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MEASUREMENT OF BODY
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PART V

EXCRETION METHODS

THE APPLICATION OF EXCRETION ANALYSES TO
THE DETERMINATION OF BODY BURDEN OF
RADIOACTIVE ISOTOPES

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Application of excretion analyses to the quantitative estimation of total body burden requires a prior knowledge of the excretion rate, preferably by man, of the material in question. The excretion rate of specific radioactive nuclides by man is not always available, so that it is necessary to use data collected from experimental animals. Extrapolation of animal data to man is subject to considerable criticism. There is no way to circumvent such criticism, however, until adequate experimental data have been collected from human subjects.

RELATION BETWEEN URINARY AND/OR FAECAL EXCRETION
AND TOTAL BODY BURDEN

Urine analyses are usually used as the basis for the determination of body burden, although, theoretically, faecal analyses may be used once the relationship between total body burden and the faecal excretion rate is established. Faecal analyses are seldom used, however, because of the greater difficulty and inconvenience of collecting a sample representing a specific time increment, and because processing the samples is usually much more difficult than for urine specimens.

For mathematical convenience, or because of lack of adequate data, it is usually customary to express urinary and/or faecal excretion as simple exponential functions of time. In this way the convenient concept of biological half-time of materials in the body may be employed. The calculations of values for maximum permissible body burdens given in Handbook 52 of the National Bureau of Standards (1953), and in the Recommendations of the International Committee on Radiation Protection (1955), embody this concept. Simple exponential excretion assumes that once the radioactive material enters the body it is retained in a single compartment, or that the rate of elimination from one of several compartments controls the overall excretion rate. In many cases experimental data indicate that these assumptions are not strictly true, over infinite time, even for materials for which the elimination process may seem on first appearance to be relatively simple.

Figure 1 shows the urinary excretion of tritium by the mouse following a single injection of a relatively high dose of tritium in the form of HTO (Pinson, 1952). These data show that the tritium excretion followed a simple exponential with a half-time of 1.9 days until the activity in the urine had dropped to approximately 0.1 per cent of the original value, beyond which the urinary excretion rate became slower, the biological half-time changing to approximately 12 days. Thompson (1952, 1953) has followed the excretion rate of injected tritium still further and has demonstrated the

existence of tritium compartments in the body with biological turn-over times of 90 days or longer. It is reasonable to assume from the data in Fig. 1 that the 1.9 day half-time represents the rate of elimination of tritium from the body water compartment and, therefore, represents the rate of turnover of the total body water. The longer biological half-times represent the mobilisation and excretion of tritium that has exchanged with organically-bound hydrogen of the tissues. These data demonstrate clearly that the rate of excretion of tritium cannot be represented by a single exponential over infinite time. Under these conditions the determination of total body burden from a single urine analysis can be certain only provided the entire urinary excretion curve (over the period of interest) and the time between exposure and collection of the sample are known. In many instances

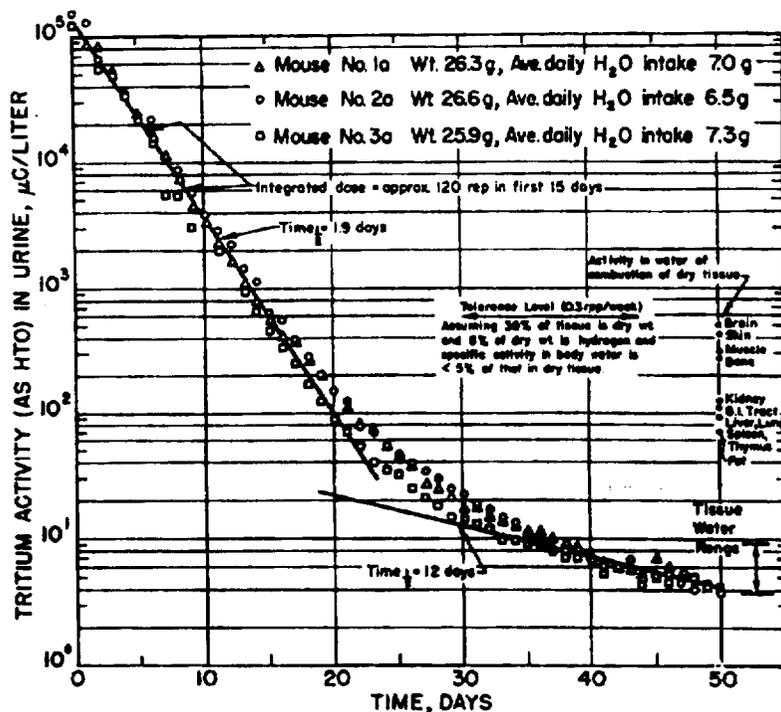


FIG. 1. Fixation and excretion of tritium by the mouse.

(as in the example given above) the assumption of simple exponential excretion does not produce serious error. In the case of exposure to HTO, the size of the body water compartment is so large, compared to those compartments with slower turnover times, that the tritium in the total body water comprises the major contribution to the total radiation dose. It is not likely one would build up enough tritium activity in the organic components of the tissues to contribute significantly to the total dose before the source of contamination was discovered and corrected.

Plutonium, unlike tritium, is a material for which the rate of urinary and faecal excretion continues to change with time. Fig. 2 shows the percentage of the original dose of plutonium excreted

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per day by human subjects as a function of days after exposure, over a period of five years (Langham, Bassett, Harris and Carter, 1950).

These data show that about 0.8 per cent of the intravenously injected dose was excreted on the first day, and that only during finite periods of time could the excretion curves be represented by simple exponentials. Even after five years the rate of elimination of plutonium from the body still seems to be changing. For calculating integrated radiation dose and diagnosing body burden the excretion rate of plutonium over long periods would appear to be expressed most conveniently as a power function of the type

$$Y = at^{-c} \quad (1)$$

where Y is the excretion rate in fraction of injected dose excreted per day, t is the time after exposure in days and a and c are constants.

One might justifiably ask why such data are not expressed as a series of exponentials in preference to the power function. The choice of expression depends on the specific application of the data.* If one is interested in applying the data to a study of the fundamental processes that take place in the body, i.e. analysing the system in terms of compartments and rates, assuming first order kinetics, then mathematical analysis leads to exponential expressions. In an analysis of this kind the power function has no simple meaning. If, however, one is interested in applying the data over long periods of time to make calculations and estimates in problems similar to those from which the original data were obtained, the power function has certain advantages. It can be integrated and differentiated easily which, in the specific case of internally-deposited radioactive isotopes, facilitates the calculation of integrated radiation dose and the prediction of body burden from excretion data.

On the basis of the above general power function expression, the best curves of fit to the data shown in Fig. 2 were established and constants a and c evaluated by a method of successive least-squares approximations. The specific expressions for the rates of urinary and urinary plus faecal excretion of plutonium by man over a period of 5 years are

$$Y_u = 0.002 t^{-0.74} \quad (2)$$

$$Y_{u+f} = 0.0079 t^{-0.84} \quad (3)$$

where Y_u and Y_{u+f} are the fractions of the injected dose of plutonium excreted per day in the urine and the urine plus faeces, respectively, and t is the time after exposure in days. It should be emphasized that the errors in the constants of the expressions may be of the order of 10 per cent.

Integration of equation (3) for urinary plus faecal excretion between limits of 0.5† and $x + 0.5$ gives the total excretion of plutonium over time $t = x$. The data in Table I show the total amount of plutonium excreted during periods of time ranging from 10 days to 50 years. The calculated values agree well with the experimental data. From the values in Table I it appears that the concept of a biological half-time cannot be applied in the case of plutonium and solution of the integrated expression for the 50 per cent excretion time suggests that about 200 years may be required for man to eliminate one-half of his body burden.

The fractional retention of plutonium (R_t) at the end of any time t may be obtained by subtracting the integrated expression for fractional rate of excretion (equation 1) from unity, in accordance with the following expression:

$$R_t = 1 - a \int t^{-c} dt = 1 - \frac{a}{(1-c)} t^{(1-c)} + C \quad (4)$$

* The author is indebted to Mr. C. J. Maletkos and Dr. E. C. Anderson for a major part of this interpretation.

† Arbitrarily chosen as a lower limit of integration because the power function is divergent for small values of t .

TABLE I
 INTEGRATED VALUES FOR URINARY-FAECAL EXCRETION OF PLUTONIUM IN PER CENT ADMINISTERED
 DOSE AT VARIOUS TIMES

Days after injection	Years after injection	Amount of Pu excreted (in % administered dose)
10	—	2.5
20	—	3.2
22	—	3.3
30	—	3.7
60	—	4.5
90	—	5.0
120	—	5.4
150	—	5.7
180	—	5.9
210	—	6.2
240	—	6.3
270	—	6.5
300	—	6.7
330	—	6.8
360	1	7.0
720	2	8.1
1,080	3	8.8
1,440	4	9.3
1,800	5	9.7
3,600	10	11.1
5,400	15	12.0
7,200	20	12.6
10,800	30	13.6
18,000	50	14.6

According to the above equation, total retention becomes negative for very large values of t , which is physically impossible. The mathematical divergence, however, occurs far beyond the point of biological interest since the retention becomes negative only when $t > 10^{20}$ days.

For a large number of other materials body retention and urinary and faecal excretion as functions of time fail to conform to single exponential expressions over the entire period of interest. Studies of the retention and excretion of radium by man were reported by Norris, Speckman, and Gustafson (1955). They were able to measure the amount of radium administered and retained by patients in the Elgin State Hospital, Elgin, Illinois, who were given several weekly injections of radium chloride in 1931.

On the basis of certain assumptions drawn from animal experimental data they expressed the retention function for radium in man by a general power function of the type

$$R_t = At^{-b} \dots \dots \dots (5)$$

where R_t is the fractional retention of radium t days after injection, A is a constant which is equal to the fraction of the injected dose retained when t is equal to 1, and b is a constant. When they applied the above expression to their data they obtained the following specific expression for the retention function of radium in man:

$$R_t = 0.54t^{-0.22} \dots \dots \dots (6)$$

Differentiation of equation (5) with respect to time gave the expression:

$$\frac{dR_t}{dt} = -Abt^{-(b+1)} \dots \dots \dots (7)$$

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in which $\frac{dR}{dt}$ is the rate of change in fractional retention with time. The expression is negative since the fraction retained must always decrease. As excretion is the rate of change of retention and is considered positive when retention is decreasing, the rate of fractional excretion, previously defined as \mathcal{Y} , is equal to $-\frac{dR}{dt}$ and, therefore,

$$\mathcal{Y} = Abt^{-(b+1)} \quad (8)$$

Substitution of the appropriate constants from equation (6) into the differentiated form of the retention function gave

$$\mathcal{Y} = 0.28t^{-1.52} \quad (9)$$

as the expression for the fraction of the injected dose (\mathcal{Y}) of radium excreted per day as a function of time. The similarity between equation (3) for the rate of excretion of plutonium and equation (9) for radium is evident.

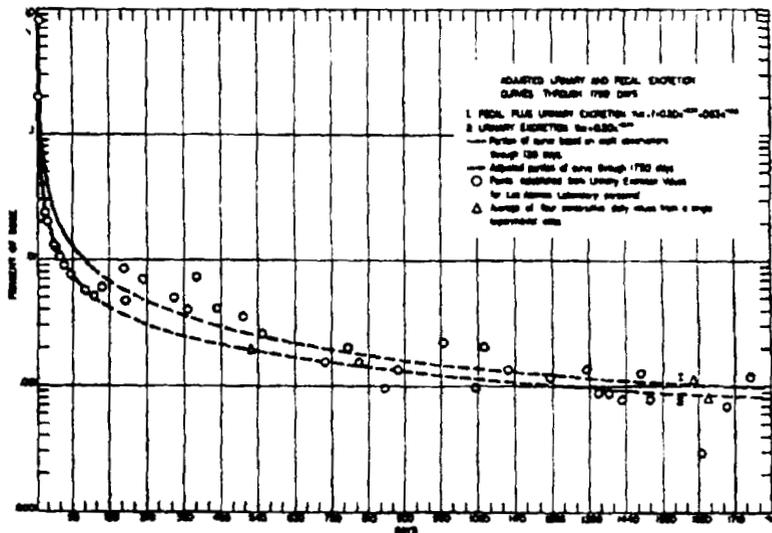


FIG. 2. Urinary and urinary plus faecal excretion of plutonium (over five years) administered intravenously to man.

A better way of comparing the excretion and retention of substances for which the functions are known is to compare their coefficients of elimination (*i.e.* the fraction of the total retained body burden excreted per day).

Norris, Speckman, and Gustafson derived the coefficient of elimination by dividing equation (8) by equation (5), as follows:

$$-\frac{dR_t}{R_t} = \frac{Abt^{-(b+1)}}{At^{-b}} = \frac{b}{t} = 0.52t^{-1} \quad (10)$$

A comparable calculation of the coefficient of elimination of plutonium gives

$$\frac{Y_{u+f}}{R_t} = 8.5 \times 10^{-3} t^{-1} \dots \dots \dots (11)$$

Because of the uncertainties in the constants for the excretion equation (of the order of 10 per cent), the above expression was derived empirically by solution of the excretion and retention equations using various values for t up to 10^4 days. These values were plotted and equation (11) obtained by a least-squares fit. The fitted curve was found to have a slope approximately equal to -1 . It may be shown mathematically that the ratio of excretion rate to retention may be represented by an infinite series in which t^{-1} appears in the first term and succeeding terms may or may not be neglected, depending on the absolute values of c and a .

Comparison of the coefficients of elimination for radium and plutonium shows that the fractional rate of elimination of the retained body burden of plutonium is only 0.016 that of radium, even though the fractional rate of excretion on the basis of injected dose appears to be significantly larger at later times.

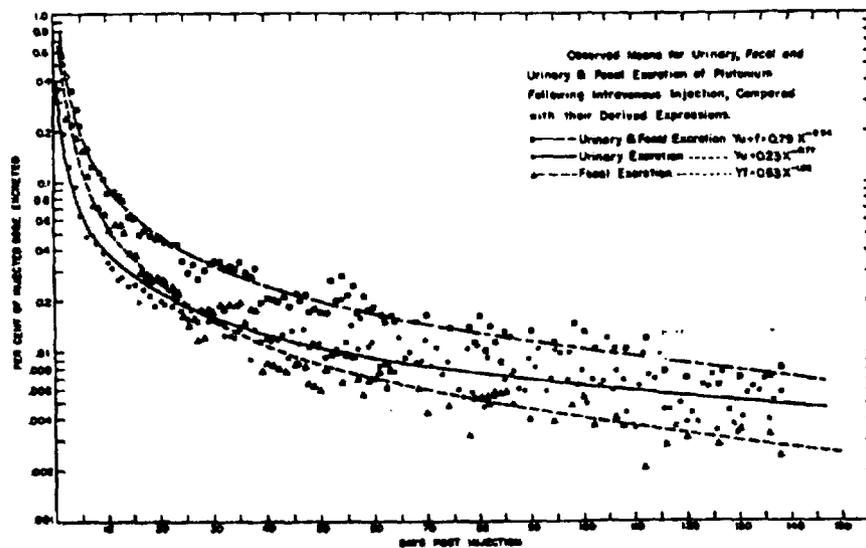


FIG. 3. Urinary, faecal and urinary, plus faecal excretion of plutonium (over 138 days) administered intravenously to man.

It is possible also to develop expressions for coefficients of urinary and faecal elimination in the manner used in equations (10) and (11) when expressions for the rates of excretion are known. The specific expressions for the coefficients of elimination of plutonium, based on the excretion data shown in Fig. 3 (Langham, *et al.*, 1950) for the first 138 days, are as follows:

$$\frac{Y_u}{R_t} = 2.3 \times 10^{-2} t^{-0.74} \dots \dots \dots (12)$$

$$\frac{Y_f}{R_t} = 6.2 \times 10^{-2} t^{-1.00} \dots \dots \dots (13)$$

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where $\frac{Y_u}{R_t}$ and $\frac{Y_f}{R_t}$ represent the fraction of the retained body burden excreted per day in the urine and faeces, respectively. The slope constants for the coefficients of urinary and faecal elimination are not equal to each other and not equal to -1 (as in the case for the coefficient of total elimination shown by equation (11)), because the urinary to faecal excretion ratio is changing with time. It is possible, however, to develop an equation for the variation of urinary to faecal ratio with time by dividing equation (12) by equation (13).

$$\frac{Y_u}{Y_f} = \frac{2.3 \times 10^{-3} t^{-0.74}}{6.2 \times 10^{-3} t^{-1.08}} = 0.37 t^{0.34} \quad (14)$$

Solution of the above expression for $t = 10$ days, and 10,000 days shows that the urinary to faecal excretion ratio for plutonium varies from 0.37 to 7 when extrapolated over a period of about 30 years.

The above treatment of the relation between excretion and total body burden of plutonium and radium provides a general method of approach to the problem of the internal radiation hazard associated with body deposition of radioactive materials when the excretion and retention functions cannot be expressed as single exponentials over the entire period of interest. From either excretion or retention data, it is possible to develop expressions for the retention and excretion functions and the coefficient of elimination of any systemically-deposited radioactive material. These expressions provide a basis for the determination of total exposure and/or retained dose from excretion analysis and a knowledge of the exposure conditions. They also provide a basis for the calculation of maximum permissible levels.

DETERMINATION OF BODY BURDEN FROM URINARY OR FAECAL ASSAYS UNDER CONDITIONS OF ACUTE AND CHRONIC EXPOSURE

If the expressions for the faecal or urinary excretion of any radioactive material are known, it is possible to determine the degree of exposure from excretion analyses. In the following discussion the expressions developed from the data given in Fig. 2 are used to demonstrate general methods for the determination of body burden from urine analyses following single acute, variable chronic and chronic invariant exposure, when the urinary excretion fails to follow a simple exponential pattern.

Determination of body burden following single acute exposure occurring at known time. Following a single acute exposure occurring at a known time the body burden of plutonium (D_E) at the time of exposure may be calculated from the assay of a 24-hour urine specimen collected t days later using equation (2). If $Y_u = 0.002 t^{-0.74}$ and $Y_u = \frac{U}{D_E}$ where U is the amount of Pu found in a 24-hour urine

sample at time t , then

$$D_E = 500 U t^{0.74} \quad (15)$$

Substitution of the proper values for t and U gives the total body burden at the time of exposure in whatever units (c/m, d/m, μ c, or μ g) are used to express U . Likewise, the retained body burden D_R at time t following a single acute exposure may be calculated from the coefficient of urinary elimination given by equation (12), since

$$\frac{U}{D_E} = \frac{Y_u}{R_t} = 2.3 \times 10^{-3} t^{-0.74}$$

then
$$D_R = R_1 D_E = 435 U t^{0.74} \dots \dots \dots (16)$$
 in which the retained body burden is again expressed in the same units as U .

Determination of body burden following variable chronic exposure of known duration. The exposure dose received by an individual as a result of chronic variable exposure of known duration (i.e. the time worked since the last negative urine assay) may be approximated from the assay of a single 24-hour urine specimen by the same expression used for acute exposure occurring at known time (equation 15). One may assume that the individual obtained all his body burden on the first day of exposure in which case t becomes the elapsed time from the beginning of work to the time of collection of the urine sample. Unless the individual actually did accumulate his body burden on the first day of work, such an estimate will be too high. One may assume also that the body burden was obtained on the last day of work in which case t becomes the elapsed time between the last day of work and the time of collection of the urine specimen. In this case the estimate may be too low. One may also average the results obtained on the basis of the two assumptions made above. The average result, of course, has the greatest chance of carrying the smallest error.

A theoretically more exact method of estimating the exposure dose following chronic variable exposure is based on the assay of two 24-hour urine samples collected sufficiently far apart (with no exposure in between) to give significantly different results. This method is based on the assumption that the exposure dose may be represented by a single effective dose occurring at some effective time intermediate to the limits of exposure.

If D_E is taken as the effective dose, then the radioactivity excreted in the first urine sample collected q days after the effective exposure is

$$U_q = 0.002 D_E q^{-0.74} \dots \dots \dots (17)$$

and the radioactivity in the second urine sample taken $q + a$ days after the effective exposure is

$$U_{q+a} = 0.002 D_E (q+a)^{-0.74} \dots \dots \dots (18)$$

Dividing equation (17) by equation (18) and solving for q gives

$$q = \frac{a}{\left(\frac{U_q}{U_{q+a}}\right)^{1.35} - 1}$$

q then is the effective time of exposure, and its substitution in equation (17) gives the effective dose, D_E , as follows:

$$U_q = 0.002 D_E \left[\frac{a}{\left(\frac{U_q}{U_{q+a}}\right)^{1.35} - 1} \right]^{-0.74} \quad D_E = 500 U_q \left[\frac{a}{\left(\frac{U_q}{U_{q+a}}\right)^{1.35} - 1} \right]^{0.74} \dots \dots \dots (19)$$

The above expression gives an approximation of the body burden at time q . The body burden is given in the same units as U_q and U_{q+a} and is expressed as a single effective dose occurring at some effective time intermediate to the limits of exposure.

A similar treatment of the problem of determining retained body burden following chronic

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variable exposure can be made starting with the coefficient of urinary elimination expressed by equation (12).

Determination of body burden following chronic invariant exposure. Chronic invariant exposure to radioactive materials might be expected to occur under conditions where air concentrations are rigidly controlled, the work is highly routine and the nature of the material being worked with is such that it is more or less uniformly distributed throughout the atmospheric environment (as for example, a radioactive gas).

Although equation (2) for the urinary excretion rate of plutonium is used as a basis for the following theoretical treatment, it is probably unrealistic to expect the results to have much practical application to plutonium processing, where the material is not usually distributed uniformly throughout the working environment.

Starting with the equation for the urinary excretion rate of plutonium following a single dose (equation 2),

$$\frac{Y}{D_E} = Y_u = 0.002t^{-0.74},$$

and letting m = time of exposure in days, n = days from the beginning of an exposure to the time a urine analysis is made with $n > m$ (preferably by more than ten days), and assuming a constant daily exposure D_m , then the counts per minute in the urine excreted on day n is:

$$U = 0.002 D_m [n^{-0.74} + (n-1)^{-0.74} + (n-2)^{-0.74} + \dots + (n-m+1)^{-0.74}].$$

U_n may also be evaluated by the following integration:

$$U_n = 0.002 D_m \int_{T_0}^{T_1} (T_2 + Z)^{-0.74} dZ$$

where $T_0 = 1/2$, $T_1 = m + 1/2$, and $T_2 = n - m$, the value $1/2$ is used because the series diverges badly as $T_0 \rightarrow 0$ and $n = m$. Solution of the above expression gives

$$U_n = \frac{0.002}{0.26} D_m [(T_2 + T_1)^{0.26} - (T_2 + T_0)^{0.26}]$$

or

$$U_n = 130 D_m [(n + 1/2)^{0.26} - (n - m + 1/2)^{0.26}].$$

Since $T_{D_m} = m D_m$ = total intake, then

$$T_{D_m} = \frac{130 m U_n}{(n + 1/2)^{0.26} - (n - m + 1/2)^{0.26}} \dots \dots \dots (20)$$

Agreement between the series and the formula (20) is good to 2 parts in 50 for a one-term "series", and to better than 1 part in 1000 for a series with more than five terms.

A specific example of the application of the above dosage calculation is given below, using the expression for seven exposure days per week. In fact, the seven-day exposure formula may be valid for either the five or six-day week. Such would be the case if one considers that absorption from the lung is the primary source of contamination and that the equilibrium between the alveolar and blood plutonium concentration is not radically altered by the one or two-day period of no exposure each week.

For purposes of presenting a specific example, one may assume the following conditions:

Duration of exposure (m) = 330 days.

Duration of time from beginning of exposure until urine sample taken (n) = 360 days.

Counts per minute of urine sample (U_n) = 2 c/m.

The total body dose T_{D_n} may be calculated from the formula:

$$T_{D_n} = \frac{130 \times m \times U_n}{(n + 1/2)^{0.24} - (n - m + 1/2)^{0.24}}$$

On substitution:

$$T_{D_n} = \frac{130 \times 330 \times 2}{(360.5)^{0.24} - (30.5)^{0.24}} = \frac{8.58 \times 10^4}{2.19} = 3.9 \times 10^4 \text{ c/m}$$

Assuming a 50 per cent counting geometry was used ($1 \mu\text{g} = 7 \times 10^4 \text{ c/m}$),

$$T_{D_n} = 0.56 \mu\text{g}$$

SPECIFIC EXAMPLE OF THE APPLICATION OF URINE ANALYSES TO THE DETERMINATION OF INTERNAL EXPOSURE

The Los Alamos Scientific Laboratory has been processing relatively large quantities of ^{239}Pu since 1944. It was essential, therefore, that methods be developed to determine exposure of personnel. The assay of 24-hour urine samples for a activity, although difficult and time consuming, proved feasible.

From 1944 to 1950 over 6000 urine analyses were made on persons working with plutonium (Hemplemann and Langham, 1953). Urine assays showed that 27 of the persons examined excreted measureable amounts of plutonium which indicated body burdens ranging from about 0.1 to 1.3 μg . All positive exposures occurred during the period 1944-1946. These data were supplemented by data collected by the nasal swab technique,* the purpose of which was to detect qualitatively whether or not individuals had been exposed to the inhalation of contamination. Table II shows the approximate average date of exposure, the estimated plutonium body burden, and the total number of high nose swab counts. It should be emphasized that the estimated body burdens are perhaps not accurate to greater than ± 50 per cent except in nine cases for which repeated urine assays were obtained. The rather large error associated with the estimates resulted from the extremely low activities being detected, and the poor counting methods available at that time.

Nine of the positive exposures occurred in the same process which involved working with water-soluble plutonium salts in dilute solutions and under conditions favourable to the production of a fine spray. Urinary excretion curves for these nine individuals are shown in Figs. 4A and 4B. Case 1 (W.B.) shows the typical urinary excretion curve following what may be considered a relatively acute exposure. The urinary excretion rate rose rapidly to approximately 23 c/m per 24-hour sample (counting geometry approximately 50 per cent), at which time he was removed from further exposure. Upon being removed from further exposure his urine assay dropped sharply and began to show a plateau after 30 to 60 days. Cases 2 (F.C.) and 4 (G.F.) show urinary excretion curves which

* The nasal swab procedure, in brief, consists of swabbing the external nares and subsequently counting the nose swab for radioactivity. The method is applicable not only to plutonium but to any particulate radioactive material. Using this technique, the presence of radioactive material in the nasal vestibule can be detected.

CASE 6 (WA)

CASE 1 (WB)

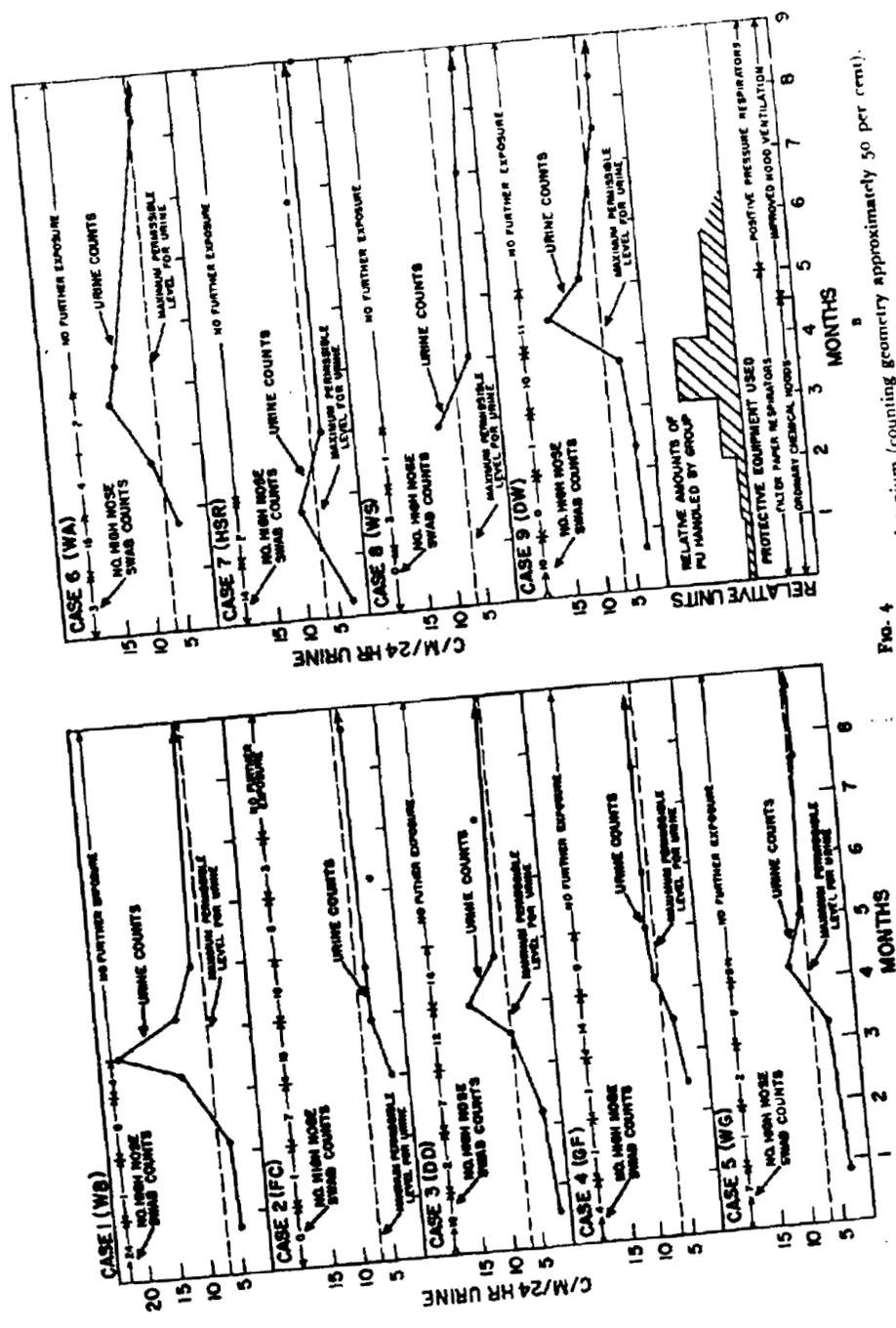


Fig. 4
 A and B) Urinary excretion of nine individuals with positive exposure to plutonium (counting geometry approximately 50 per cent).

may be considered characteristic of prolonged chronic exposure. These individuals did not show sharp peaks in their urinary excretion and upon removal from exposure their urine assays did not drop sharply.

TABLE II
RESULTS OF URINE ASSAYS AND NOSE SWAB COUNTS CONDUCTED ON LOS ALAMOS PLUTONIUM OPERATORS SHOWING POSITIVE EXPOSURE

Case code	Average date of exposure	Estimated body burden μg ($\approx 50\%$)	Total No. high nose swabs
W. G.	June 1945	1.3	24
W. B.	May 1945	1.2	37
D. D.	June 1945	1.2	55
D. W.	June 1945	1.0	32
W. A.	July 1945	1.0	22
G. F.	June 1945	1.0	28
R. D. B.	July 1945	0.8	24
F. C.	June 1945	0.7	60
H. R.	Aug. 1945	0.7	14
W. S.	Aug. 1945	0.6	9
T. M.	Late 1944	0.5-1.0	1 (a)
H. L.	Aug. 1945	0.5	8
T. E.	July 1946	0.4	6
R. A. B.	July 1945	0.4	23
M. W.	Aug. 1945	0.3	6
D. K.	Aug. 1945	0.3	28
D. H.	Aug. 1945	0.3	22
K. E.	Oct. 1945	0.3	3
J. C.	Sept. 1945	0.3	8
J. B.	July 1945	0.3	8
J. A.	Oct. 1945	0.3	11
E. R.	July 1945	0.2	2
C. H.	July 1945	0.2	7
N. D.	Late 1944	0.1-0.5	3 (a)
J. O.	Sept. 1945	0.1	8
C. D.	July 1945	0.1	4
A. B.	Sept. 1945	0.1	8

(a) Incomplete records were available for these cases.

The curves in Figs. 4A and 4B further emphasize the fact that the positive urine values in the nine unquestionable cases were preceded by or occurred simultaneously with periods of high nose swab counts. Because some persons were more co-operative than others, no quantitative significance can be attached to the absolute numbers of high nose swabs for the various individuals during any given period. Both the urine assays and the number of high nose swab counts correlate roughly with the scale of relative amounts of plutonium processed per month by this group. These data suggest that the nine operators accumulated their plutonium burdens largely through respiratory exposure.

RADIOACTIVE MATERIAL IN THE LUNG

It must be emphasized that urinary excretion analyses do not measure unabsorbed radioactive material deposited in the lung and cannot, therefore, be directly applied to the determination of lung exposure. Urinary excretion is an index of the "systemic burden" only, i.e. the amount of material that has been taken into the blood stream and subsequently deposited in the tissues.

Attempts were made at the Los Alamos Scientific Laboratory to apply urinary to faecal ratios as a measure of lung burden. If the urinary to faecal ratio as a function of time after exposure, expressed

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in equation (14), is a measure of the relative amounts of systemically-deposited plutonium excreted in urine and faeces, then extremely low ratios (high faecal excretion) would indicate the presence of plutonium in the faeces that must have been excreted from the lung by ciliary elimination and subsequently swallowed. The data in Table III show the urinary and faecal excretion of plutonium by Los Alamos workers in relation to their mode of exposure. Instead of the urinary to faecal ratios being in agreement with the values indicated by equation (14) they were on occasion as low as 10^{-3} . Undoubtedly these data establish qualitatively the presence of a lung burden in several of the exposed subjects.

TABLE III
COMPARISON OF FAECAL AND URINARY EXCRETION OF PLUTONIUM BY LOS ALAMOS WORKERS IN RELATION TO MODE OF EXPOSURE

Subjects	Type of exposure	Approximate time after exposure (months)	Faeces (c/m/24 hour)	Urine (c/m/24 hour)*
Average of 25	No exposure	—	0.9 ± 0.4	0.7 ± 0.4
D. L.	Slight, general	1	0.7	1.1
S. H.	Moderate, general	1	25	1.0
V. S.	High, general	6	68	0.9
W. S.	Dry box explosion	6	7	0.7
I. M.	Dry Box Explosion	6	23	0.7
J. C.	Burning Pu metal	6	2	0.8
J. D. C.	Burning Pu metal	6	19	0.5
E. Z.**	Burning Pu metal	1/2	1190	1.2
E. F.	Burning Pu metal	1/2	70	0.8
L. D. R.	Burning Pu metal	1/2	950	0.6
T. A. E.**	Spray of $PuO_2(NO_2)_4$	1	3400	5.0
F. C.**	Spray of $Pu(NO_3)_4$	9	196	2.6
W. A. B.**	Spray of $Pu(NO_3)_4$	10	130	7.3
D. D.	Spray of $Pu(NO_3)_4$	12	21	4.9
W. E. G.**	Spray of $Pu(NO_3)_4$	11	237	4.3
G. F.	Spray of $Pu(NO_3)_4$	10	24	3.6

* Counts of less than one have no statistical significance.

** Used to calculate values for lung burden given in Table IV.

The quantitative estimation of lung burden from excretion analyses, as well as the calculation of lung exposure from non-absorbed radioactive materials, necessitates prior knowledge of the kinetics of lung retention and elimination. The problem appears almost hopelessly complex. Lung retention and elimination have been shown to be dependent on particle size (Van Wijk and Patterson, 1940; Drinker, Thompson, and Finn, 1928; Brown, 1931a, b; Hatch and Kindsvatter, 1947; Wilson and LaMer, 1948; Hatch and Hemeon, 1948); solubility (Drinker, Shaw and Drinker, 1923); hygroscopicity (Landahl and Herrimann, 1948); wetting (Brown, 1931b); concentration and respiration rate (Drinker *et al.*, 1928; Brown, 1931a, b); particle density (Brown, 1931b; Hatch and Kindsvatter, 1947; Wilson and LaMer, 1948; Hatch and Hemeon, 1948); flocculation (Hatch and Hemeon, 1948); and on the chemical nature of the material inhaled (Abrams, Seibert, Potts, Lohr and Postel, 1946; Abrams, Seibert, Potts, Forker, Greenberg, Postel and Lohr, 1947). The various aspects of dust retention in the lungs of man are reviewed by Drinker and Hatch (1954).

Insufficient data are available to permit satisfactory elucidation of the kinetics of lung retention and elimination for a single radionuclide under any specific set of conditions. Some data, which may permit generalisation, are available from the excellent work of Abrams, *et al.* (1946, 1947), and

Scott, Axelrod, Crowley and Hamilton (1949), on the fate and deposition of plutonium and various fission products inhaled as aerosols by rats.

Figures 5, 6, and 7 are taken from the work by Abrams *et al.* to illustrate the types of elimination and distribution patterns found following inhalation of aerosols. Their data, which were reported on the basis of amount retained in the lungs as 100 per cent, have been converted to inhaled dose assuming 75 per cent retention. This assumption may be in considerable error because of the very

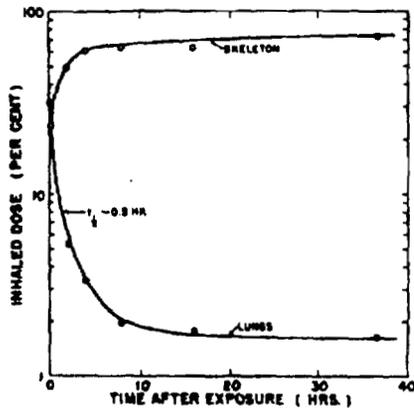


FIG. 5.

FIG. 5. Distribution of Sr as a function of time after inhalation of a $^{88}\text{SrCl}_2$ aerosol (rats) (Abrams *et al.*, 1946).

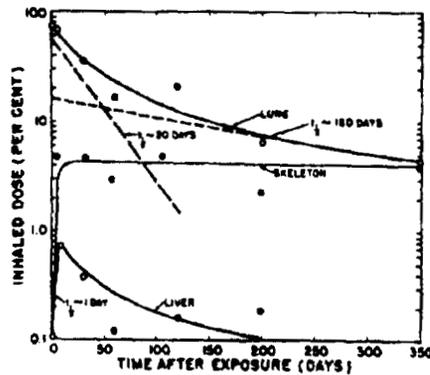


FIG. 6.

FIG. 6. Distribution of Pu as a function of time after inhalation of a PuO_2 aerosol (rats) (Abrams *et al.*, 1947).

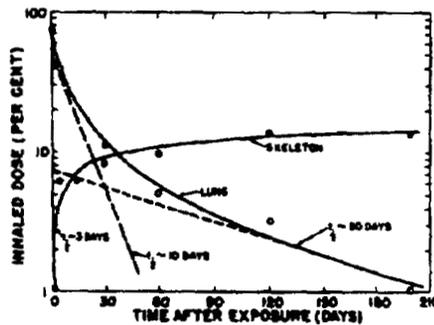


FIG. 7. Distribution of Ce as a function of time after inhalation of a $^{144}\text{CeO}_2$ aerosol (rats) (Abrams *et al.*, 1946).

small particle sizes employed ($< 1 \mu$). Fig. 5, for a $^{88}\text{SrCl}_2$ atomised aerosol, shows the behaviour of a soluble material. The half-time in the lung was extremely short (hours or less) and there was equally rapid appearance of the radioactivity in the organ of deposition, in this case the skeleton. The process involved is apparently direct solution in the body fluids and rapid entrance into the system. Fig. 6 shows the very different behaviour of an insoluble material, in this case a PuO_2 smoke of fine particle size, produced in an electric arc. The half-time in the lung was much

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longer, components of roughly 20 and 180 days seem indicated, and a small amount (< 10 per cent) rapidly reached the liver and skeleton. This very rapid entry of a small amount of supposedly insoluble material was always evident. In fact, the major amount of material entering the systemic circulation did so within a matter of hours or a few days. Direct solution, phagocytic solution, or direct passage of very fine particles into the body fluids before flocculation may provide an explanation. That physical transport out of the lung is involved is confirmed by the excretion data. During the period from 50 to 150 days the faecal excretion was 100 times the urinary excretion. An intermediate case is illustrated in Fig. 7 for an aerosol of ^{144}Ce . The half-times observed were very similar to those found with PuO_2 , but in this case there was a rapid significant entry into the skeleton. Faecal to urinary excretion ratios were again very high compared with those found following intramuscular or intravenous injection, so removal from the lung must be by ciliary action and subsequent swallowing. In this case there may be significant uptake into the system from the gut. The long half-times associated with ciliary transport are confirmed by the studies of Marinelli and co-workers (1953) on RaSO_4 accidentally inhaled by humans. They found lung elimination times of from 30 to 140 days with an average half-time of about 120 days over the first year.

It is clear that the elucidation of the kinetics of lung retention and elimination is an extremely complex problem and requires much detailed information on the fate of nuclides of interest as a function of chemical form, particle size, etc. However, even with the preliminary data now available certain generalisations are suggested:

(1) If the material is truly soluble in body fluids (e.g. $^{89}\text{SrCl}_2$), removal from the lung is essentially instantaneous and no lung hazard persists. In this case urinary excretion data may be used to determine total body burden.

(2) "Insoluble" particles (i.e. PuO_2) are removed with half-times of a few weeks and about six months presumably by two different mechanisms. Both mechanisms apparently involve transport through the GI tract. About 5 to 10 per cent of the inhaled dose may enter the blood stream rapidly and constitute the systemic burden.

(3) "Slightly soluble" particles act in general like particles of insoluble materials, except a higher percentage may enter the systemic circulation and contribute to the systemic burden.

(4) While urinary excretion data are a measure of systemic burden, faecal excretion may be quantitatively related to pulmonary elimination of relatively insoluble materials and to the burden of such materials deposited in the lung. Beyond ten days after exposure the lung excretion data given in Fig. 6 may be represented by a single hyperbolic function

$$C_L = 6.4t^{-0.8} \dots \dots \dots (21)$$

where C_L is the fraction of the initial dose remaining in the lung and t is the time in days.

Since the amount excreted from the lung after this time appears in the faeces, the negative derivative of this expression gives the faecal excretion rate as

$$-\frac{dC_L}{dt} = E_f = 5.12t^{-1.8} \dots \dots \dots (22)$$

where E_f is the rate of faecal excretion in fraction of the lung dose excreted per day. The urinary to faecal excretion ratio $\left(\frac{Y_u}{Y_f}\right)$ following intravenous injection is given by equation (14). This ratio is an index of the excretion pattern for systemic plutonium and a decrease in the ratio at any time after exposure reflects the presence in the faeces of plutonium from a non-systemic source, most likely the lung.

It should be possible, therefore, to estimate both the systemic burden and the lung burden from the assay of urine and faecal samples taken at known times after exposure. Starting with the expression for the systemic urinary to faecal excretion ratio (equation 14)

$$Y_f = \frac{Y_u}{0.37} t^{-0.32}$$

If the total faecal count on day t after exposure is Y_f , and the total urine count is Y_u , then the portion of the total faecal activity (Y_{fL}) due to lung contamination is given by the following expression:

$$Y_{fL} = Y_f - \frac{Y_u}{0.37} t^{-0.32} \quad (23)$$

and it follows from equations (22) and (23) that

$$C_L = \frac{Y_{fL}}{E_f} = \frac{Y_f - 0.37 Y_u}{5.12 t^{-1.8}} \quad (24)$$

where C_L is the lung burden at 10 days post-exposure expressed in the same units as were used for Y_u and Y_f . Since at ten days ~ 10 per cent of the original lung burden has entered the systemic circulation ($t^{1/2} \approx 1$ day) the amount in the lung at time of exposure is

$$\frac{C_L}{0.9} = 1.1 C_L \quad (25)$$

If the data in Fig. 6 are applicable and approximately 10 per cent of the lung burden is absorbed within a few days, the amount of material in the lung at the time of exposure may be estimated by multiplying the systemic burden by ten. Table IV shows a comparison of the lung burdens of five of

TABLE IV
PLUTONIUM LUNG BURDEN IN LOS ALAMOS WORKERS WHEN DERIVED FROM SYSTEMIC BURDEN AND FROM URINARY TO FAECAL EXCRETION RATIOS

Subjects	Systemic Burden (μC)	Lung burden	
		Systemic Burden X10 (μC)	From urinary/faecal ratios (μC)
F. C.	0.11	1.1	1.2
E. Z.	0.004	0.043	0.027
T. A. E.	0.095	0.95	0.28
W. A. B.	0.086	0.86	0.72
W. B. G.	0.094	0.94	1.1

the individuals listed in Table III, when calculated from the systemic burden and from the urinary to faecal excretion ratios. The agreement between the values derived by the two different methods is surprisingly good.

Because of the extreme complexity of the problem, the lack of specific data and the need for a basis for calculating maximum permissible air concentrations from lung exposure, a general model for the fate of radioactive particles in the lung has been proposed.* The model is based largely on

* AEC Harriman Conference, Harriman, New York, 1953. Participants, K. Z. Morgan, J. G. Hamilton, W. H. Langham, L. D. Marinelli and others. Many of the features of the model as shown were added by the author.

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the data of Abrams *et al.* (1946, 1947) and Scott *et al.* (1949) for rats and completely ignores most of the factors mentioned earlier as affecting particle retention in the lung. The assumption is made that the particle size distribution of the inhaled aerosol is such that the total lung retention is 75 per cent of the inhaled dose. It is quantitative only to the extent the specific conditions of exposure coincide with the general pattern on which the model is based.

According to the model shown in Fig. 8, when 100 particles are inhaled, 25 are exhaled without deposition in the respiratory system. These do not contribute to the production of a health hazard. Of the 75 particles deposited in the lung, 50 deposit in the upper bronchial tree and are excreted by ciliary action and swallowed. The half-time of elimination of these 50 particles is ~ 20 days regardless of solubility. Of the 25 particles entering the gut from the lung, 10-20 per cent of the soluble

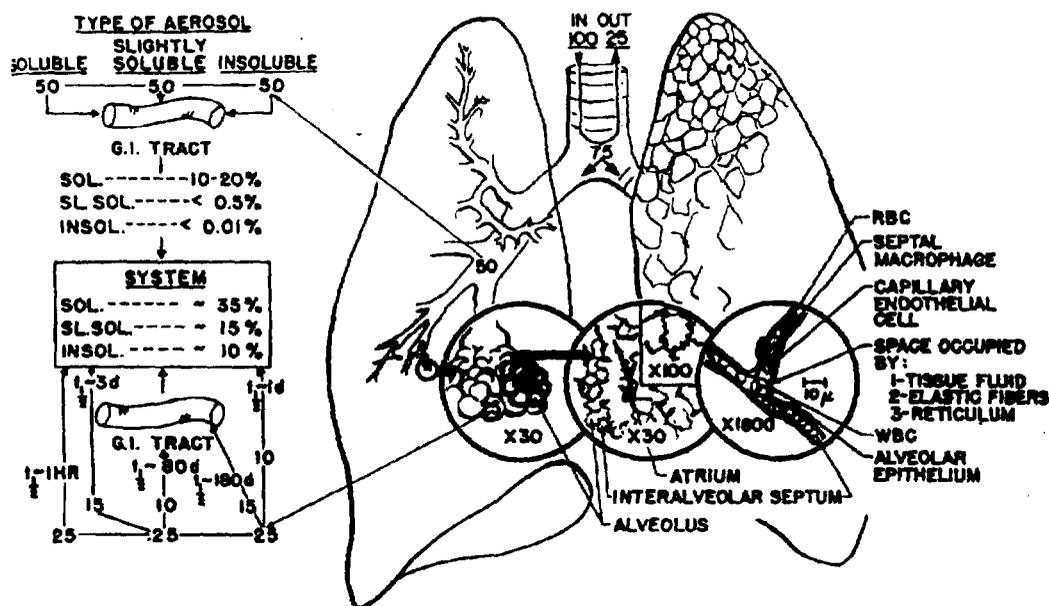


FIG. 8. General model for the retention, distribution and excretion of inhaled radioactive aerosols.

particles, < 0.5 per cent of the slightly soluble and < 0.01 per cent of the insoluble materials, may be absorbed and end up in the system. The 25 particles remaining in the lung are assumed to be deposited on the alveolar surfaces. If these particles are "insoluble" 15 (15 per cent of the originally inhaled dose) are phagocytised or otherwise removed up the bronchial tree and eliminated *via* the gut with an elimination half-time of about six months. The other remaining 10 per cent of the material passes through the alveolar wall into the systemic circulation with a half-time of a few days at most.

If the 25 particles in the alveoli are "slightly soluble", the kinetics of retention and excretion may be essentially the same as for "insoluble particles". A slightly higher percentage may be absorbed and contribute to the systemic burden and a slightly lower percentage may be removed by bronchial elimination with a somewhat shorter half-time. If the particles are soluble, all 25 are absorbed into the systemic circulation with a half-time of an hour or so.

The data in Fig. 5 for a soluble aerosol ($^{87}\text{SrCl}_2$) do not fit the general pattern. This may be explained on the basis of the exceedingly small particle size (0.1μ) which would result in much lower deposition in the upper bronchial tree and much higher in the alveoli (Hatch and Hemeon, 1948).

It should be emphasized that the numbers given in the model are only crude generalisations based on obviously inadequate data and future research should be directed toward obtaining specific numbers for specific nuclides.

The model poses two different radiation hazards: (1) direct radiation of the lung by the deposition of 75 per cent of the inhaled radioactivity, taking into account the respective abundances and the half-times of the three components of the elimination process, and (2) the systemic radiation hazard produced by absorption and subsequent deposition of a fraction of the inhaled dose in the tissues. The model may be of some value in estimating (in the general case) the magnitudes of these hazards from isotopes for which inadequate data exist.

AVAILABILITY OF HUMAN EXCRETION AND RETENTION DATA AND THE APPLICATION OF WHOLE BODY COUNTING

Excretion and retention data for rats and mice (and occasionally other species) are available for a large number of isotopes. Data for humans, however, are available for only a very few materials, among which are ^{239}Pu (Langham *et al.*, 1950), ^{226}Ra (Norris *et al.*, 1955), ^{210}Po (Fink, 1950), ^{131}I (Hamilton and Soley, 1940; Hamilton, 1942), ^{86}Rb (Burch, Threefoot, and Ray, 1955; Ray, Threefoot, and Burch, 1955), ^{42}K (Ray, Threefoot, and Burch, 1955; Hevesy, 1942), ^{24}Na (Hevesy, 1942), ^{22}Na (Threefoot, Burch, and Reaser, 1949), ^{32}P (Lawrence, Scott, and Tuttle, 1939; Erf, 1941), ^{89}Sr (Harrison, Raymond, and Tretheway, 1955), ^3H (as HTO) (Anderson, 1950; Pinson, 1951, 1952a, b, c, d), ^{137}Cs (Woodward, Richmond, and Langham, 1955), and isotopes of U. Human data for some of the above isotopes are fragmentary and only extend over very short periods. Some human data are available for other nuclides, but since they were collected incidental to studies unrelated to the present problem they are essentially valueless for the calculation of maximum permissible levels and the determination of body burden from excretion analyses.

The development of *in vivo* whole body counters such as those discussed at this Conference may facilitate future collection of much needed retention and excretion data for a large number of radioactive nuclides.

The Los Alamos Scientific Laboratory has constructed a large 4π liquid scintillation counter for the determination of γ -emitting nuclides in man (Anderson, Schuch, Perrings, and Langham, 1956). This instrument has been discussed by Dr. Anderson at this Conference. Its sensitivity permits measurement of quantities of γ emitters in the human body as low as 1/100th to 1/1000th of the maximum permissible levels in only 200 seconds of counting time. Its high sensitivity and its fast operation time will enable rapid experimental collection of excretion and retention data for humans without having to subject them to near maximum permissible levels of radioactivity. This may well be one of the most important applications of the *in vivo* whole body counters.

In vivo counting techniques, as a means of determining internal body burdens of radionuclides, are subject to the following limitations:

(1) They do not differentiate between internally-deposited material and surface contamination, although this limitation may be overcome in part by making a series of measurements interspersed with surface decontamination procedures.

(2) Absorption of the radiations within the body prevents external measurement when the radionuclide is a pure α or β emitter, although Bremsstrahlung counting, in some cases, has been mentioned as a remote possibility.

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(3) High immediate capital outlay and space requirements will make the necessary equipment inaccessible to many potential users.

Because of the above limitations, it is hardly likely that *in vivo* counting will replace completely excretion analyses as a method of determining internal body burdens of radionuclides.

The possibility of determining plutonium by *in vivo* counting of its 17 keV X ray was discussed at this Conference as being theoretically possible. Because of the difficulty of determining plutonium body burden by urine analysis, that possibility should be explored. It should be pointed out also that a collimated, Marinelli type crystal counter may be the method of choice for the determination of lung burden of γ -emitting isotopes.

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