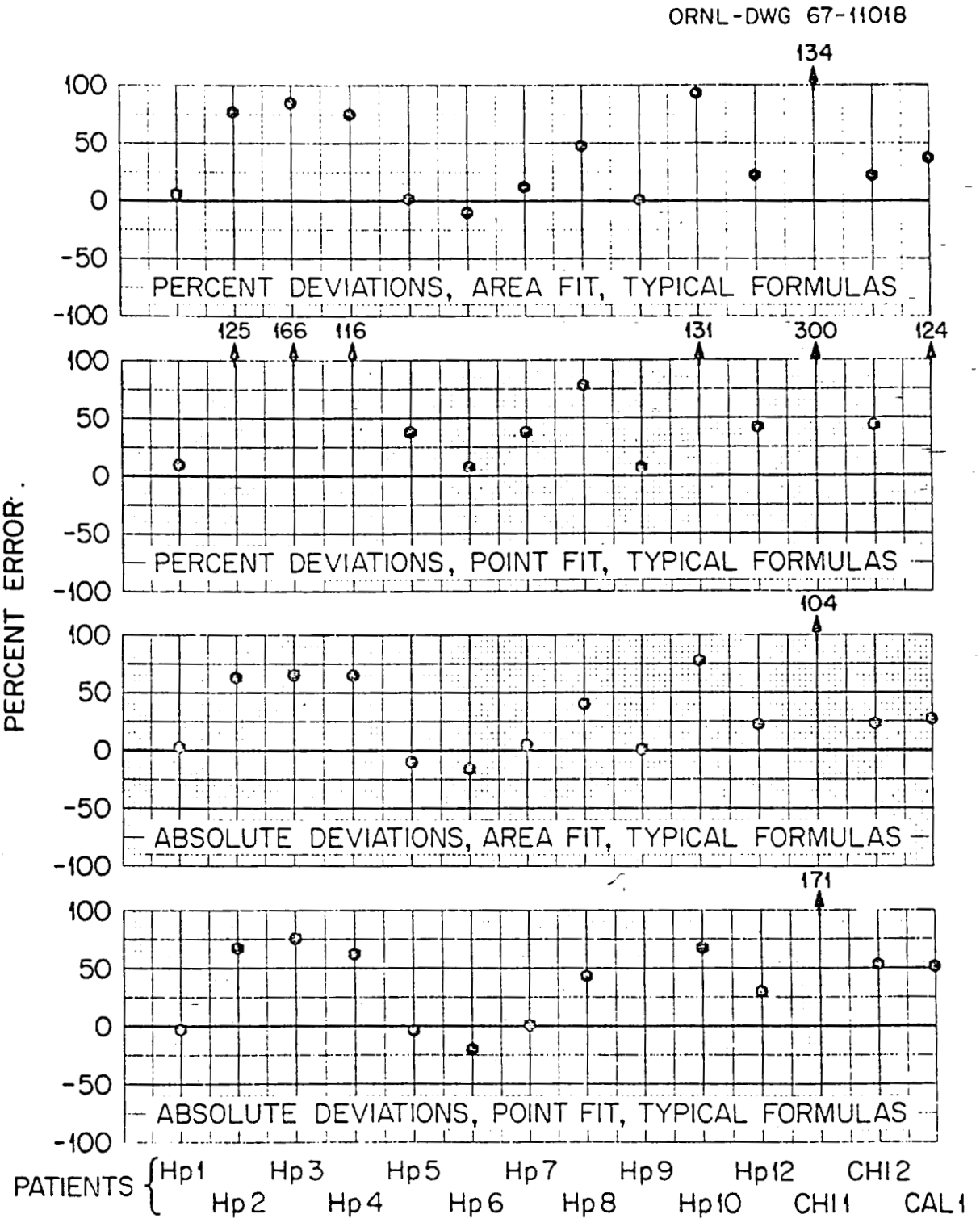

Percent Error of Estimated Intake.

(FLUCTUATION ALLOWANCE: NONE)

Fig. 5

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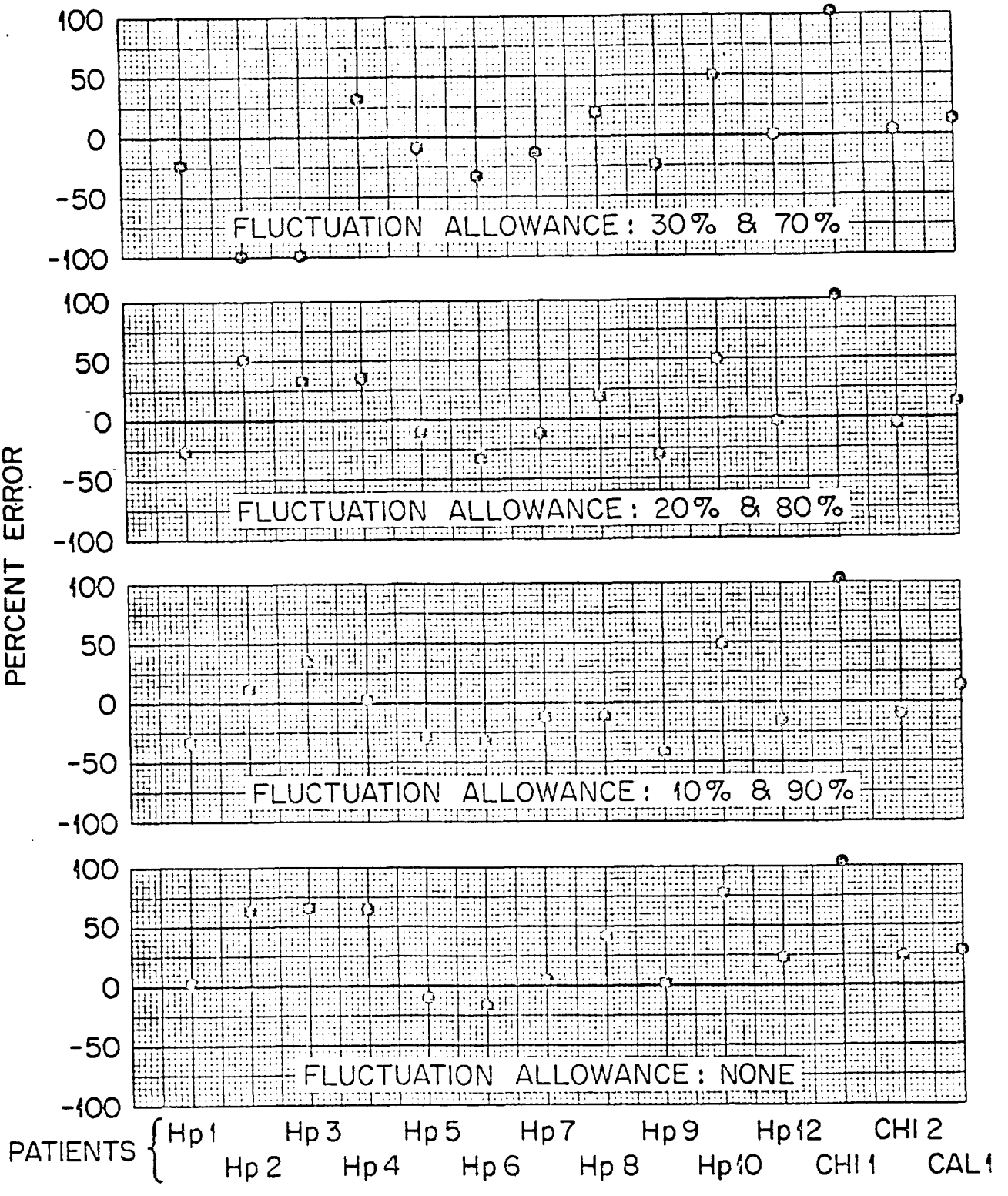

Percent Error of Estimated Intake.

(ABSOLUTE DEVIATIONS, AREA FIT, TYPICAL FORMULA)

Fig. 6

in a criticality accident in 1958. The case has been studied previously by these methods (see refs. 2 and 3), but it may be of interest to compare the values obtained by the present code with some of those reported earlier. Our study of the case leads to estimates of about 0.0075 μCi if the area model is used and 0.013 μCi if the point model is used. As with the hospital patients, the confidence level used does not materially affect these estimates. Since excretion is small, one may regard these as an estimate of the systemic body burden which on the basis of autopsy data would be about 0.015 μCi. This estimate includes the amounts present in skeleton, liver, muscle, heart, spleen, kidneys, and the balance of the body but excludes that present in lung and pulmonary lymph nodes.

It would be of great value to test any or all of these models on further employee data that may be available, and the author invites any who may have such data to supply it to him if possible, and he will be glad to provide the estimates of systemic body burden that are obtained by these methods.

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