718536

REPOSITORY MARES / X-10
COLLECTION Office of Rad. Protection
BOX No. Snyder Files
FOLDER

IAEA/SM-150/35

A METHOD OF INTERPRETING EXCRETION DATA WHICH ALLOWS FOR STATISTICAL FLUCTUATION OF THE DATA*

W. S. Snyder
Health Physics Division, Oak Ridge National Laboratory
Oak Ridge, Tennessee, USA

When plutonium enters blood, a certain small fraction of the amount is excreted, and it is the usual practice to collect samples of urine regularly from employees potentially exposed to plutonium and to make estimates of their exposure based on this excretion data. The samples may be spaced rather widely in time, intervals of 30 d or more being not uncommon; but if a potential exposure occurs, samples of urine and feces may be collected daily. There are considerable differences of opinion concerning the best methods of collecting and interpreting such data and its usefulness in evaluating the employee's exposure status. Every health physicist recognizes that there are many conditions of the exposure situation which may affect the interpretation of the data—the chemical form of the plutonium, the particle size if the exposure is by inhalation, the fact that in most cases the plutonium does not enter the blood in a short time but solubilizes slowly from the lungs or from a wound site during periods of weeks or months. Add to this the fact that the daily excretion fluctuates widely even in experimental situations where one can be sure there is no recurrent exposure, and one can understand why so many methods of interpretation have been tried and why many health physicists have little faith in any of them.

However, we have little else to rely on if we wish to estimate the systemic burden of plutonium, that is, the deposition in bone or in liver, which are the principal organs of deposition once the plutonium has entered blood. Some authors have indicated

*Research sponsored by the United States Atomic Energy Commission under contract with the Union Carbide Corporation.

A-00276

1134228

Human Studies Project

that the lungs always will be the critical organ following exposure by inhalation, and they point to the data on experimental animals where, thus far, malignancies of the lung and associated tissues far outweigh any other cause of death. However, there are good reasons not to dismiss liver or bone completely: (1) because we know from injection studies that malignancies do occur in these organs from plutonium and (2) because the inhalation experiments have not been at low levels where enough animals survive the initial high dose to lungs to manifest injury to liver or skeleton. For man, who has a much greater life span before him, and at lower levels of exposure, the case may be different. To illustrate this possibility, the accumulated doses to lungs and to bone as a function of time are shown in Fig. 1, the former calculated according to the lung model of the ICRP [1] for a Class Y material (clearance half-time of 500 d) and the latter assuming equal deposition in liver and bone with only 10% elimination from bone. It is clear that during the first 5 yr postexposure, the lung has a far higher dose; but if the animal survives this period, the dose to bone will continue to accumulate while the lung receives little more dose, and eventually the skeleton accumulates the greater dose. I am not suggesting that bone or liver replace lung as our only organ of concern but rather that we should be concerned for all three and not be swayed too much by results of animal experiments which are not representative of human exposure either in level or in the duration of the exposure. Thus it seems important to have some estimate of the systemic burden, and the principal means of estimating this is by interpreting excretion data.

The only plutonium excretion data we have on humans from carefully designed and controlled experiments is that obtained by Langham and Hamilton in 1945-1946. Urinary and fecal excretion data were obtained on 15 terminal patients who were given plutonium nitrate or dioxide complexed with citrate and followed until death. This data was analyzed by LANGHAM [2] who expressed the general trend of the urinary and fecal excretion in terms of power functions. Later he studied the excretion of employees and found substantially the same trend in their excretion data for a period of about 5 yr. These power functions obtained by Langham by fitting the curves to all the excretion data of the hospital patients have been the basis for most, if not all, of the methods described for interpretation of plutonium excretion data.

In most routine cases one has available only urinary excretion data to consider in evaluating an internal exposure. Although Langham gave one power function ($bt^{-\beta}$) fit to the urinary data of all the patients, there was considerable variation about this curve. In a previous study [3,4] the author has obtained a power function $bt^{-\beta}$ fit to the data of each patient. This has been done by several techniques of curve fitting, and the designations "point fit," "area fit," "absolute deviations," and "percent deviations," on the figures identify the procedure used. However, these methods are not discussed here, but the interested reader may consult the references. Needless to say, there was a considerable range of variation of the parameters b and β in the individual cases. The power functions so obtained are shown graphically in Fig. 2. When fit to all the urinary data, a curve (called here the "typical curve") was obtained, and the parameters ranged by a factor of about 3 above and below these "typical" values. In the case of an employee, there is no way to determine a priori which of these power functions might best represent his excretion.

1134229

The existence of this variation and the occurrence of day-to-day fluctuations of the daily urinary excretion about the power function which defines the trend of the data are some of the complications which make estimation of the amount of plutonium reaching blood rather difficult. In principle, having chosen a power function as model for excretion, one attempts to choose intakes to blood whose excretion by the model will reproduce—or essentially reproduce—the excretion data. Generally this is done sequentially. Having chosen a first intake, perhaps with reference to a known "incident," which provides for the first sample excretion, one then calculates by the model how well, or poorly, this reproduces the rest of the excretion record. If the excretion on certain days is significantly higher, one puts in additional intake just preceding that day to provide for the excess. If this procedure is followed, one will produce a pattern of intake which suffices to produce the excretion data, or rather to overestimate it, for clearly if one puts in intakes to reproduce all the high excretion values and ignores the lower values, one would expect to obtain an overestimate of intake. This is illustrated schematically in Fig. 3. The solid line suggests a power function trend of data which fluctuate about it. The dotted line represents the hypothetical excretion obtained by postulating an intake for the first daily sample, a second intake for the next daily sample which chances to lie above this line, a third intake for the next sample exceeding the new power function, and so on. Clearly, much of this intake is a result of statistical fluctuations and is not required by the data if one recognizes that the data may be expected to fluctuate about the trend curve. The effect of the above method can be demonstrated for the hospital patients whose intake to blood is known. In a previous study [4], the author produced estimates as described above for the hospital patients, and the results, expressed as a ratio to the activity of plutonium injected, are shown in Fig. 4. As will be noted, these estimates tend to be high.

The remedy is easy to find. If one examines the ratio $U(t)/bt^{-\beta}$ or $(1-\beta)\,U(t)/b\,[t^{1-\beta} - (t-1)^{1-\beta}]$ (that is, the ratio of actual urinary excretion to that predicted by the model) for the hospital patients, one has a measure of the extent to which the daily urinary excretion $U(t)$ exceeds the excretion predicted by the power function. The cumulative distribution of these ratios is shown in Fig. 5 where every line represents the cumulative distribution of the ratio for one of the patients. It can be noted that the ratio lies between 1/2 and 2 for all of the patients except for 40% of the days and between 1/3 and 3 except for 20% of the days. Thus, while fluctuations by a factor of 2 are not unusual, fluctuations by a factor of 3 or more are fairly rare. When one is not sure whether a high excretion level of an employee is due to a new intake or whether it represents a chance fluctuation, one may disregard any fluctuation which is by less than a factor of 3 and be rather confident that any new and significant intake to blood is not missed. Of course, there is a 10% chance that such a high value is due to a new and significant intake; and if this is the case, the excretion should run high for later values as well—and thus one would expect to find the intake required for some of the later data. This game may be played at any level of significance one chooses. One can easily design a computer program which allows one to preassign a level of

1134230

significance, and only when the ratio $U(t)/bt^{-\beta}$ exceeds this level will one select an additional intake. When this program was used to estimate the intake to blood of the hospital patients, it produced the estimates shown in Fig. 6 where the ratio of the estimate to the injected amount is shown. Comparison with Fig. 4 reveals that the results do not run systematically high as formerly. Of course, one may make no allowance for fluctuations and obtain a conservative estimate as before. These cases were programmed for the computer using the "typical formula" fit to the data of all the patients and not using the patients' own formulas since such information would not be available in the case of an employee.

If one has a considerable amount of excretion data, he may hope to approximate, roughly, to something like the particular excretion curve of the employee. The basis for this is the fact that if the trend of the curve is not steep enough, then there should be a preponderance of points below the curve. Now a new intake might make the excretion higher than the trend curve, but nothing can place them too low except (1) faulty collection or analysis of samples (and even a computer must have good data!) or (2) chance fluctuations. If the chance fluctuations are systematically too low, then it is likely that the curve should be steeper.

The computer program can be modified to include such a change in the slope of the excretion curve. In doing this, it seems best to start with a low value of the exponent β since, as mentioned above, new intakes might make excretion values be high; but it is difficult to imagine a reason, short of faulty data, which would cause them to be lower than the proper curve for an individual. This concept is illustrated in Fig. 7. Beginning with a power function with too low an exponent, the computer tests and finds that the data will largely fall below the line. It increases the exponent step-by-step until the fraction of points below does not exceed a pre-set level. The excretion data of the hospital patients have been analyzed from this point of view, using the starting slope of $\beta = 0.2$ which is well below the exponent found for any of the patients. Whenever the proportion of excretion values below the curve exceeded the highs by more than a factor of $1+k$, the exponent was increased, k being a pre-assigned value. The results are shown in Fig. 8 where the value of the exponent β obtained by the curve-fitting procedures mentioned earlier is shown together with the value produced by the computer in the course of its estimate of the intake to blood. No doubt these cases, which correspond to a single intake to blood, are simpler than one will find usually in analyzing data on exposure of employees, but you will note that the computer did rather well in approximating to the correct slope for the individual. The results in Fig. 8 are the best of many cases tried for different choices of k and the other parameters used in the computer code. The method of adjustment seems to do best when there is little allowance for statistical fluctuations of the data and when the value of k is rather small. These results seem of interest because they demonstrate the possibility—at least in these cases of a single intake to blood—of letting the excretion data provide the information needed concerning the slope of the power function used in the model. How well the procedure will work for more complex patterns of exposure remains to be determined, and further exploration of cases is under way.

1134231

The writer is aware of only two cases of actual employee exposures where a reasonable amount of excretion data are available and where autopsy data on the systemic burden were obtained later. In neither case did the death of the subject result from his exposure to plutonium. When the excretion data of these employees are analyzed by the methods outlined above, the predictions of the systemic body burden agree surprisingly well with the estimates based on autopsy specimens. The first case, reported by FOREMAN et al. [5], has been analyzed by these methods and reported previously [6]. By all the methods tried, the estimate by the computer was higher than the estimate based on autopsy specimens, but by a factor of less than 2. This employee's exposure to plutonium was sporadic but extended over about 11 yr. The second case is reported by LAGERQUIST et al. [7], and the urinary excretion data extend over about 5 yr. The report indicated that the computer estimate was high by about a factor of 5. When the methods of analysis discussed here are used, the computer estimates are well within a factor of 2, and, undoubtedly, this is largely due to the fact that allowance is made for fluctuations of the data.

REFERENCES

[1] ICRP Task Group on Lung Dynamics, Deposition and retention models for internal dosimetry of the human respiratory tract, Health Physics 12 2 (1966) 173.

[2] LANGHAM, W.H., et al., Distribution and Excretion of Plutonium Administered Intravenously to Man, USAEC Rep. LA-1151 (1950).

[3] SNYDER, W.S., FORD, M.R., WARNER, G.G., "The use of excretion data to predict the systemic body burden of plutonium," Diagnosis and Treatment of Deposited Radionuclides (KORNBERG, H.A., NORWOOD, W.D., Eds.), Reidel, Dordrecht, Holland (1968) 279.

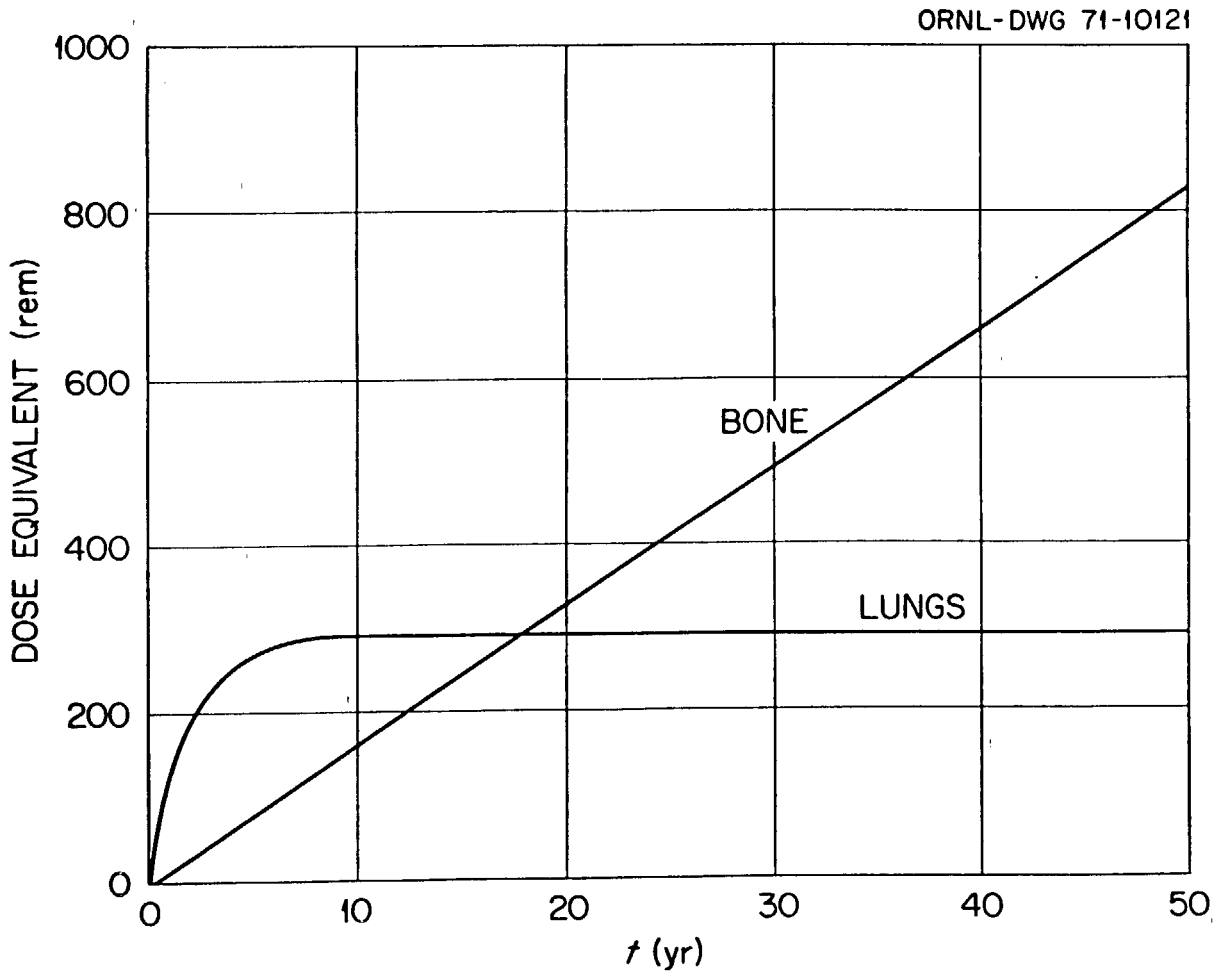
[4] SNYDER, W.S., FORD, M.R., WARNER, G.G., A study of individual variation of excretion of plutonium by man and of its significance in estimating the systemic burden, Proc. 13th Annual Bioassay and Analytical Chemistry Meeting, October 12-13, 1967, Berkeley, California, USAEC Rep. CONF-671048 (April 1968) 123.

[5] FOREMAN, H., MOSS, W., LANGHAM, W.H., Plutonium accumulation from long-term occupational exposure, Health Physics 2 4 (1960) 326.

[6] SNYDER, W.S., Major sources of error in interpreting urinalysis data to estimate the body burden of Pu^{239}: A preliminary study, Health Physics 11 11 (1965) 1177.

[7] LAGERQUIST, C. R., et al., Plutonium content of several internal organs following occupational exposure, Proc. 13th Annual Bioassay and Analytical Chemistry Meeting, October 12-13, 1967, Berkeley, California, USAEC Rep. CONF-671048 (April 1968) 103.

1134232

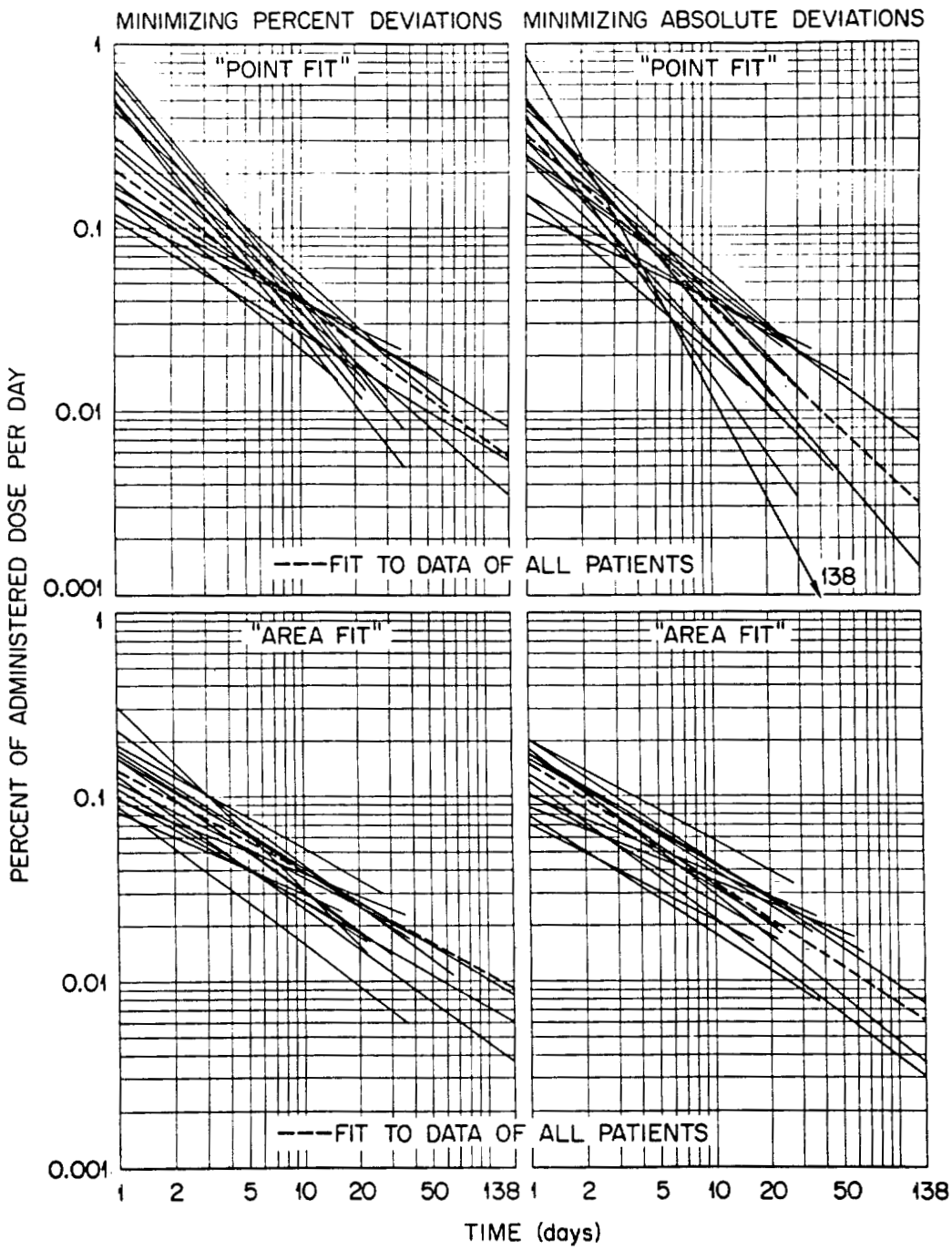


Accumulated Dose Equivalent to Lungs and Bone Following Inhalation of 1 μCi of ^{239}Pu. (Class Y Material, AMAD = 1 μm)

Fig. 1.

1134233

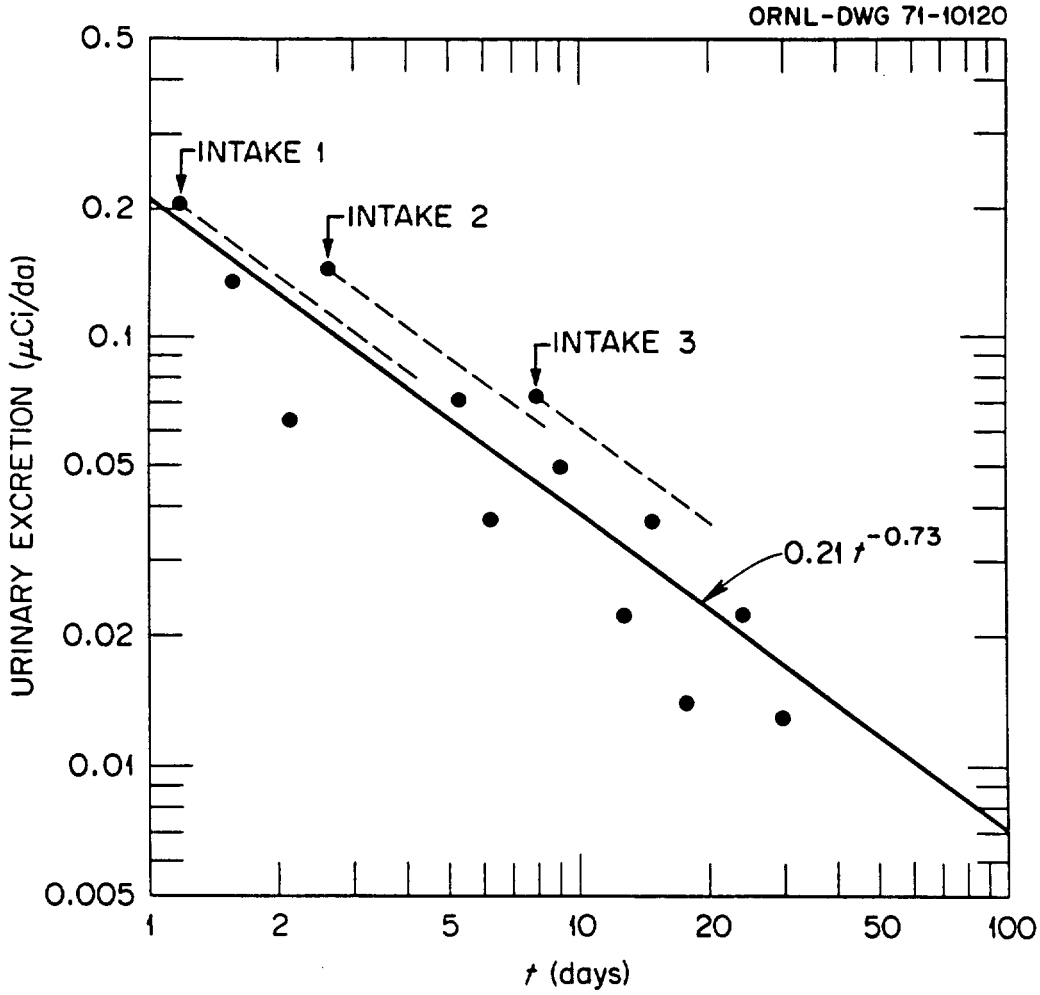
ORNL-DWG 70-10348



Individual Models for Excretion of Plutonium.

Fig. 2.

1134234

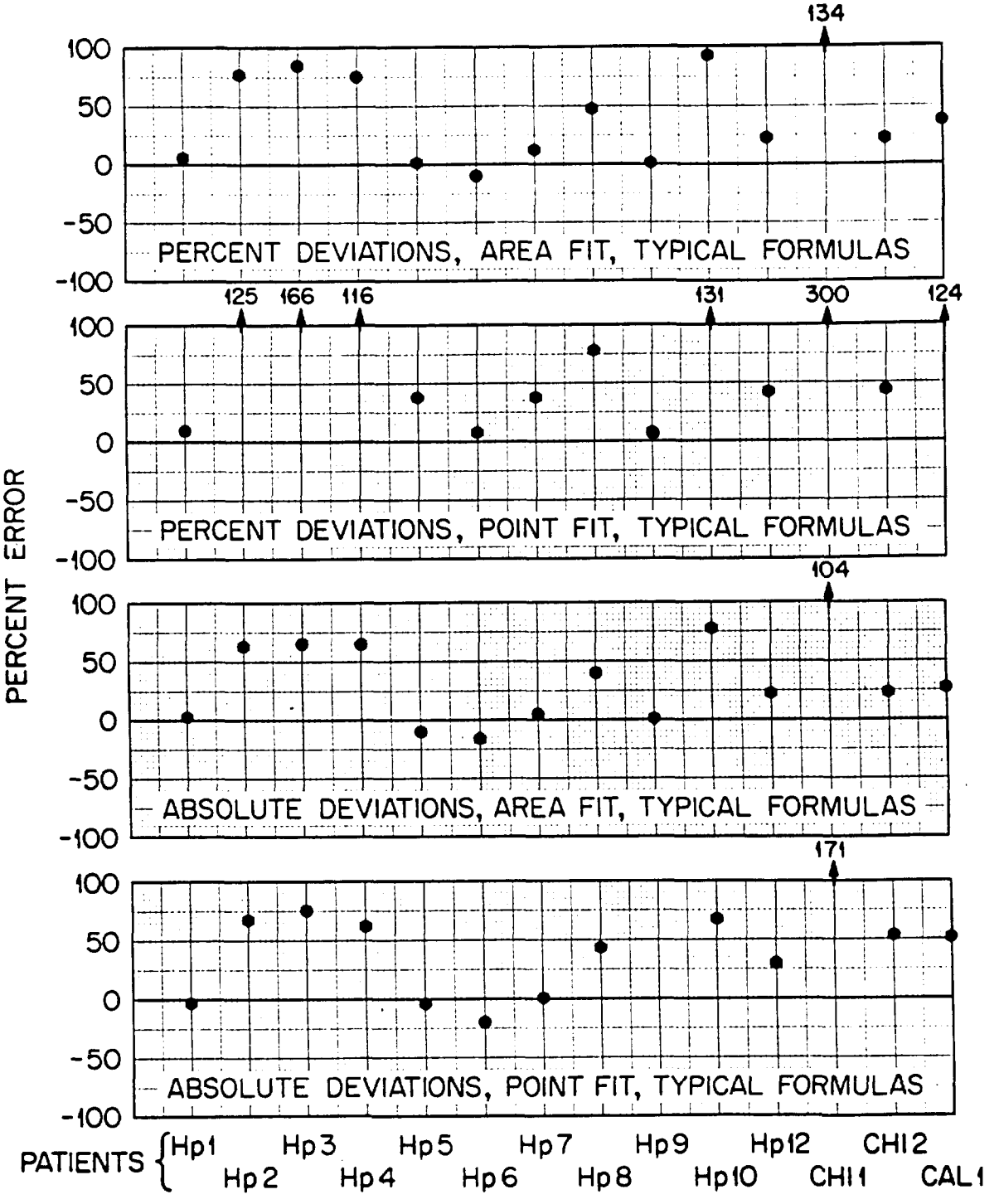


Schematic Illustration of Result of Introducing New Intake for Each High Excretion Sample.

Fig. 3.

1134235

ORNL-DWG 67-11018

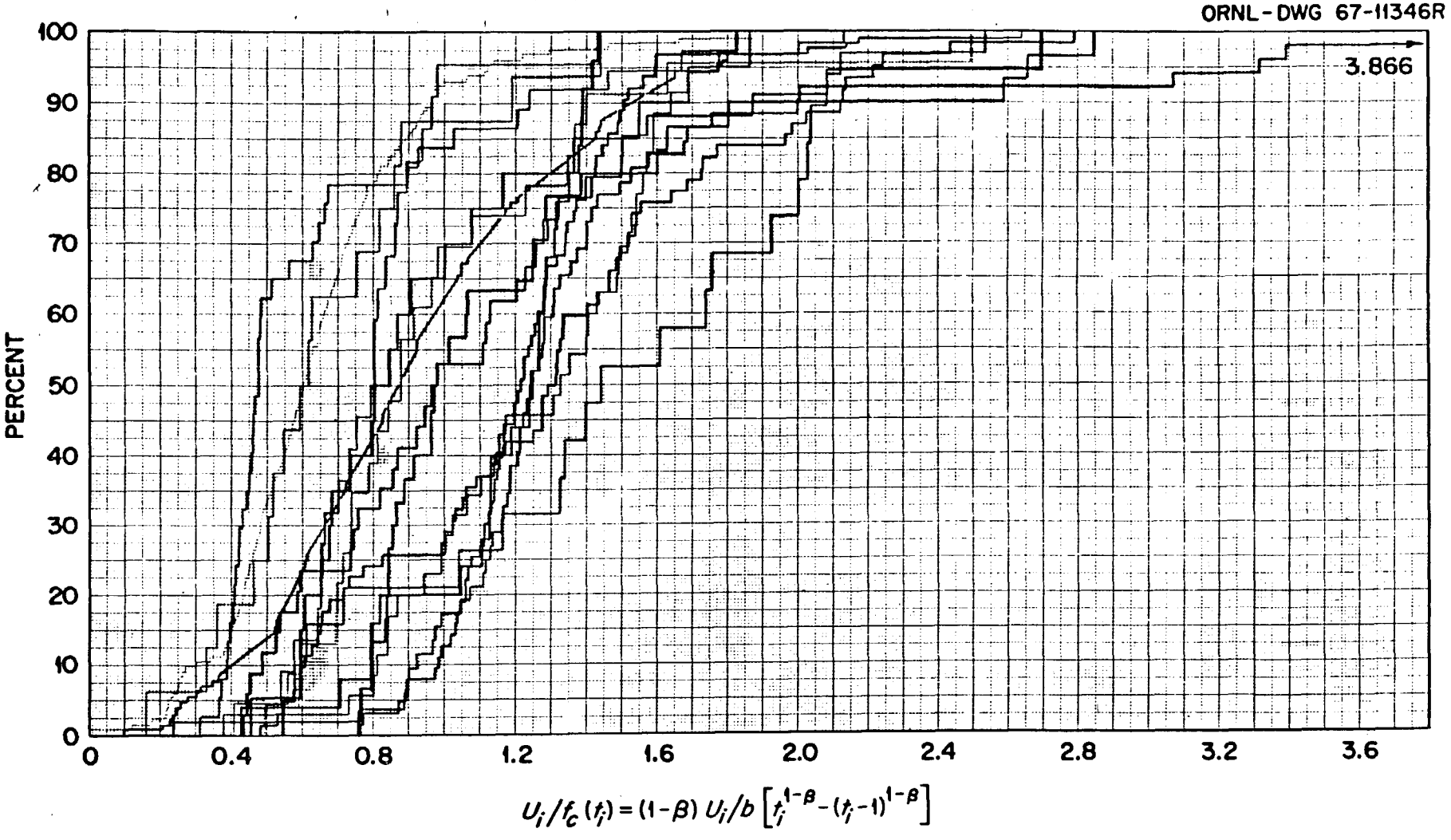


Percent Error of Estimated Intake.

(FLUCTUATION ALLOWANCE: NONE)

Fig. 4.

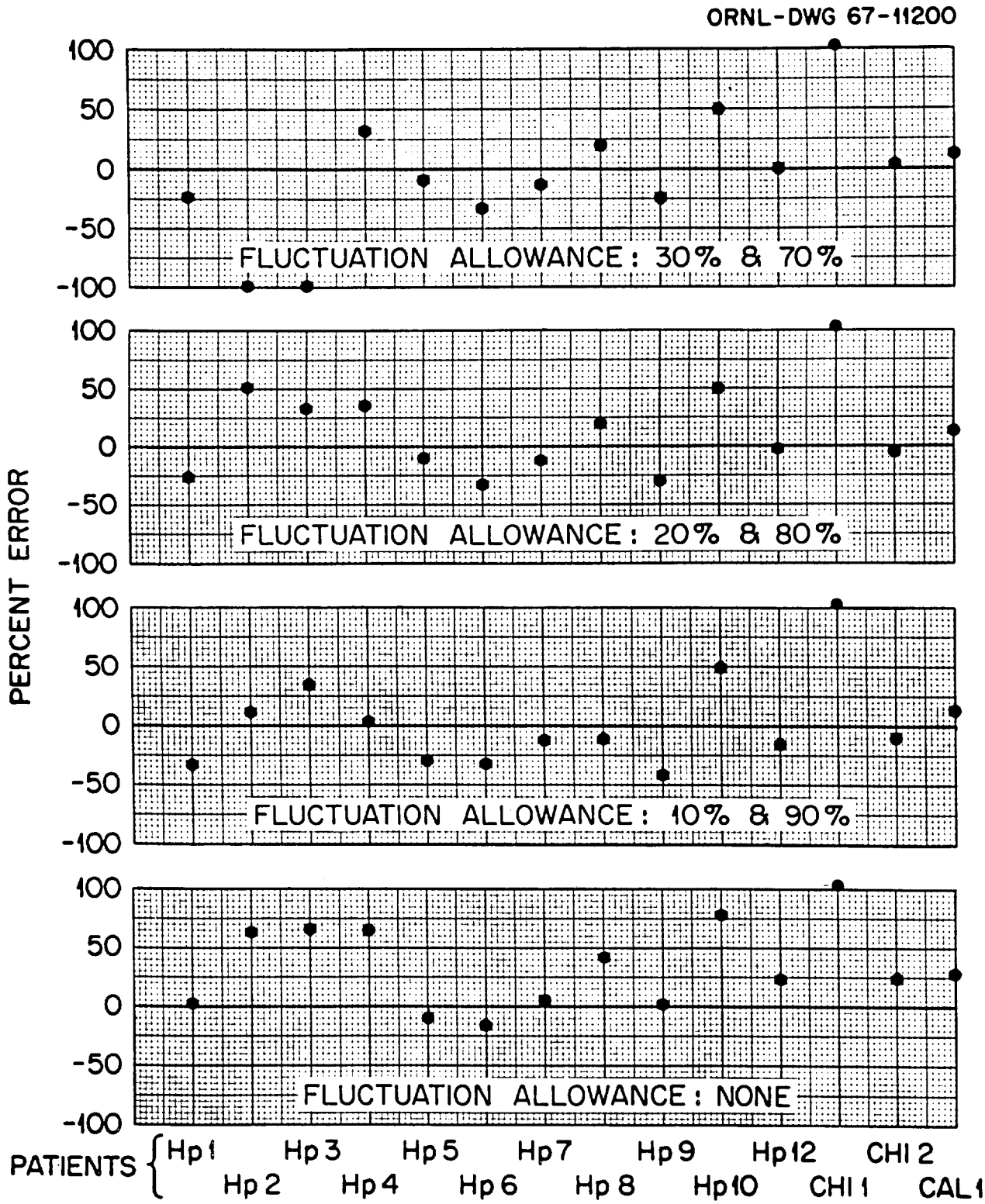
1134236



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. 5.

1134237

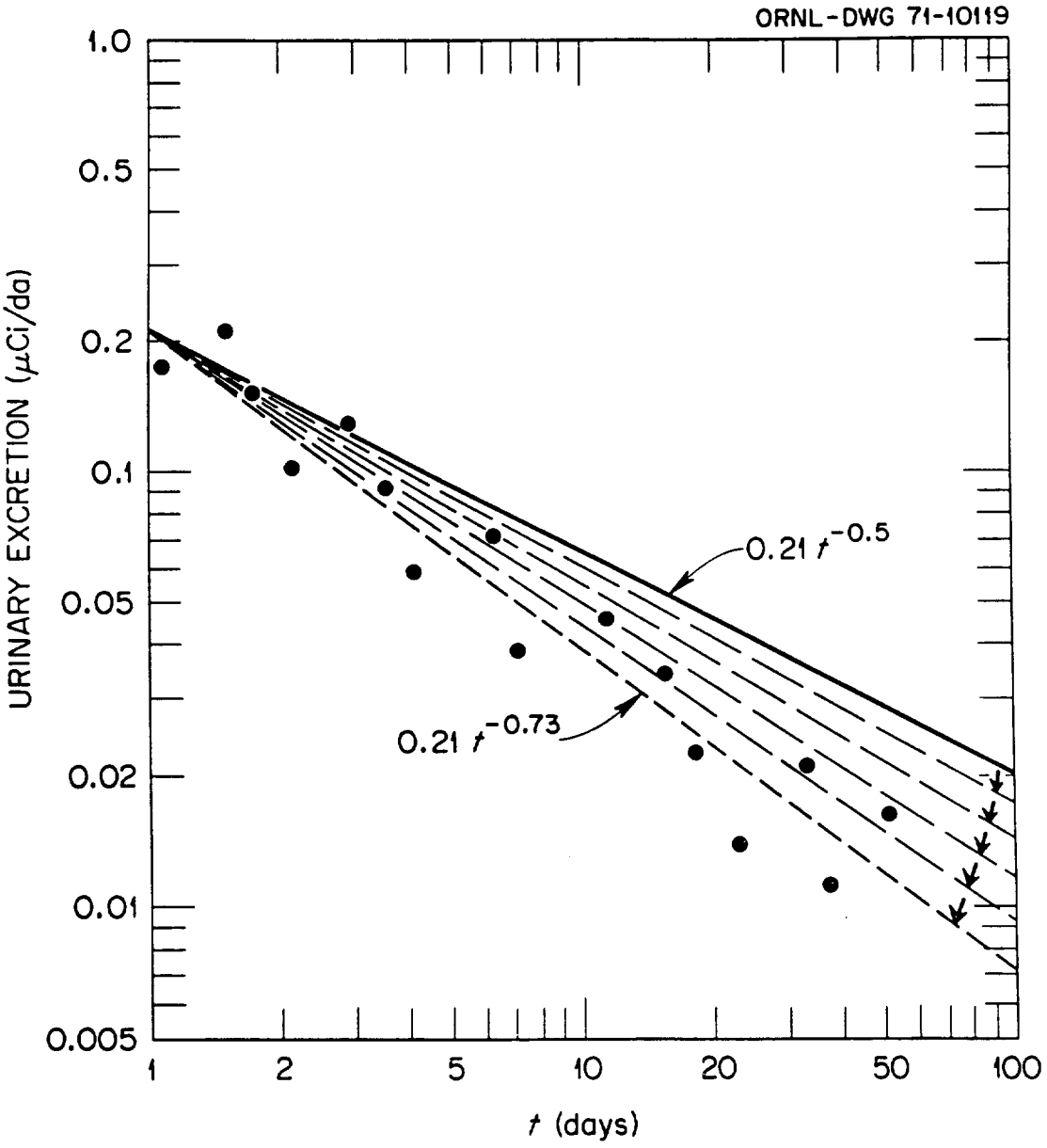


Percent Error of Estimated Intake.

(ABSOLUTE DEVIATIONS, AREA FIT, TYPICAL FORMULA)

Fig. 6.

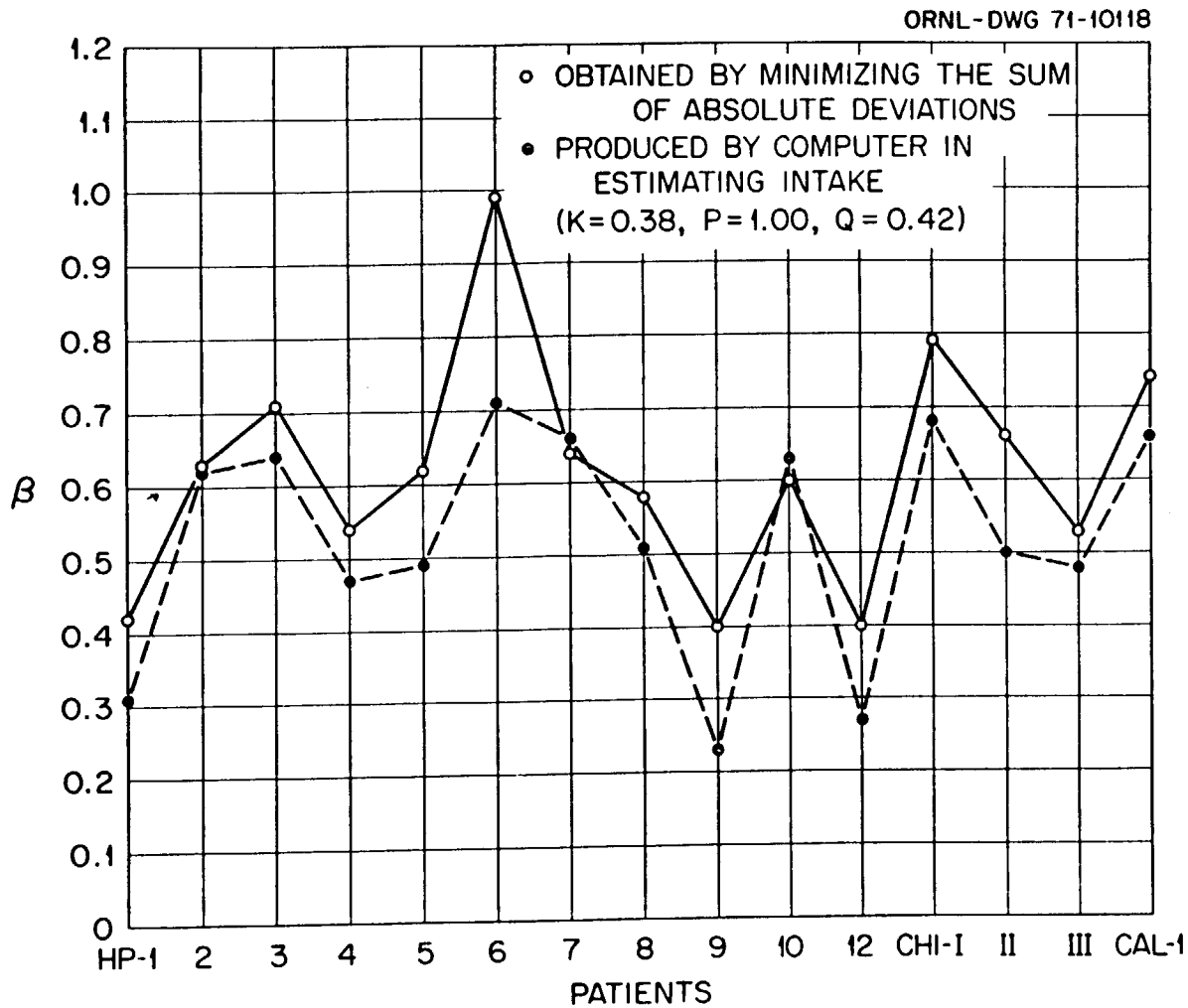
1134238



Basis for Adjustment of Slope of the Excretion Model.

Fig.7.

1134239



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

Fig. 8.

1134240