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health and safety laboratory

THE SIGNIFICANCE OF URINE URANIUM EXCRETION DATA

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UNITED STATES ATOMIC ENERGY COMMISSION
NEW YORK OPERATIONS OFFICE

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HEALTH AND SAFETY LABORATORY

ABSTRACT

Urine uranium excretion data for persons exposed to uranium by inhalation are analyzed. Data from both chronic and single massive exposures are included, and a generalized excretion pattern, applicable to any uranium compound absorbed by inhalation, is proposed. For a single exposure, the subsequent urine excretion rate, y , can be described as a function of time, t , by the equation in the form: $y = at^{-\beta}$, with $\beta = 1.5 \pm 0.2$. For multiple or chronic exposures, excretion following the final exposure can be described by three equations of the same form. The first and third equations have $\beta = 1.5 \pm 0.2$, while the second equation covers the intermediate phase with $\beta = 0.3 \pm 0.1$. The time range covered by the intermediate phase is a function of the level and duration of the exposures. Using this model, estimates can be made of previous exposure levels, future excretion values, and body burdens, based on appropriate urine data.

It is shown that it is not usually practical to use urine samples to monitor individual exposures. Such an evaluation is possible only with a suitable series of samples collected at known intervals past the exposure.

It is also shown that it is not possible to determine chronic exposure levels from routine urine samples. Chronic exposure levels and body burdens can only be estimated with a sample series collected two or more weeks after the termination of exposure.

This report also contains three Appendices describing the detailed mathematical manipulations made on the available urine data and on some trends suggested by the data as plotted in various forms.

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I. INTRODUCTION

Uranium is considered a nephro-toxic chemical agent with a similar order of toxicity to other heavy metals such as lead, mercury, and arsenic. When introduced into the body via inhalation, a portion of the deposited material is solubilized and passes through the blood stream to the kidneys.

Since uranium in urine is indicative of uranium in the body, and since urine samples are about the easiest of all biological specimens to obtain and analyze, thousands of samples are collected and analyzed each year at many of the installations handling uranium bearing materials. Various investigators at these installations have attempted to correlate urine concentrations with air concentrations, job locations, and other plant variables. While some of them have had varying degrees of success for their particular operations, these correlations do not have general application. Many of the variables involved behave as constants for limited correlations, but introduce large uncertainties when considered as constants for data from different operations and locations.

In order to determine the significance of urinalysis, and its value in a control program, the HASL initiated a study to determine what patterns, if any, could be developed to account for the observed human urine uranium elimination data. The accumulated urine and exposure data in the Laboratory's records proved very useful in this study. Data were available on elimination rates following both routine chronic exposures and accidental single massive exposures. Of special value in tying together all of the various aspects of the problem was a controlled laboratory chronic exposure series performed by a human volunteer subject⁽¹⁾.

The mass of apparently unrelated uranium in urine excretion data was sifted, scrutinized, manipulated, and plotted in various graphical forms in the hope that, with the right combination of variables, consistent patterns might emerge. Appendix I is a discussion of the initial studies devoted to the choice of variables and their form. In these studies it was determined that the most advantageous form of the sample time variable was midway between the excretion time and the time of the previous excretion. For excretion rate, the choice was mass per unit time, specifically $\mu\text{g/hr}$.

The patterns of uranium excretion following inhalation exposures which emerged from the studies to be discussed were utilized to develop various working techniques. It was found that these techniques could be used for the estimation of past exposures from urine data, for the estimation of "body burden" from urine data, and to suggest the considerations appropriate to the design of a realistic urine sampling program.

II. PATTERNS OF URANIUM EXCRETION FOLLOWING INHALATION EXPOSURES

A. Single Exposures

A single brief exposure to uranium represents the simplest case with the fewest variables, and was therefore studied first. Only by understanding the elimination process following a single exposure can the patterns of excretion for repeated exposures be recognized. Fortunately for the purpose of this discussion, there have been a number of massive inhalation exposures to workers in the uranium industry and, in many of these, urine samples were collected for long periods of time thereafter.

Figures 1 and 2 illustrate the best documented excretion pattern for these massive exposure cases. Exposure in this case was to U_3O_8 fume. The individual excretion points are plotted on logarithmic coordinate paper in Figure 1 and appear to form a single straight line. It would not be practical to plot the data on arithmetic paper because of the large number of decades through which the coordinates vary. On the semi-logarithmic plot of Figure 2, the data appears to fit a number of distinct straight line segments, with fairly well defined inflection points. The significance derived from a treatment in this manner is being investigated. The log-log plot, however, by virtue of being a single relation, provides the handiest yardstick for the intercomparison of data. Therefore, Figure 1 was adopted as a reference curve for comparison with excretion patterns from other exposure cases. Figures 3 and 4 illustrate excretion data from additional single massive exposures plotted to the same coordinates as in Figure 1.

Four single exposure cases are plotted in Figure 3. Curve 2 resulted from a single massive inhalation exposure to U_3O_8 fume; curve 3 from a single massive inhalation exposure to UO_2F_2 ; curve 4 from a single low-level inhalation

exposure to UF_4 (the first of the series of exposures described in Ref. #1); and curve 5 from immersion in a UO_2 - $(\text{NO}_3)_2$ solution. As shown in Table I, the slopes of curve 1 (Fig. 1) and curves 2,3, and 5 (Fig. 3) fall within the range -1.5 to -1.7. In two controlled injection studies involving human volunteer subjects⁽²⁾, the excretion curves were similar, and the average slopes were -1.5 and -1.8 respectively.

Curve 4 of Figure 3, and curves 6,7, and 8 of Figure 4 have slopes ranging from -1.0 to -1.2. The reason for the less negative slopes of these curves, as compared to curves 1, 2,3, and 5, may be due to the fact that the exposures in these instances were complicated by ingestion. While curve 4 followed a nominally pure inhalation, the size of the aerosol was such that approximately two-thirds of it deposited in the upper respiratory tract, from which it was rapidly removed to the gut by ciliary action and eliminated through the GI tract.

Curve 6 followed a UO_3 exposure by both inhalation and ingestion. The significance of the b and c segments of this curve will be discussed in a subsequent section. Curve 7 followed an accident involving burning uranium chips. Uranium was taken in by both inhalation and absorption through burned skin areas. Curve 8 followed an accident in which an employee fell into a tank of yellow cake (impure ammonium diuranate). Intake was by inhalation and ingestion.

Thus, a single exposure to uranium is followed by a urine excretion pattern in which the log of excretion rate is directly proportional to the log of the elapsed time. For pure inhalations, intravenous injections, and immersion, the slope of the excretion curve appears to conform to a narrow range (-1.5 to -1.8). For exposures involving significant ingestion as well as inhalation, the excretion curve is still log-log, but the slope is less negative (-1.0 to -1.2).

The most interesting conclusion that can be drawn from these data is that similar patterns of concentration decline are indicated in all cases. This occurs despite the fact that many different chemical forms of uranium were involved in the various cases. Apparently uranium is rapidly solubilized and eliminated after exposure to compounds ordinarily considered insoluble as well as compounds considered soluble. The compounds involved range from the highly soluble hexavalent hydrolysis product UO_2F_2 to the highly insoluble tetravalent UF_4 . This apparent similarity in behaviour may be due to the very small size of the particles which can penetrate to the

lower lung regions where solubilization takes place. Particles aerodynamically small enough to penetrate to these regions have such a large surface-to-volume ratio that their solubility is greatly enhanced.

Table I lists the exposure compound, the slope, standard deviation and standard error of the curves plotted in Figures 1, 3 & 4. Despite the variation in exposure level and chemical compound, there is no statistical difference between the slopes of the excretion curves in either the low slope or the higher slope group. This suggests that it may be possible to estimate past excretion rates by extrapolating back to early conditions on the basis of samples taken long after an exposure. For example, if a very high sample turns up in a routine urine sampling program, and is verified by further sampling, it may be possible to estimate when a massive exposure occurred and what the exposure level was. The potential accuracy of such estimates will be evaluated in the discussion which follows.

B. Chronic Exposures

While a single massive exposure is interesting in itself, and provides a simplified excretion model, it tells very little about what to expect following chronic, low-level exposures. However, an indication that high-level chronic exposure provides a similar excretion pattern to the single massive exposure cases can be seen in Figure 5. On this curve, there are several hundred points representing urine samples contributed by workers chronically exposed to high airborne concentrations of UO_2F_2 and UF_4 . Also included, for the sake of comparison, are points derived from the single massive exposure data of Figures 3 and 4. Each point represents a pair of samples. One sample was taken at the end of exposure and the second sample was taken 48 hours later, which for the men chronically exposed was immediately prior to their reporting for the following work week. It may be noted that for the chronic exposure points, some of the initial uranium concentrations are higher than the initial concentrations in some of the single "massive" exposure cases. Some of these chronically exposed individuals contributed one or more before-weekend urine samples in excess of 1 mg/liter each month over periods extending many months.

The upper line in Figure 5 is a 45° reference line. The lower line was constructed so that approximately 90% of the points fell between it and the reference line. It is

believed that the few points below the lower line in Figure 5 resulted either from analytical errors or sample contamination. For the bulk of the points, that is, those between the two lines, it can be seen that for before-weekend concentrations greater than 1000 $\mu\text{g/liter}$ there is a decline of 90% or more in urine concentration in 48 hours. On the other hand, for concentrations of 100 $\mu\text{g/liter}$ and below in the before-weekend sample, the variation in the amount of fall-off in concentration is extremely large, and the magnitude of the after-weekend sample can not be predicted from a knowledge of the before-weekend sample. This far greater variability at the low end of the scale may be attributable to two factors. One is the analytical uncertainty, which at the time these samples were analyzed was approximately ± 10 micrograms per liter. The other factor is the elimination of the uranium previously absorbed, which is being mobilized at a slower rate. It has been shown⁽³⁾ that the so-called "body burden" excretion may persist for months or years following the end of exposure. Data for other groups exposed chronically to high concentrations of uranium have shown⁽⁴⁾ almost identical slopes and variability to that of Figure 5.

The previously mentioned controlled experimental series of 17 inhalations of uranium⁽¹⁾ provides additional clues as to the relationship between urine uranium excretion and exposure. Figure 6 is a semi-logarithmic plot of urine excretion versus time, and in addition, shows the timing and magnitude of the exposures as represented by the triangles. It can be seen that the concentration decline following the initial and second exposures has the same slope as the single massive exposure cases. However, in addition, several other trends are suggested. The dashed curve is an estimate of the calculated build-up following successive inhalations. This curve appears to flatten and approach an asymptotic level. Furthermore, curve 9 of Figure 7, which is a log-log plot of the urines collected after the last exposure, shows that the decrease in uranium concentration with time is less marked than the decrease following a single exposure. The slope of the excretion curve decreases with the increasing number of exposures. Following the 17th and last exposure of the series, the log-log excretion curve maintained a slope of -0.36 for approximately 100 days. At 100 days, there is an apparent break in the curve. The slope of the curve following the break (-1.72) appears to be conforming to the model as shown in Figure 1.

The curve 9 pattern is repeated by curve 10 for data

representing samples submitted by a volunteer who worked in the same uranium refinery as the men whose urine samples were represented in Figure 5. This individual contributed weekly spot samples starting 50 days after he left the plant, and continuing for almost 900 days. The study was terminated at that point for two reasons. One, no significance was attached to samples as low as a few $\mu\text{g/l}$ at that time, and two, concentration levels being measured were falling more and more into a detection range of very limited accuracy. Since that time, the Analytical Division of the HASL has greatly improved the accuracy of measurement for extremely low levels of uranium in urine. A successful attempt was made to locate the individual and extend the data. Seven additional urine samples were contributed at weekly intervals and are plotted on curve 10 (Fig. 7) at the right of the curve. These samples indicate that the individual is still above the range of normal background levels of uranium in urine⁽⁵⁾, and substantiates the hint of a break in the curve at about 500 days. The best estimate of the slope of the plus 500 days' points was -1.84 without the additional data and -1.62 with the additional data. Again, the terminal phase slope appears to be indistinguishable from that of the standard curve of Figure 1.

Another case in which extensive urine data were collected following a series of over-exposures is illustrated by curve 11 of Figure 7. The samples were collected from a worker exposed to undetermined air concentrations of enriched U_3O_8 fume and dust. Evidence of higher than normal excretion was initially discovered by a high routine urine sample collected on a Monday morning. Investigation⁽⁶⁾ revealed that the individual was probably exposed to higher than normal air concentrations over a period of about 10 days. Prior to the abnormal exposures, he had been working with normal and enriched uranium for about 3 1/2 months without evidence of significant exposure.

The excretion data for this worker shown in curve 11 of Figure 7 exhibits excretion patterns observed in curves 9 and 10. The final break in the curve takes place about 35 days after the last exposure.

The least square equations for the second, low-slope phases and the terminal, steep slope phases on the log-log plots were calculated for the cases illustrated in curves 9, 10, and 11. Curve 6 of Figure 4 exhibits a departure from the single straight line relationship of the other massive exposure cases. When the excretion level dropped to about 1 $\mu\text{g/hr}$, the

contribution of the previous chronic exposures was no longer masked by the single massive one. The second phase region is relatively short, and was succeeded at about 30 days post exposure by the third phase excretion pattern. The equations, standard errors and points of intersection are presented in Table II.

The differences in intersections or break-points in curves 9, 10 and 11, for the three cases, can be accounted for by the differences in levels and durations of exposure. The data of curve 9 of Figure 7 resulted from seventeen exposures averaging about 2000 μg each, and the data of curve 11 resulted from about 10 exposures of a few hundred micrograms each, while the data of curve 10 followed five years of exposures averaging about 50,000 $\mu\text{g/day}$. Thus, the reservoir of uranium in the body available for drainage was by far the greatest for the case represented by curve 10. For all these individuals, regardless of the length and severity of the exposure, the break appears to take place at the same urine excretion level (1 $\mu\text{g/hr}$). When the excretion drops to this point, it appears to begin to decline at a greater rate. The upper level for the intermediate range of slow decline in concentration is less definable than the lower level and probably not as constant, but appears to be in the order of 10 micrograms per hour. Ten micrograms per hour corresponds to approximately 160 micrograms per liter which is interesting in relation to the data shown in Figure 5. In Figure 5 the upper and lower curves begin to diverge greatly at a few hundred micrograms per liter, suggesting that the slow decline region, or so called "body burden" excretion, may become predominant at these levels.

Further speculation may be directed at the previously unproven but widely held belief that uranium workers exposed to air concentration levels in the range of 1/2 to 5 times the threshold limit values for long periods of time will consistently exhibit urine values in the range of 5 to 50 micrograms per liter. Indeed numbers like 25 or 50 micrograms per liter are often used in individual laboratories as urine levels to indicate body burden accumulations. The validity of such assumptions is discussed in the section on "body burden".

III. ESTIMATING PAST EXPOSURES FROM URINE DATA

The excretion data previously discussed may be combined to form a generalized excretion pattern applicable to any uranium compound absorbed by inhalation. This pattern is shown in

Figure 8 and is defined by the following equations:

- (1) $y = \alpha t^{-1.5} \pm 0.2$ during initial phase,
- (2) $y = \gamma t^{-0.3} \pm 0.1$ during intermediate phase, and
- (3) $y = \int t^{-1.5} \pm 0.2$ during terminal phase,

where constants α , γ , and $\int$ are determined by the magnitude and duration of the exposures.

For a single exposure, the first equation covers the entire range. Following repetitive exposures, however, the excretion pattern departs from the single straight line of equation (1) in the range of y values somewhere between 1 and 10 $\mu\text{g/hr}$. Excretion then follows equation (2) until $y = 1 \mu\text{g/hr}$, whereupon equation (3) takes over. The range covered by the low slope region of equation (2) is apparently a function of the duration of exposure.

Thus, in order to estimate past and future urine data from current samples, it is essential that a series of samples be collected to establish the stage in the excretion pattern in which the data lies.

A. Single Exposure

In the simplified case of a single exposure, it should be possible to estimate A) the time of exposure (if it is not known), B) cumulative excretion between the time of exposure and the present time, and C) future excretion. Such estimates may be desirable if an unusually high sample turns up in a routine urinalysis program and is verified by additional samples.

In the equation $y = \alpha t^{-1.5}$, t represents a time interval. For convenience t can be replaced by the difference between two absolute times, such as, a reference time t_0 , the time excretion starts, and any subsequent time t_x . Thus, in the equation $y = \alpha(t_x - t_0)^{-1.5}$, y and t_x are variables, and α and t_0 are constants to be determined. Urine data invariably have a large scatter. Therefore, the larger the number of individual samples, the better the predictions will be. Once α and t_0 are

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*Except, as noted previously, for exposures complicated by significant ingestion, in which case the slope may fall in the range -1.0 to -1.2.

determined, the equation will define all future and past values of y . Of course, if t_0 is known in the first place, fewer samples will be needed to estimate α .

The time excretion starts, t_0 , is not exactly equivalent to the time exposure ceases. This difference can be observed in practice and also derived mathematically. In the massive exposure cases of Figure 3, and also in controlled injection studies involving human volunteer subjects⁽²⁾, the urine excretion rates do not reach their peaks until two to six hours after the introduction of the uranium. In Appendix II of this report, this time interval is defined analytically and designated by the Greek symbol τ .

When dealing with excretion data which is more than a few days removed from the most recent exposure, little error will be introduced by equating the time the exposure ceases ($t_0 - \tau$) and the time the excretion starts (t_0). At earlier times, predictions neglecting τ may be subject to large errors.

Appendix III develops two approaches to the problem of estimating the total absorbed dose, which lead to the two equations below. The cumulative excretion at infinite time is designated E and can be estimated from the equations:

$$E = U_e(\infty) = U_e(t_1) + \frac{A}{(\beta-1)t_1^{\beta-1}} \quad \text{and}$$

$$E = \frac{A}{(\beta-1)\tau^{\beta-1}},$$

where:

$U_e(t_1)$ = cumulative excretion after time interval t_1 , and

$$A = e\alpha.$$

The second equation is interesting since it defines E on the basis of three constants (A, β, τ) which can be determined from a graphical plot of early data. Furthermore, the average values of β and τ which have been observed in the cases so far uncovered are $\beta = 1.5$ and $\tau = 4$ hours. Under such conditions:

$$E = \frac{A}{(1.5-1)4^{.5}}$$

$$= A$$

Thus, E , the cumulative excretion at infinite time would be

equivalent numerically to the excretion rate intercept A! This relationship might prove to be a convenient rule of thumb.

B. Chronic Exposure

With chronic exposures, t_0 is usually known and excretion patterns show up best from an examination of a plot on log-log paper. The initial data will be in the range of equation (1) for a few days at most following the termination of exposure, and then only if the last exposure were relatively high.

Future excretion rates can be predicted by extrapolating the data along the second phase curve to its break point at $1 \mu\text{g/hr}$, and along the equation curve (3) thereafter. Past excretion rates for the first week after the end of exposure cannot be estimated, since it cannot be determined how long the equation (1) curve persisted.

An estimate of the magnitude of the chronic exposure can also be derived from a study of the equation (2) segment of the excretion curve. The time intercept at $y = 1 \mu\text{g/hr}$, the level at which the curve breaks into the equation (3) range, is related to exposure. For the three cases illustrated in Figure 7, the time of the break was a function of the previous exposures. For a lung dose of 3-5 mg taken in over a five week period, the urine curve break took place at about 30 days; for a lung dose of about 10 mg taken in over a period of 17 days, the urine curve break took place at about 80 days, and for a lung burden estimated to be greater than a few hundred milligrams at the end of exposure, the curve broke at about 500 days.

IV. ESTIMATING "BODY BURDEN" FROM URINE DATA

To estimate "body burden" from urine data, it must be assumed that all or at least all but an insignificant fraction of the uranium in the body will eventually be eliminated in the urine. This assumption is not valid in the first week or so following exposure, when fecal elimination may still be significant. However, this qualification is not a major limitation since the uranium material eliminated in the feces was never deposited in the lungs or kidneys, which are the potential "critical organs" for radiation and toxic damage.

If the preceding assumption is accepted, then it follows that the "body burden" is the summation of all future urine

excretion. Future excretion can therefore be predicted with reasonable accuracy from current data as outlined in the previous section. Thus, body burden may be defined by the integral of y between the present time and some remote time, e.g., the 50 years used by NCRP in Maximum Permissible Concentration calculations. If the calculation is made at least a week or more after the last exposure, only the phase (2) and (3) curves need be considered. The break point between the two regions is determined by $y = 1 \mu\text{g/hr}$. It can therefore most easily be determined graphically, by plotting the data as in Figure 8.

The accuracy of estimates arrived at by this method is dependent on how well the excretion pattern is defined, which in turn is dependent on the number of samples. Any estimate based on only one or two samples, especially samples collected within a week or two of exposure, would be subject to enormous errors.

V. DESIGN OF A URINE SAMPLING PROGRAM

Urine samples have significance only in terms of the information they can provide about human exposure and absorption. Excretion data that cannot be interpreted is less than worthless, since it can be positively misleading. Without a basis for interpretation, urine data can provide only the grossest kind of range-finding information, such as elevated average concentrations indicating increased average exposures.

A. Objectives for Urine Sampling Programs

A rational basis for the interpretation of urine uranium excretion data was created by defining the patterns of excretion. Using these patterns as a guide, it is possible to suggest the optimum sampling program for obtaining desired information. Urine samples have been routinely collected for the following purposes:

1. To detect brief exposures to personnel that go undetected by air sampling or other evidence.
2. To monitor exposure levels in conjunction with, or in place of, air sampling.
3. To determine "body burden".

The possibility of developing a rational sampling program for each of these purposes requires further discussion:

1. To Detect Brief Exposures

The collection of urine samples to detect brief exposures not detected by air sampling is usually a waste of time and effort. The excretion rate following a brief higher-than-normal exposure declines so rapidly that a urine sample must be collected within a few days of the exposure to indicate anything at all. By the time the results are recorded, at least a few more days will have passed. If the high number is represented by a single sample, it will require verification to rule out the possibility of contamination. But, by the time a follow-up sample can be collected, it is likely that the excretion rate will have declined to the level where it is indistinguishable from background. Thus, unless an enormous number of samples are routinely collected (at enormous expense), it is likely that some exposures will go completely undetected, while others that may be detected will be unverifiable.

2. To Monitor Exposure Levels

Some organizations prefer to use man as a sampler of the atmosphere in preference to air sampling. They cite the difficulties involved in collecting meaningful air samples (variations in particle size, solubility, etc.), and argue that the only material of real interest is that which actually is absorbed by man. They then conclude that a urine sample, which is unquestionably a function of absorption, is a better estimate of exposure than an air sample. This argument is valid insofar as its assumptions are correct. The key assumption is that the urine concentration is directly related to absorption. This relationship has just been shown to be highly time dependent and complex. Unless the interval between exposure time and urine collection time is accurately known, estimates of exposure based on urine excretion have no value. Furthermore, in chronic exposure, the exposure time can rarely be assigned a single meaningful number.

3. To Determine Body Burden

Individual spot samples collected during or just after the work week defy meaningful interpretation. A single high sample may not indicate an over exposure or excessive body-burden. It might just represent the peak excretion following an exposure within permissible limits. For example, in a previous paper⁽³⁾, it was reported that for men exposed to soluble uranium compounds at average air concentrations equivalent

to the current MPC_a, the average before-weekend urine sample was about 500 µg/l (about 30 µg/hr).

Of all the possible types of urine samples collected from men chronically exposed to uranium, the one most likely to provide useful information is the after-weekend sample collected just before a new work week begins. For men working a normal five day week, it is at least 64 hours removed from the most recent exposure. Unless there was an unusually large exposure late the previous week, the after-weekend sample will probably fall in the phase 2 range of the excretion pattern, rather than phase 1. Thus, it will represent as good an indication, as any single sample can, of the long-term accumulation or so-called "body burden". However, it should always be remembered that a single sample can never by itself provide an accurate estimate of body burden.

After-weekend samples can be used, with some justification, for comparison purposes. A trend of rising concentrations is usually indicative of increasing absorption and should be promptly evaluated by follow-up environmental studies.

B. Urine Sampling For Production Workers

Production workers usually perform repetitive tasks and their exposures can readily be determined by air sampling. If samples are collected at each individual operation performed, and accurate time-study data is available, an accurate time-weighted average exposure level can be calculated. Sampling refinements, such as the use of size-selective samplers⁽⁷⁾ to determine respirable fractions, can be used to increase the significance of the samples. When a good preventive maintenance program is followed and supervisors are alert, any departures from normal operations will be apparent, and resulting potential exposures can be promptly evaluated. Under these circumstances, it is extremely doubtful that sufficient useful information can be derived from routine urine samples to justify their expense.

C. Urine Sampling For Maintenance Workers

The situation is different for maintenance workers and others whose jobs are continuously changing. Their exposures cannot be determined by air sampling unless a sampler is carried continuously by the worker. Miniaturized samplers which make such a sampling program possible are now available^{8,9}, but have yet to find widespread application. In the absence

of such samplers, the next best indication of exposure may be urine samples. The frequency and timing of the sample collections should be scheduled to maximize the likelihood of obtaining meaningful samples. For workers performing non-repetitive tasks, it may be desirable to collect an after-weekend urine each week. Expense could be kept to a minimum by analyzing only selected samples, e.g., one from each working crew. If these samples are high, samples from the other crew members can be analyzed and the original sample contributors can be requested to submit additional samples.

VI. SUMMARY AND CONCLUSIONS

Urine uranium excretion data for persons exposed to uranium by inhalation were studied and analyzed. Urine data was available from single massive exposure cases resulting from industrial accidents, from workers who had high level chronic exposures in the early days of the atomic energy program, and from a recent controlled study involving a series of low-level inhalation exposures to a human volunteer subject.

From these data, it was possible to construct a generalized excretion pattern applicable to any uranium compound absorbed by inhalation. For a single exposure, the subsequent urine excretion rate y can be described by an equation in the form: $y = \alpha t^{-\beta}$, with $\beta = 1.5 \pm 0.2$. For multiple or chronic exposures, excretion following the final exposure can be described by three equations of the same form. The first and third equations have $\beta = 1.5 \pm 0.2$, while the second equation covers the intermediate phase with $\beta = 0.3 \pm 0.1$. The time range covered by the intermediate phase is a function of the level and duration of the exposures.

These equations can be used in the estimation of past exposures from urine data if sufficient samples are collected to determine the phase in which the current excretion lies. Several procedures were outlined in this study for the estimation of exposure level and 'body burden' from such data.

In discussing a rational urine sampling program, the following conclusions were drawn:

1. It is not usually practical to use urine samples to monitor individual exposures, since a limited number of samples cannot be interpreted accurately. The information that can be derived from continuous

or frequent collections can usually be obtained more economically and reliably by other means, such as air sampling. When adequate means of exposure evaluation by air sampling are not available, selected urine samples, properly interpreted, may provide valuable information at justifiable expense.

2. It is not possible to determine chronic or average exposure levels from urine samples collected from working populations, unless the samples are collected after two or more weeks removal from exposure.
3. With urine excretion values determined from a series of urine samples collected after two or more weeks removal from exposure, reasonably reliable estimates can be made of exposure level and "body burden".

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TABLE I

Urine Uranium Excretion Following Single Exposures - Data Plotted on Figures 1, 3, & 4

<u>Case No.</u>	<u>Figure No.</u>	<u>Exposure Compound</u>	<u>Type of Exposure</u>	<u>No. of Samples</u>	<u>Time Range (Days)</u>	<u>Intercept α</u>	<u>Slope β</u>	<u>Standard Error S</u>
1	1	U ₃ O ₈	Inhalation	386	0.17-66	4.6	-1.5	0.65
2	3	U ₃ O ₈	"	21	1-35	5.4	-1.7	0.97
3	3	UO ₂ F ₂	"	23	0.5-35	3.1	-1.5	0.98
4	3	UF ₄	Inhalation & Ingestion	9	0.31-2.0	0.45	-1.1	0.14
5	3	UO ₂ (NO ₃) ₂	Immersion	24	0.062-10	1.5	-1.7	1.91
6a	4	UO ₃	Inhalation & Ingestion	57	0.28-22	2.9	-1.0	0.74
6b,c	(See Table II)							
7	4	U ₃ O ₈	Inhalation & Skin Absorption	19	0.073-18	0.39	-1.2	2.16
8	4	Yellow Cake	Inhalation & Ingestion	30	0.50-36	5.2	-1.2	0.25

TABLE II

Urine Uranium Excretion Following Chronic Exposures - Data Plotted on Figures 4 & 7

<u>Case No.</u>	<u>Figure No.</u>	<u>Exposure Compound</u>	<u>Type of Exposure</u>	<u>No. of Samples</u>	<u>Time Range (Days)</u>	<u>Intercept α</u>	<u>Slope β</u>	<u>Standard Error S</u>
9b	7	UF ₄ & UO ₃	Inhalation & Ingestion	85	0.07-64	1.8	-0.36	0.48
9c	7	"	"	13	93-529	7.7	-1.7	0.45
10b	7	Mixed	Inhalation	52	50-500	1.3	-0.24	0.53
10c	7	"	"	56	500-4600	9.9	-1.6	0.53
11b	7	U ₃ O ₈	"	32	0.5-32	1.2	-0.31	0.29
11c	7	"	"	84	32-398	4.5	-1.32	0.59
6b	4	UO ₃	Inhalation & Ingestion	0	-	-	-	-
6c	4	"	"	12	26-148	4.7	-1.4	0.68

URANIUM EXCRETION vs. TIME

Figure 1. Log Urine Excretion Rate vs. Log Time Following Exposure for Case 1 - Single Massive Exposure to U_3O_8 Fume.

Figure 2. Log Urine Excretion Rate vs. Time Following Exposure for Case 1 - Single Massive Exposure to U_3O_8 Fume.

Figure 3. Log Urine Excretion Rate vs. Log Time Following Exposure for Cases 2,3,4 and 5 - Single Exposures to Various Forms of Uranium. See Table I.

Figure 4. Log Urine Excretion Rate vs. Log Time Following Exposure for Cases 6,7 and 8 - Exposures to Various Forms of Uranium. See Tables I and II.

48 HOUR DECLINE IN URINE URANIUM EXCRETION

Figure 5. Forty-Eight Hour Decline in Urine Concentration vs. Before-Weekend Concentration for Both Chronic and Single Massive Exposures to Various Forms of Uranium.

Figure 6. Log Urine Excretion Rate vs. Time During and After a Series of Controlled Uranium Inhalations.

The numbers below the triangles represent the micrograms deposited in the lower lung at each inhalation.

The dashed line represents the estimated build-up in background excretion rate during the exposure series.

Figure 7. Log Urine Excretion Rate vs. Log Time Following the Last Exposure for Cases 9,10 and 11 - Chronic Exposures to Uranium Compounds. See Table II.

Figure 8. Generalized Urine Excretion Pattern to Serve as a Model for the Estimation of Future Excretion and Body Burden on the Basis of Current Data.

APPENDIX I

CHOICE OF VARIABLES

I. INTRODUCTION

In the study of excretion patterns following exposure, the important variables are obviously excretion rate and time. However, there are many possible ways to express these two variables, and the curves of excretion data plotted with differing variants of these variables may appear grossly dissimilar. Thus, the first investigation performed was directed toward the choice of the most significant forms of the variables of excretion rate and time.

II. EXCRETION RATE AND TIME VARIABLES

A. Excretion Rate

Excretion rate can be expressed either in terms of mass per unit time, or mass per unit volume of urine. Mass per unit time was chosen for several reasons. Time is a known quantity, while urine volume varies greatly with time for given individuals and between individuals. Time data can be integrated directly, while concentration data cannot. Finally, excretion per unit time was felt to be the more significant variable, since in several cases where urine excretion was artificially increased in an attempt to increase uranium output, a volumetric plot showed a sharp decrease in concentration, whereas a time plot showed little, if any break in the excretion pattern.

The unit selected for plotting was micrograms per hour. The choice of the mass unit makes little difference. Other units would serve as well. Hours rather than days was chosen as the time unit to avoid confusion, especially in regard to the early days following exposure. Excretion rates expressed in days might imply 24 hour samples, when in fact all samples were plotted individually. Also, the peak rates persist for only a few hours, and results expressed per day might suggest otherwise.

B. Time of Excretion

Selecting the proper period of time to plot against excretion rate is more complicated than it might seem at first glance. The problem was attacked empirically using the data

from an individual massive exposure case, which will be referred to as Case 1. This case was chosen because it was by far the most complete and best documented set of data available.

The uranium excretion rate data from Case 1 was plotted against the time of excretion in several forms. The variables selected were:

y = excretion rate for individual urine sample ($\mu\text{g/hr}$)

Y = excretion rate for 24-hour pooled urine sample or data ($\mu\text{g/hr}$)

t = elapsed time between last exposure and sample time (days)

t_1 = starting time of sample accumulation (time of previous urination)

t_2 = sample collection time

t' = "plotting time", i.e., $t' = (t_2 + t_1)/2$

The relations plotted were:

1. $\log y$ vs t_2
2. $\log y$ vs t' (See Figure 2 in main text)
3. $\log y$ vs $\log t_2$
4. $\log y$ vs $\log t'$
5. $\log Y$ vs $\log t_2$
6. $\log Y$ vs $\log t'$ (See Figure 1 in main text)

The two semi-log plots show a very rapid initial decrease of $\log y$ with time. However, the rate of decline in excretion falls off with increasing time. The log-log plots appear to be best satisfied by single straight line curves, except that in the third and fifth plots there are apparent deviations during the first few days.

A straight line on a log-log plot indicated that

$$\begin{aligned}\log y &= \alpha + \beta \log t, \text{ or} \\ y &= \alpha t^\beta.\end{aligned}\tag{1}$$

The uncertainties in the data are greatest at the lowest and highest values of the time range. During the first day, when a deviation of an hour can make a significant difference in $\log t$, large errors can be introduced unless the times of the exposure and the urine sample collections are accurately recorded. At the other end of the time scale, the uranium excretion rates are close to the lower limit of detection and have limited accuracy.

III. DISCUSSION OF TIME VARIABLES

Urine excretion data is most often plotted against t_2 , the time of the sample collection, and t_2 is often the only time information recorded. But y is an excretion rate and is equivalent to a derivative. If the urine sample gives an amount of uranium μ , and covers the time interval t_1 to t_2 , then the computed y equals $\mu/(t_2 - t_1)$. Consequently, y is an approximation to the derivative at time $(t_2 + t_1)/2$ rather than at time t_2 . A mathematical analysis verifies this.

If some function of y versus t (not $\log t$) was plotted for the daily average excretion rate,

where

$$(t_2 + t_1)/2 = t_2 - 1/2,$$

then plotting at $(t_2 + t_1)/2$ is equivalent to plotting at t_2 and shifting all points over half a day. This treatment will not curve straight lines. However, by using $\log t$ quite different results are obtained. One day is 2 times 0.5 days, while ten days is 1.05 times 9.5 days. This difference is large for urines in the first day or two, and has a negligible effect after ten days.

The effect can be seen when the data are plotted. If for example, the data are plotted on log-log paper, with excretion rate versus the elapsed time (t_2) and also versus the plotting time (t'), we find that the elapsed time plot differs markedly from the plotting time plot on the first day (t_2 of 1.02 days, t' of 0.51 days) and then less on the later days.

A. Initial Exposure Period

Thus, the plotting time concept $(t_2 + t_1)/2$ turns out to be necessary and useful. By the nature of $\log t$, the effect of an error in time is much larger during the first day than

during later days. In order to estimate the amount of uranium ingested, or to estimate the parameters α and β of the straight line on log-log paper, the time of the first few (or first days) urinations must be known quite accurately. Recording "first day" or "first two days" is not sufficient. These specific times were recorded quite satisfactorily for Case 1, but were not as clearly defined for some of the other exposure cases.

B. Low Uranium Concentration Data Range

The difficulties at the other end of the time scale are a combination of reproducibility errors of chemical analyses and the fact that $\log 0 = \infty$. The major difficulty arises with the low concentrations of uranium, particularly concentrations reported as 0.003, 0.002, 0.001, and 0.000 milligrams per liter. Clearly, the rounding of the data can have a noticeable effect. This can be seen by adding plus or minus 0.0005 to these concentrations. There will be a large effect on the location of the resulting values when plotted on log-log coordinates, as compared to the effect of adding plus or minus 0.0005 to higher concentrations.

The readings are affected by a background contribution of 0.0006 or higher. If there are errors, this will appear as an apparent marked curvature of the relation for small concentrations, when the true relationship may be a straight line. This did not occur with the Case 1 data, but cannot be ruled out in a number of the other sets of data. Values of 0.003 milligrams per liter began appearing on the 71st day for Case 1 and of course became more frequent as the final sample on the 142nd day approached. A volume of 1500 milliliters per day was assumed in these low concentration cases, and this leads to the plotted uranium excretion rates of 0.1875, 0.125, 0.0625 micrograms per hour. Since these values occur over a wide spread of time, scatter results. However, the straight line determined by the higher concentration points seems to go approximately through the center of these lower concentration points. Further, the scatter which was assumed to be due to rounding or chemical analysis error, seems to be about the same as the scatter of the daily urine values from the 10th day to the 70th day.

IV. CONCLUSION

It may be concluded that the straight line on log-log paper quite satisfactorily fits the relation between the uranium excretion rate and time over the entire time interval examined.

This concept should be extremely useful for the prediction of future excretion rates following a single exposure to uranium on the basis of a small number of urine samples. In addition, it should be possible to make reasonably accurate estimates of the amount of uranium absorbed by integrating the area under the extrapolated excretion curve.

APPENDIX II
MATHEMATICAL ANALYSES OF THE CONCEPT OF URANIUM IN THE BODY

I. INTRODUCTION

The amount of uranium excreted in the urine during various time periods can be measured. It is also possible to measure or calculate the total amount of uranium excreted over an extended interval. For Case 1, every urine excretion was collected during the first 74 days, and spot samples were collected thereafter. In order to estimate the total uranium excreted in the urine, intermediate urines between the spot samples after the 74th day were obtained by interpolation. The objective was to determine if there is any consistent relation between excretion and the amount of uranium in the body. One possibility is that the excretion rate depends on the amount left in the body. The amount of uranium remaining in the body that will be ultimately excreted in the urine may be a useful parameter. It will be shown that certain relationships are simpler if expressed in terms of the uranium which will eventually be excreted from the body.

II. MATHEMATICAL INVESTIGATIONS

Certain mathematical relationships should first be established:

E = total amount of uranium excreted in urine

$U_e(t)$ = total amount of uranium excreted in urine by time t

$U_b(t)$ = total amount of uranium remaining in the body at time t that will be excreted in the urine.

$$U_b(t) = E - U_e(t) \quad (2)$$

If the uranium excretion rate is a straight line on log-log paper, then:

$y(t)$ = uranium (in urine) excretion rate at time t .

$$\begin{aligned} &= \frac{dU_e(t)}{dt} \\ &= - \frac{dU_b(t)}{dt} \end{aligned}$$

$$y(t) = At^{-\beta} . \quad (3)$$

It should be noted that $A = y(1)$. Upon integrating,

$$\begin{aligned} U_e(t_2) - U_e(t_1) &= U_b(t_1) - U_b(t_2) \\ &= A \int_{t_1}^{t_2} t^{-\beta} dt \\ &= \frac{A}{-\beta+1} (t_2^{-\beta+1} - t_1^{-\beta+1}) \\ &= \frac{A}{\beta-1} \left(\frac{1}{t_1^{\beta-1}} - \frac{1}{t_2^{\beta-1}} \right) \end{aligned} \quad (4)$$

If $t = t_2$, and t_1 can be any fixed value, then

$$U_e(t) = U_e(t_1) + \frac{A}{\beta-1} \left(\frac{1}{t_1^{\beta-1}} - \frac{1}{t^{\beta-1}} \right) \quad (5)$$

and

$$U_b(t) = U_b(t_1) - \frac{A}{\beta-1} \left(\frac{1}{t_1^{\beta-1}} - \frac{1}{t^{\beta-1}} \right) . \quad (6)$$

Note that (5) can be written as

$$U_e(t) = K - \frac{At^{-\beta+1}}{\beta-1} \quad (7)$$

and (6) can be written as

$$U_b(t) = H + \frac{At^{-\beta+1}}{\beta-1} \quad (8)$$

where K and H are constants.

Up to this point, the results do not depend on whether $\beta > 1$ or $\beta < 1$, but from this point on the mathematics is quite different for these two cases. If $\beta > 1$ (which is the usual rule) then the total amount of uranium excreted, $U_e(\infty)$, is finite. Thus, we can establish the concept of the total amount of uranium excreted, E . However, the amount excreted at time zero is $-\infty$, that is

$$U_e(0) = -\infty .$$

This is equivalent to saying that the amount in the body at time zero is infinite, that is

$$U_b(0) = +\infty .$$

Clearly, the mathematical model breaks down for very small times and needs to be replaced by something else.

Since $\beta > 1$ is the only alternative actually observed following known single exposure cases, further discussion will be restricted to this alternative. If,

$$\beta > 1, \quad (9)$$

then as $t \rightarrow \infty$, a finite amount of uranium is excreted, and this amount is designated E.

$$\begin{aligned} U_e(\infty) &= U_e(t_1) + \left(\frac{A}{\beta-1} \right) \left(\frac{1}{t_1^{\beta-1}} \right) \\ &= E \end{aligned} \quad (10)$$

$$\begin{aligned} U_b(\infty) &= U_b(t_1) - \left(\frac{A}{\beta-1} \right) \left(\frac{1}{t_1^{\beta-1}} \right) \\ &= 0 \end{aligned} \quad (11)$$

(That is, $K = E$ and $H = 0$.)

Substituting back into equation (5) and (6), we have

$$U_e(t) = E - \frac{At^{-\beta+1}}{\beta-1} \quad (12)$$

$$U_b(t) = \frac{At^{-\beta+1}}{\beta-1} \quad (13)$$

From equation (13) the simple relationship is

$$-\left[\frac{U_b(t)}{(dU_b(t)/dt)} \right] = t/(\beta-1) \quad (14)$$

In terms of the excretion rate $y(t)$, this is

$$\frac{\int_t^\infty y(t)dt}{y(t)} = \frac{t}{\beta-1} \quad (15)$$

Some ideas suggested by this relationship were considered to be useful in studying the deviation of uranium excretion from equation (5) for small times; and in estimating E.

Another approach is to find the differential equation that equation (13) satisfies, or more intuitively, to express the uranium excretion rate

$$y(t) = - \frac{dU_b(t)}{dt} - \beta$$

in terms of the uranium in the body U_b . Now by equation (3),

we have

$$y(t) = - \frac{dU_b(t)}{dt} = At^{-\beta}, \quad (3)$$

and from equation (13), we have

$$t^{-\beta+1} = \frac{\beta+1}{A} U_b(t).$$

Hence,

$$t = \left(\frac{\beta-1}{A} \right)^{-\beta+1} [U_b(t)]^{-\frac{1}{\beta-1}}.$$

- Substitution for t in equation (3)

$$- \frac{dU_b(t)}{dt} = A \left(\frac{\beta-1}{A} \right)^{\frac{\beta}{\beta-1}} [U_b(t)]^{\frac{\beta}{\beta-1}}. \quad (16)$$

That is, the uranium in the body $U_b(t)$ is a solution to the situation where the excretion rate is proportional to the amount of uranium in the body raised to a power greater than one. (For example, in Case 1, $\beta = 1.5$, and the exponent is $1.5/.5 = 3$). Now the exponent becomes

$$\frac{\beta}{\beta-1} = 1 + \frac{1}{\beta-1}$$

and it can be seen that for the exponent to equal 1, β must be equal to ∞ . Thus,

$$\log y(t) = \alpha - \beta t.$$

Thus, if the excretion rate is straight on semi-log paper, then the uranium in the body would be a solution to the differential equation

$$- \frac{dU_b(t)}{dt} = \beta U_b(t)$$

that is, the exponent is 1. Since none of the observed β 's were large, it is clear that the data is not semi-log.

Now to return to the differential equation (equation (6)) let

$$\frac{\beta}{\beta-1} = 1 + \frac{1}{\beta-1} = 1 + \frac{1}{\gamma} \quad (17)$$

and call for all the solutions to the differential equations

$$- \frac{dz}{dt} = Gz^{1+\frac{1}{\gamma}} \quad (18)$$

where G and γ are constants and $G > 0$. The solutions will be interpreted as possible solutions for $U_p(t) = z(t)$. Solving,

$$z^{-(1+\frac{1}{\gamma})} dz = -G dt .$$

Integrating between 0 and t ,

$$z(t)^{-\frac{1}{\gamma}} - z(0)^{-\frac{1}{\gamma}} = -Gt .$$

Clearing,

$$z(t) = \left[\frac{G}{\gamma} t + z(0)^{-\frac{1}{\gamma}} \right]^{-\gamma} \quad (19)$$

if $z(0) = E$, then

$$z(t) = \left(\frac{G}{\gamma} t + E^{-\frac{1}{\gamma}} \right)^{-\gamma} \quad (20)$$

If γ is positive, $\gamma > 0$, then clearly $z(\infty) = 0$ and everything is fine.

If $\gamma > 0$ then

$$\begin{aligned} z(t) &= \left[\frac{G}{\gamma} \left(t + \frac{\gamma E^{-\frac{1}{\gamma}}}{G} \right) \right]^{-\gamma} \\ &= \left(\frac{\gamma}{G} \right)^{\gamma} (t + \tau)^{-\gamma} \end{aligned} \quad (21)$$

where

$$\tau = \frac{\gamma}{G} E^{-\frac{1}{\gamma}} \quad (22)$$

This τ can be considered to mean that the process of excretion really starts at time τ . In any case it gives us the much more satisfactory result that

$$z(0) = E \text{ and } z(\infty) = 0$$

which is desirable for our function $U_p(t)$. To put this result in terms similar to equation (13) let

$$A = \gamma \left(\frac{\gamma}{G} \right)^{\gamma} \quad (23)$$

and

$$\gamma = \beta - 1$$

Substituting in equation (21) we obtain the following two

equations providing that $\beta - 1 > 0$

$$z(t) = \frac{A}{\beta - 1} (t + \tau)^{-\beta + 1} \quad (24)$$

and

$$\begin{aligned} E &= z(0) \\ &= \frac{A}{\beta - 1} (\tau)^{-\beta + 1} \end{aligned} \quad (25)$$

These are the possibilities of estimating E from early data. They are obtained by estimating τ . Differentiating equation (24) we obtain

$$-\frac{dz(t)}{dt} = A(t + \tau)^{-\beta} \quad (26)$$

Therefore, if

$$z(t) = U_b(t),$$

it may be concluded that

$$\log y(t) = \log A - \beta \log (t + \tau). \quad (27)$$

APPENDIX III
VARIOUS SUGGESTIONS FOR ESTIMATING THE TOTAL AMOUNT OF
URANIUM THAT WILL BE EXCRETED IN THE URINE ON THE BASIS
OF EARLY DATA FOLLOWING A SINGLE EXPOSURE

I. INTRODUCTION

The objective of this investigation was to develop various techniques for estimating cumulative excretion in order to make a careful estimate of the total uranium E absorbed by the body during a single massive exposure. Case 1, described in the text of this report, is studied. Various estimates of E, computed on the basis of various early portions of the data, can be subsequently compared with that calculated from a complete set of samples.

II. TWO TECHNIQUES FOR ESTIMATING TOTAL URANIUM EXCRETION, E

The two techniques considered for estimating E are as follows:

A. Technique One

This technique is the simpler of the two approaches. The amount of uranium observed in the first, or first few urines was used to estimate the excretion to that time. If t_1 is the time, then $U_e(t_1)$ is estimated from the amount of uranium observed to time t_1 , and the remaining uranium is estimated by integrating the log-log relationship from t_1 to ∞ . (This is mathematically sound as long as β is greater than 1). The result is given by equation (10)

$$E = U_e(\infty) = U_e(t_1) + \frac{A}{(\beta-1)t_1^{\beta-1}}$$

where

$$A = e^{\hat{\alpha}}.$$

That is, $U_e(t_1)$ is estimated by direct observation, and both A and β are obtained by fitting a straight line to the plot of uranium excretion rate versus time on log-log paper.

It is evident that the result is sensitive to the accuracy of the time measurement t_1 . For example, if t_1 is recorded as 4 hours, when it really is 2, or is recorded as 2 days when it really is 1, the estimate of E will be quite inaccurate.

B. Technique Two

Here the ideas that resulted from the solutions to the differential equation given by equation (18) are used. The method of Technique One can be looked on as introducing a third parameter (in addition to A and β) which is $U_e(t_1)$, and a minimum of three urine samples are needed to estimate E by this technique.

A different parameter, in this case τ , can also be introduced. We can consider that the chronological time t measured from the time of the accident is not the correct time describing the process but requires some shifting. Perhaps the excretion process does not start at time zero, but at some later time τ . Thus, the equivalent of equation (3) is

$$\begin{aligned} y(t) &= dU_e(t)/dt \\ &= -dU_b(t)/dt \\ &= A(t+\tau)^{-\beta} \end{aligned} \quad (28)$$

where there are now three parameters (A, β and τ) to be fitted to the data.

Solving,

$$U_e(t) = U_e(t_1) + \frac{A}{\beta-1} \left[(t_1 + \tau)^{-\beta+1} - (t + \tau)^{-\beta+1} \right] \quad (29)$$

$$U_b(t) = U_b(t_1) - \frac{A}{\beta-1} \left[(t_1 + \tau)^{-\beta+1} - (t + \tau)^{-\beta+1} \right] \quad (30)$$

and at $t=0$,

$$U_e(0) = 0.$$

Thus,

$$\begin{aligned} U_e(0) &= 0 \\ &= U_e(t_1) + \frac{A}{\beta-1} \left[(t_1 + \tau)^{-\beta+1} - \tau^{-\beta+1} \right] \end{aligned} \quad (31)$$

By combining equations (29) and (31), we have

$$U_e(t) = \frac{A}{\beta-1} \left[\frac{1}{\tau^{\beta-1}} - \frac{1}{(t+\tau)^{\beta-1}} \right] \quad (32)$$

$$U_b(t) = E - \frac{A}{\beta-1} \left[\frac{1}{\tau^{\beta-1}} - \frac{1}{(t+\tau)^{\beta-1}} \right] \quad (33)$$

These equations adhere to equation (11) for all positive values of β . However, if $\beta > 1$, then $U_e(\infty)$ is finite and we have $U_e(\infty) = E$ and $U_b(\infty) = 0$. Hence, if $\beta > 1$

$$E = \frac{A}{(\beta-1)\mathcal{T}^{\beta-1}} \quad (34)$$

and

$$U_e(t) = E - \frac{A}{(\beta-1)(t+\mathcal{T})^{\beta-1}} \quad (35)$$

$$U_b(t) = \frac{A}{(\beta-1)(t+\mathcal{T})^{\beta-1}} \quad (36)$$

III. DISCUSSION OF TECHNIQUE TWO

The parameter of starting time was initially introduced on an intuitive basis, but the work, on the differential equation (18), later confirmed it. That is, if uranium in the body is excreted at a rate proportional to some power (greater than one) of the amount in the body, then the results given above are obtainable. Thus, the $\mathcal{T}$ arises from a mathematically real situation, and there is no mathematical breakdown for $t = 0$ or $t = \infty$. Since it is better to have a mathematical model which could arise from even a hypothetical situation, than one that cannot, equations 34 -36 seem appropriate.

For example, consider the Case 1 data, where $\beta = 1.5$. By equation (16) where $(\beta/(\beta-1)) = 1.5/.5 = 3$, the observed excretion rate $y(t)$ is proportional to the 3rd power of the amount of uranium in the body.

By utilizing equation (34) above, we can solve for the value of $\mathcal{T}$ that is implied by the total amount of uranium excreted.

$$\mathcal{T} = \left[\frac{A}{(\beta-1)E} \right]^{\frac{1}{\beta-1}} \quad (37)$$

Using a value of $E = 16,520 \mu\text{g}$, which is in the right numerical range and which simplifies the example, we obtain

$$\mathcal{T} = \left[\frac{24(140)}{0.5(16,520)} \right]^{\frac{1}{0.5}} = \left(\frac{24}{59} \right)^2 = 0.165 \text{ days} = 4.0 \text{ hrs.}$$

It is then clearly seen that $\mathcal{T}$ can be estimated from the early urines, and will affect computed estimates.

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