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TABLE 8

PLUTONIUM URINE ASSAYS ON LOS ALAMOS PERSONNEL AFTER REMOVAL FROM FURTHER PLUTONIUM EXPOSURE

W.B.G.			W.A.B.			D.L.W.		
Days⁽¹⁾	c/m/24-hr.⁽²⁾	P Error⁽³⁾	Days⁽¹⁾	c/m/24-hr.⁽²⁾	P.Error⁽³⁾	Days⁽¹⁾	c/m/24-hr.⁽²⁾	P.Error⁽³⁾
1	9.4	0.53	1	21.3	0.60	1	13.0	0.55
27	6.9	0.51	20	11.6	0.54	21	8.4	0.52
104	5.8	0.50	48	8.2	0.52	94	3.9	0.49
205	6.4	0.51	192	7.7	0.51	118	3.5	0.49
251	4.6	0.49	370	6.7	0.50	195	3.2	0.49
315	3.7	0.48	1460⁽⁴⁾	1.3	0.17			
387	3.8	0.48						
450	3.9	0.48						
506	2.4	0.47						
652	1.4	0.46						
707	1.9	0.47						
734	1.4	0.46						
796	0.9	0.46						
831	1.3	0.46						
947	2.1	0.47						
1022	0.9	0.48						
1044	1.0	0.47						
1142	1.2	0.48						
1203	1.1	0.46						
1294	1.3	0.47						
1332	0.8	0.48						
1348	0.8	0.48						
1370	0.7	0.46						
1448	0.7	0.46						
1575	0.3	0.45						
1636	0.6	0.46						
1698	1.1	0.46						

W.A.B. . . . . D_Z⁽⁵⁾ = 1.3 μg
W.B.G. . . . . D_Z = 1.3 μg
D.L.W. . . . . D_Z = 1.0 μg

(1) Days after removal from further plutonium exposure.

(2) Alpha counts per minute per 24-hour urine sample at 50 per cent counting geometry.

(3) Probable error calculated from empirical formula derived specifically for the cupferron extraction procedure for determining plutonium in urine (15).

(4) Result due to H. M. Parker in private communication to N. E. Bradbury, July 7, 1949

(5) Estimated by equation [6] Page 29.

Figure 5 shows the adjusted curve through 1750 days represented as a heavy broken line. The points representing the three sets of data collected from Hp-3 and Hp-6 beyond 138 days after injection are shown on the graph as triangles. Points originating from the urine assays of the three Los Alamos workers are shown as circles and the theoretical curve [2] through 138 days is given as a heavy solid line for comparison. The standard error of estimate for the adjusted expression is 42 per cent due largely to the poorer fit during the first few days and to the small number of observations during the later time period.

Integration of the expression $Y_{ua} = 0.20\ X^{-0.74}$ between the limits of $X = 1/2$ and $X = (n+1/2)$ gives the area (A_{ua}) under the urinary excretion curve which represents the total per cent of the injected dose of plutonium excreted in the urine up to and including the nth day after injection.

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$$A_{ua} = 0.20 \int_{1/2}^{n+1/2} X^{-0.74}\, dX = \frac{0.20}{0.26}\left[(n+1/2)^{0.26} - (1/2)^{0.26}\right]$$

$$= 0.77\,(n+1/2)^{0.26} - 0.64 \qquad [8]$$

When n = 1750 days, A_{ua} (the total amount of plutonium excreted in the urine through 1750 days) is only 6.3 per cent of the total injected dose.

2. Fecal Excretion

The same cases used for urinary excretion studies were used for the study of fecal elimination of plutonium following intravenous administration of Pu^{+4} - citrate. Fecal samples were collected daily for the first few days. Later stools were pooled at four day intervals because of the uncertainty of obtaining representative 24-hour samples. Plutonium analyses were made on aliquots of each specimen using methods described earlier. The results of analysis of individual fecal specimens are given in Table 9. Results are expressed as per cent of the administered dose excreted per day. Fecal excretion data could be obtained for only one of the cases (Chi.-1) reported by Russell and Nickson (13). The original data were no longer available and it was necessary to read individual values from the graph given in their report. The original fecal excretion data were not available for the one case studied

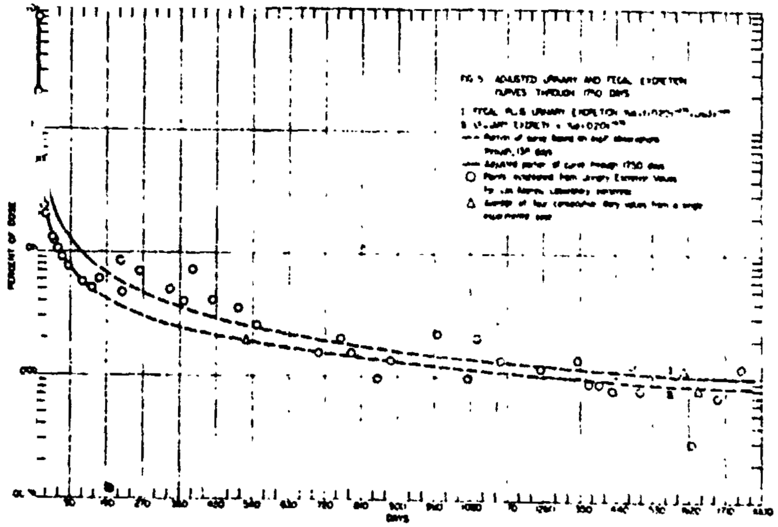

FIG. 5 ADJUSTED URINARY AND FECAL EXCRETION CURVES THROUGH 1750 DAYS

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TABLE 9

INDIVIDUAL FECAL EXCRETION VALUES OF PLUTONIUM FOLLOWING INTRAVENOUS ADMINISTRATION[1] TO HUMAN SUBJECTS (EXPRESSED AS PER CENT OF DOSE EXCRETED PER DAY)

DAYS POST INJECTION	PER CENT OF INJECTED DOSE EXCRETED PER DAY											
	Hp-1	Hp-2	Hp-3	Hp-4	Hp-5	Hp-6	Hp-7	Hp-8	Hp-9	Hp-10	Hp-12	Chl-1[2]
1	.052*	.204	.018*	.134	.004*	.085	.147	.178	.333	.087	.370	.250
2	.221	.204	.157	274	.311	.085	.120	266	.389	.087	.370	.486
3	241	.204	.157	.274	.311	.179	.087	.210	.389	.087	.297	.294
4	.050	.317	095	306	.185	.179	.080	080	.131	.110	.297	.380
5	.105	.317	.099	.306	.110	.179	.055	080	.131	.110	.183	.223
6	046	-	070	.126	.110	.179	.055	080	.131	.110	.183	.118
7	021	-	.070	126	.110	037	.055	080	.131	.110	.020	.083
8	.021	.120	.070	.126	.084	.037	055	070	.131	.034	.020	.113
9	021	.120	.070	128	.051	.037	032	070	.131	.034	.020	-
10	.021	.084	.027	117	051	.037	032	.070	.131	.034	.020	.021
11	.046	084	.027	117	.052	023	032	070	.118	.034	.020	-
12	046	084	027	117	.052	.023	.032	045	.118	.034	.020	.083
13	046	084	.027	117	.032	.023	023	045	.118	.034	.020	.045
14	046	.062	.023	085	032	023	023	045	118*	.022	020	.044
15	035	062	023	085	.032	015	023	045	118*	.022	.023	.043
16	035	.062	023	040	.017	.015	.023	032	.414*	.022	.023	.034
17	035	.062	023	040	.017	.015	.016	032	.157*	.022	.023	-
18	035	.055	016	040	017	.015	.016	025	.157*	.022	.023	.031
19	.015	.055	016	028	.017	015	.016	025	.055	.012	.053	.027
20	015	.055	.016	.028	.020	.015	.016	025	.055	012	.053	.019
21	015	.055	016	028	020	.010	008	025	.055	.012	.053	.019
22	015	.022	006	028	020	.010	.008	.045	055	.012	.053	.018
23	017	.022	.006	.028	-	-	008	.045	.052	.012	.026	.010
24	017	.022	-	-	-	-	008	.009	.052*	.012	.026	.023
25	-	.022	-	-	-	-	.011	.009	.052*	.006	.026	.013
26	-	.021	-	-	-	-	.011	.009	.052*	.006	.026	.023
27	-	.021	-	-	-	-	.011	.009	.043*	.006	.016	.0083
28	-	-	-	-	-	-	.011	.009	.043*	.006	.016	.0049
29	-	-	-	-	-	-	-	.009	.043	.006	.016	.0158
30	-	-	-	-	-	-	-	.018	.043	.006	.016	.0063
31	-	-	-	-	-	-	-	.018	.035	-	.018	.0076
32	-	-	-	-	-	-	-	.018	.035	-	.016	.0062
33	-	-	-	-	-	-	-	.018	.035	-	.016	.0070
34	-	-	-	-	-	-	-	.018	035	-	.016	.0079
35	-	-	-	-	-	-	-	.018	.035	-	.022	.0054
36	-	-	-	-	-	-	-	.018	-	-	.022	.0054
37	-	-	-	-	-	-	-	.028	-	-	.022	.0050
38	-	-	-	-	-	-	-	.028	-	-	.022	.0042
39	-	-	-	-	-	-	-	.011	-	-	-	.0047
40	-	-	-	-	-	-	-	.011	-	-	-	.0068
41	-	-	-	-	-	-	-	.011	-	-	-	.0064
42	-	-	-	-	-	-	-	.011	-	-	-	.0053
43	-	-	-	-	-	-	-	.011	-	-	.008	.0047
44	-	-	-	-	-	-	-	.011	-	-	.008	.0063
45	-	-	-	-	-	-	-	.014	-	-	.008	.0042
46	-	-	-	-	-	-	-	.014	-	-	.008	.0033
47	-	-	-	-	-	-	-	.014	-	-	-	.0028

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TABLE 9 (Contd)

INDIVIDUAL FECAL EXCRETION VALUES OF PLUTONIUM FOLLOWING INTRAVENOUS ADMINISTRATION[1] TO HUMAN SUBJECTS (EXPRESSED AS PER CENT OF DOSE EXCRETED PER DAY)

DAYS POST INJECTION	PER CENT OF INJECTED DOSE EXCRETED PER DAY											
	Hp-1	Hp-2	Hp-3	Hp-4	Hp-5	Hp-6	Hp-7	Hp-8	Hp-9	Hp-10	Hp-12	Chl-1[2]
48	-	-	-	-	-	-	-	.008	-	-	-	.0054
49	-	-	-	-	-	-	-	.008	-	-	-	.0047
50	-	-	-	-	-	-	-	.008	-	-	-	.0040
51	-	-	-	-	-	-	-	.008	-	-	-	-
52	-	-	-	-	-	-	-	.010	-	-	-	-
53	-	-	-	-	-	-	-	.010	-	-	-	-
54	-	-	-	-	-	-	-	.010	-	-	-	.0038
55	-	-	-	-	-	-	-	.010	-	-	-	-
56	-	-	-	-	-	-	-	.010	-	-	-	-
57	-	-	-	-	-	-	-	.007	-	-	-	-
58	-	-	-	-	-	-	-	.007	-	-	-	.0043
59	-	-	-	-	-	-	-	.007	-	-	-	-
60	-	-	-	-	-	-	-	.007	-	-	-	-
61	-	-	-	-	-	-	-	.008	-	-	-	-
62	-	-	-	-	-	-	-	.008	-	-	-	.0048
63	-	-	-	-	-	-	-	.008	-	-	-	-
64	-	-	-	-	-	-	-	.008	-	-	-	-
66	-	-	-	-	-	-	-	-	-	-	-	.0063
70	-	-	-	-	-	-	-	-	-	-	-	.0045
74	-	-	-	-	-	-	-	-	-	-	-	.0050
78	-	-	-	-	-	-	-	-	-	-	-	.0033
79	-	-	-	.006	-	-	.005	-	-	-	-	-
80	-	-	-	.006	-	-	.005	-	-	-	-	-
81	-	-	-	.006	-	-	.005	-	-	-	-	-
82	-	-	-	.006	-	-	.005	-	-	-	-	.0042
83	-	-	-	-	-	-	.006	-	-	-	-	-
84	-	-	-	-	-	-	.006	-	-	-	-	-
85	-	-	-	-	-	-	.006	-	-	-	-	-
86	-	-	-	-	-	-	-	-	-	-	-	.0050
90	-	-	-	-	-	-	-	-	-	-	-	.0042
94	-	-	-	-	-	-	-	-	-	-	-	.0040
98	-	-	-	-	-	-	-	-	-	-	-	.0050
100	-	-	-	-	-	-	-	-	-	-	-	.0056
102	-	-	-	-	-	-	-	-	-	-	-	.0038
106	-	-	-	-	-	-	-	-	-	-	-	.0043
108	-	-	-	-	-	-	-	-	-	-	-	.0038
112	-	-	-	-	-	-	-	-	-	-	-	.0021
116	-	-	-	-	-	-	-	-	-	-	-	.0029
120	-	-	-	-	-	-	-	-	-	-	-	.0032
126	-	-	-	-	-	-	-	-	-	-	-	.0030
130	-	-	-	-	-	-	-	-	-	-	-	.0037
136	-	-	-	-	-	-	-	-	-	-	-	.0034
138	-	-	-	-	-	-	-	-	-	-	-	.0025

*Values eliminated from revised mean on basis of the Chauvenet Criterion.

[1] All cases except Chl-1 received Pu^{+4} in 0.4 per cent $Na_3C_6H_5O_7 \cdot 2d_2O$ Solution.

[2] Russell, E.R., Nickson, J.J., Argonne National Laboratory Report CH-3607.

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by Hamilton and co-workers (14) and it was not feasible to include their results. The present report of the fecal elimination of plutonium is, therefore, confined to twelve cases.

The means, revised means, and standard deviations for the daily fecal excretion of plutonium from 0 to 138 days post injection are given in Table 7 (Page 26). The best curve of fit for the observed means was established by the method of least squares and was found to be:

$$Y_f = 0.63\,X^{-1.09} \qquad [9]$$

with a standard error of estimate of 28 per cent. In the above expression Y_f is the amount of plutonium excreted in the feces on a specific day (expressed as per cent of the injected dose) and X is the day of measurement in days after injection. The agreement between the observed values and the derived expression is shown graphically in Fig. 4 (Page 28). In this figure the derived expression is represented by a heavy broken line and the observed points are represented as open triangles. The fecal excretion of plutonium in per cent of the injected dose excreted per day is plotted against time in days.

No representative fecal excretion data beyond 138 days were available from Los Alamos personnel because of small but significant contamination of feces from swallowed material removed from the lungs of the workers by ciliary action. One may ask why the small amount of lung contamination does not prevent the use of the urinary excretion results from these workers to adjust the 138 day urinary excretion curve to 1750 days. This material does not reach the absorbing area of the lung and is not absorbed appreciably from the gastrointestinal tract (probably less than 0.01 per cent). The small amount of material which has reached the alveoli is being absorbed into the blood at an infinitesimal rate. Of the amount absorbed only a fraction of a per cent contributes to the daily urinary excretion.

Studies of the excretion of plutonium by mice, rats, rabbits and dogs (1), (2), (18), (19) showed the urinary excretion of all species was quite uniform. The plutonium excretion in the urine thirty to fifty days after injection was 0.01 - 0.02 per cent of the administered dose per day. The urinary/fecal excretion ratio varied widely, however, for the various species. The ratio was 1/10 - 15 for the rat and only 1 2 - 3 for the dog.

Russell and Nickson (13) reported a plutonium urinary/fecal excretion ratio of 3/1 in man based on the observation of one case through 140 days. The California group (14) reported an excretion ratio of 3-4/1 by one subject followed for 341 days.

The adjusted urinary excretion curve for 0 to 1750 days and the fecal excretion curve for 0 to 138 days may be solved for the urinary to fecal excretion ratio:

$$\frac{Y_{ua}}{Y_f} = \frac{0.20\,X^{-0.74}}{0.63\,X^{-1.09}} = 0.32\,X^{0.35} \qquad [10]$$

The urinary/fecal ratio is 1.8/1 at 138 days post injection and 4.4/1 at 1750 days when calculated from the above expression. Unfortunately no applicable fecal excretion data are available from the Los Alamos personnel to permit adjustment of the expression for fecal excretion beyond 138 days. If the urinary/fecal ratios at 138 and 1750 days are calculated from the unadjusted expressions (Y_u and Y_f) for both urinary and fecal excretion, the values are 1.7/1 and 3.9/1 respectively. Although extrapolation beyond 138 days is subject to increasing uncertainty with increasing values of X, the above values lead to the conclusion that the urinary/fecal plutonium excretion ratio is not constant, over the range (0-138 days) measured, but approaches 4/1 as a limit at some later time. The results obtained by Hamilton (14) on the case followed for 341 days seem to support the above conclusion.

The expression $Y_f = 0.63\,X^{-1.09}$ gives the amount of plutonium (expressed as per cent of injected dose) excreted in the feces on a particular day (X) after injection. Integration of the expression between the limits of X = 1/2 and X = n+1/2 gives the total per cent (A_f) of the injected dose excreted through day n:

$$A_f = .63\int_{1/2}^{n+1/2} X^{-1.09}\,dX = -7.00\left[(n+1/2)^{-0.09} - (1/2)^{-0.09}\right]$$
$$= -7.00\,(n+1/2)^{-0.09} + 7.45 \qquad [11]$$

From the above expression A_f = 2.96 per cent through the first 138 days.

3. Total Excretion (Urine plus Feces)

From the practical point of view the total urinary plus fecal excretion rate of plutonium is extremely important. The summed elimination rate determines how long a worker should avoid further exposure to plutonium after having reached an accepted maximum permissible body level.

The observed mean urinary plus fecal plutonium excretion values are given in Table 7 (Page 26). Results are expressed as per cent of injected dose excreted per day. The means were obtained from the individual urinary excretion data from fifteen cases and the individual fecal excretion data from eleven. The results reported by the Chicago and California groups were used when available and applicable.

Application of the method of least squares gives the expression

$$Y_{u+f} = 0.79\,X^{-0.94} \qquad [12]$$

as the best curve of fit for the urinary plus fecal excretion data for 0 to 138 days. The standard error of estimate of the computation is 17 per cent. Y_{u+f} is the total plutonium excreted in feces plus urine on a particular day (expressed as per cent of injected dose) and X is the time after injection in days.

The observed means and derived expressions are compared graphically in Fig. 4 (Page 28). Observed values are represented by squares and the derived expression by the heavy broken line designated Y_{u+f}.

The expression $Y_{u+f} = 0.79\,X^{-0.94}$ represents the total excretion of plutonium only through the 138th day. Adjustment can be made, however, for urinary excretion measurements through 1750 days by summing the expression for fecal elimination [9] and the adjusted expression for urinary excretion [7].

$$Y_{ua+f} = Y_{ua} + Y_f = 0.20\,X^{-0.74} + 0.63\,X^{-1.09} \qquad [13]$$

This equation is adjusted to include all urinary excretion results from Los Alamos Laboratory personnel through 1750 days, and gives the total per cent of an injected dose of plutonium which may be excreted on a given day (X) after the time of injection.

The adjusted expression for total elimination rate (Y_{ua+f}) through approximately five years and the observed means are presented graphically in Fig. 5 (Page 31) for comparison with the adjusted urinary excretion rate (Y_{ua}) for the same time interval.

Integration of the adjusted expression for total elimination rate between X = 1/2 and X = n+1/2 days, gives the total amount of plutonium expected to be excreted up to and including day n

$$A_{ua+f} = 0.20\int_{1/2}^{n+1/2} X^{-0.74}\,dX + .63\int_{1/2}^{n+1/2} X^{-1.09}\,dX$$
$$= 0.77\,(n+1/2)^{0.26} - 7.00\,(n+1/2)^{-0.09} + 6.81 \qquad [14]$$

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Table 10 compares the observed and calculated values of total plutonium excretion for various time intervals using the integrated expression [14].

These results emphasize the relatively slow rate of elimination of systemically deposited plutonium by man. According to these data only 8.7 per cent of a single injected dose is excreted in 1750 days (approximately 5 years).

TABLE 10

OBSERVED AND DERIVED TOTAL URINARY PLUS FECAL PLUTONIUM EXCRETION VALUES FOR VARIOUS TIMES AFTER ADMINISTRATION OF A SINGLE DOSE OF PLUTONIUM TO MAN

TIME AFTER INJECTION	PER CENT OF INJECTED DOSE	
	Observed	Calculated*
10 days	2.43	2.56
20 days	3.06	3.17
30 days	3.41	3.53
40 days	3.70	3.81
50 days	3.90	4.03
60 days	4.11	4.21
70 days	4.27	4.38
80 days	4.42	4.50
90 days	4.54	4.62
100 days	4.67	4.74
120 days	4.87	4.93
140 days	5.01	5.10
1 year		6.26
2 years		7.22
3 years		7.83
4 years		8.30
5 years		8.68
10 years		9.98
20 years		12.17

*Calculated from the integrated expression for adjusted urinary plus fecal excretion [14]. The calculated values appear higher than the observed values by a constant amount because of the decision to accept a poor curve fit during the first ten days (See Page 23).

IV. DISCUSSION

A. Distribution of Plutonium in Tissues and Organs of Man

Table 3 (Page 18) contains all available data (up to the time of this report) on the distribution of plutonium in the tissues and organs of man. These data were the results of analysis of a miscellaneous group of samples collected from seven human subjects. The subjects were elderly persons or persons suffering from an incurable chronic disease. The samples were often small and poorly representative and not obtained from the seven cases at comparable times after injection of the plutonium. These unavoidable difficulties must be recognized and accepted when considering the results. Despite the above difficulties, the data are extremely valuable as a supplement to a much greater and more reliable mass of data

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concerning the distribution of plutonium in the tissues and organs of laboratory animals. The data on man are in good agreement with results of similar studies in rats, mice, rabbits, and dogs. The good agreement permits the conclusion that there are no major differences in the quantitative distribution of plutonium in the tissues and organs of man and those of common laboratory animals with perhaps one exception - the liver. The results indicate that the retention of plutonium in the liver following its intravenous injection as Pu^{+4}-citrate complex and as plutonyl ion may be 20 - 40 per cent for man as compared to 10 per cent or less for rats. The "biological half-time" of plutonium in the liver of man is probably much greater than that for rats.

The average amount of plutonium found in vertebra, sternum and rib was 0.0063 per cent of the injected dose per gram of whole bone. Assuming vertebra, sternum and rib as representative of the entire skeleton, 66 per cent of the injected dose would be deposited in a 10 kg skeletal system (7 kg of bone, 3 kg of marrow) of a 70 kg man.

The observed concentration of plutonium in bone may be used to estimate the radiation dose received per gram of skeletal system when a "standard man" has accumulated the official maximum permissible plutonium body content of 0.5 μg (0.032 μc). Using the dosage rate formula: rep/day = 54 CE (where C = concentration of radioisotope in μc/g, E = energy of the radiation in Mev, and the rep = 93 ergs/g), the radiation dosage received per gram of skeleton from 0.032 μc of plutonium is as follows:

$$\text{rep/day} = 54 \times 6.6 \times 10^{-5} \times 0.032\ \mu c \times 5.15\ \text{Mev} = .00057$$

A similar calculation for the official maximum permissible radium content of 0.1 μc may be made for comparison. If 50 per cent of the radon from radium decay is retained in the body, then approximately 15 Mev of energy will be released in the body by the alpha particles per decay. If 100 per cent of the radium is deposited in a 10 kg skeletal system, then the radiation dosage in rep per day is given as follows:

$$\text{rep/day} = 54 \times 1 \times 10^{-5} \times 15 = 0.0081$$

According to the above calculation, the radiation dosage per gram of skeleton delivered by 0.1 μg of radium would be 14 times that delivered by the maximum permissible dose of plutonium if the two materials were distributed in a comparable manner in the skeleton. Autoradiographic studies show conclusively, however, that radium and plutonium do not distribute in a comparable manner. Plutonium is more localized and concentrates in the endosteal and periosteal surfaces. The choice of a more conservative body tolerance dose for plutonium was made to allow for its more specific localization in the skeletal system. It should be noted, however, that radium does not distribute uniformly throughout bone and Evans (20) has reported that analyses of bone samples from radium cases showed the radium to be unevenly distributed by as much as a factor of 10. It may be necessary, therefore, for plutonium to be concentrated by a factor of 140 over radium in order that 0.5 μg will give radiation intensities comparable to that which may occur with 0.1 μg of radium. Evans (21) has also pointed out that the presence of mesothorium in the radium responsible for the early radium poisoning cases may account for an additional safety factor of 5 in the 0.1 μg radium tolerance.

The above discussion supports the possibility that the 0.5 μg maximum permissible tolerance dose for plutonium is extremely conservative.

B. "Biological Half-Time" of Plutonium in Man

The "biological half-time" of plutonium in man can be estimated from the excretion data presented in this report. Although the adjusted urinary plus fecal excretion curve is (empirically at least) logarithmic in nature, it appears that the curve approaches an exponential for longer times. Such an exponential curve would be in keeping with the assumption that

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metabolic processes are primarily first order reactions. Whatever the true process is, from the data and curves given in this report, it is possible to calculate the absolute minimum half-time of plutonium in the body. It is assumed (not unreasonably) that the excretion of the plutonium measured in terms of the amount in the body at a given time does not increase at some time. If one takes the last point on the combined urinary plus fecal excretion curve (a single value of the ordinate in Fig. 5) and assumes exponential excretion thereafter, an absolute minimum value is obtained for the biological half-time. On this figure, which is a plot of $\Delta C / C_0$ versus Δt exponential excretion would be represented by a straight line with zero slope. Examination of the adjusted curve shows that 0.001± .00035 per cent per day is excreted at 1750 days (approximately 5 years) after exposure. Up to five years 8.7 per cent of the total has been excreted. The time required to excrete an additional 41.3 per cent (assuming exponential excretion beyond 1750 days) is

$$\frac{41.3}{0.001 \pm 0.00035} = 41{,}300 \text{ days} = 113 \text{ years with limits of 84 and 175 years.}$$

Thus, the mean minimal biological half-time estimate is 118 years. From the above, one may conclude that the excretion coefficient is too small to be of any practical significance in elevating the maximum permissible dose of plutonium or in permitting the return to work of an individual who has reached the maximum permissible body burden. Once a worker is retired from work with plutonium because of a maximum tolerance exposure, it must be assumed that he is retired from such work for the balance of his lifetime.

C. Determination of Plutonium Body Burden from Urinary Excretion

In the determination of exposure doses by the use of excretion data, one is primarily concerned with three different situations. First is the case of a single acute exposure dose occurring at a known time. Second is the case of a variable chronic or subacute dose with only the total exposure time being known. Third is the case of a chronic invariant (usually low level) exposure dose with the time limits known.

The evaluation of the single acute exposure dose occurring at a known time is the basis of this paper. A urinary excretion curve through 138 days after a single acute exposure is given in Fig. 4 (Page 28). This curve has been extended beyond the observation limit to 1750 days (Fig. 5) by applying data collected on exposed personnel from the Los Alamos Laboratory. The method used to apply these data was explained earlier (Pages 23 and 29). It is worth noting that the difference between the adjusted curve and the extrapolated 138-day curve at 1750 days is less than the standard error of estimate of the former. This finding allows more confidence in further extrapolation beyond 1750 days post exposure. The calculation of the body burden from a single acute exposure is simple.

Since

$$Y_{ua}(\%) = 0.20\,X^{-0.74}$$

$$Y(c/m) = 0.0020\,D_E\,X^{-0.74}$$

Then

$$D_E = 500\,Y(c/m)\,X^{0.74} \qquad [16]$$

Thus, a single urine count, Y, made X days after an unknown single acute exposure, D_E, determines D_E in counts per minute. The exposure dose in µc or µg is easily determined if the counting geometry, etc., is known.

In the Los Alamos exposures, we have an illustration of the variable chronic exposure case with known time of exposure. Only under conditions of stress when safety factors of design may be exceeded will this type of exposure be seen. There are three methods of

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estimating the total exposure dose under such conditions. Past practice at the Los Alamos Laboratory was to assume that an individual contracted his total exposure dose on the last day of the exposure period. His total body burden was then determined by substitution in the urinary excretion formula as shown above. In this case, zero time is the last day of exposure. Obviously this method gives too low a value for the exposure dose as the estimated dose is directly proportional to time. A second method which has been used is exactly the same as the previous one except that zero time is taken as the first day of exposure which assumes that all of the dose was accumulated on exposure day one. It is evident that this estimate of total exposure is too high. The third method, which was used in this paper to determine the adjusted urinary excretion curve, is believed to more closely approximate the true situation. In this method it has been assumed that the total exposure dose may be represented by a single <u>effective</u> dose occurring at some <u>effective</u> time intermediate to the limits of exposure. The equations and steps to be followed with this method are shown on Pages 23 and 29. Ordinarily the first urine count is used to determine whether an individual should or should not be withdrawn from exposure. It is not used as one of the two significantly different dose determining counts. This is due to the fact that the initial withdrawal count may reflect the high urinary excretion resulting from the previous ten days exposure, and to the relatively high per cent excretion during the first 10 days post-exposure period. The high rate of elimination resulting therefrom may relatively obscure any exposure doses accumulated previous to that time.

The case of chronic invariant exposure is probably of primary interest. This is the type of exposure (within limits) that occurs in processing procedures in the plutonium industry in which air concentrations, etc., are rigidly controlled and the work is routine. An analysis of the general case is presented as follows:

If m = time of exposure in days, and
  n = days from the beginning of an exposure to the time a urine analysis is made
    with n > m (preferably by more than 10 days)

then the counts per minute in the urine excreted on day n is:

$$Y_n = 0.0020\left[D_1 n^{-0.74} + D_2(n-1)^{-0.74} + D_3(n-2)^{-0.74} + \ldots\ldots + D_m\,[n-(m-1)]^{-0.74}\right]$$

where D_1 is the exposure dose in counts per minute on exposure day 1,

D_2 is the exposure dose in counts per minute on exposure day 2,

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D_m is the exposure dose in counts per minute on exposure day m.

Considering the case in which we are interested, namely, $D_1 = D_2 \ldots\ldots = D_m = D_j$ (the constant daily exposure dose), then

$$Y_n = 0.002\,D_j\left[n^{-0.74} + (n-1)^{-0.74} + \ldots\ldots + [n-(m-2)]^{-0.74} + [n-(m-1)]^{-0.74}\right]$$

Thus

$$D_j = \frac{Y_n}{0.0020\left[n^{-0.74} + (n-1)^{-0.74} + \ldots\ldots + [n-(m-2)]^{-0.74} + [n-(m-1)]^{-0.74}\right]}$$

Considering the bracketed term in the denominator:

$$n^{-0.74} + (n-1)^{-0.74} + \ldots\ldots + [n-(m-1)]^{-0.74} =$$

$$(n-m+1)^{-0.74} + (n-m+2)^{0.74} + \ldots\ldots + n^{-0.74}$$

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term is similar to the infinite series r! where r has the limiting values (n - m + 1) and (n) and t = -0.74. The sum of the series $r^{-0.74}$ may be written:

$$\sum_{r=1}^{r=R} \frac{1}{r^{-0.74}} = \frac{1}{1^{0.74}} + \frac{1}{2^{0.74}} + \frac{1}{3^{0.74}} + \ldots\ldots + \frac{1}{R^{0.74}}$$

Thus we may write:

$$(n-m+1)^{-0.74} + (n-m+2)^{-0.74} + \ldots\ldots + n^{-0.74} = \sum_{r=(n-m+1)}^{r=n} \frac{1}{r^{0.74}}$$

$$= \sum_{r=1}^{r=n} \frac{1}{r^{0.74}} - \sum_{r=1}^{r=(n-m)} \frac{1}{r^{0.74}} = \sigma(n) - \sigma(n-m)$$

and on substitution

$$D_j = \frac{Y_n}{0.002\,[\sigma(n) - \sigma(n-m)]}$$

The following empirical formula* is good to 2 parts in 50 for r = 1 and to better than 1 part in 1000 for r > 5:

$$\sigma(r) = 3.8462\,(r+1/2)^{0.26} - 3.2880 \qquad [16]$$

Thus, on substitution we have:

$$D_j = \frac{Y_n}{0.002\left[3.8462(n+1/2)^{0.26} - 3.8462(n-m+1/2)^{0.26}\right]}$$

or

$$D_j = \frac{130\,Y_n}{\left[(n+1/2)^{0.26} - (n-m+1/2)^{0.26}\right]}$$

Since the total exposure dose = $mD_j = T_{D_m}$

$$T_{D_m} = \frac{130\,mY_n}{\left[(n+1/2)^{0.26} - (n-m+1/2)^{0.26}\right]} \qquad [17]$$

In addition to the empirical formula for $\sigma(r)$ a plot of the real values of $\sigma(r)$ versus (r) for values of r up to 90 days has been included (Fig. 6) from which the values of the sums may be read directly.

In the equation for T_{D_m} seven exposure days per week are assumed. The formula for T_{D_m} may be adjusted for six exposure days per week as follows:

We assume that exposure begins on the first working day of a week for simplicity.

Obviously the only days not contributing to exposure are those on which $D_j = 0$. In the six day week, therefore, $D_7 = D_{14} = D_{21} = \ldots\ldots D_{7a} = 0$ where a = number of weeks worked by the subject. Thus, the terms corresponding to D_7, D_{14}, D_{21} ..... etc., must be subtracted from the dose equation.

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*Determined by Bengt Carlson of the Los Alamos Theoretical Division.

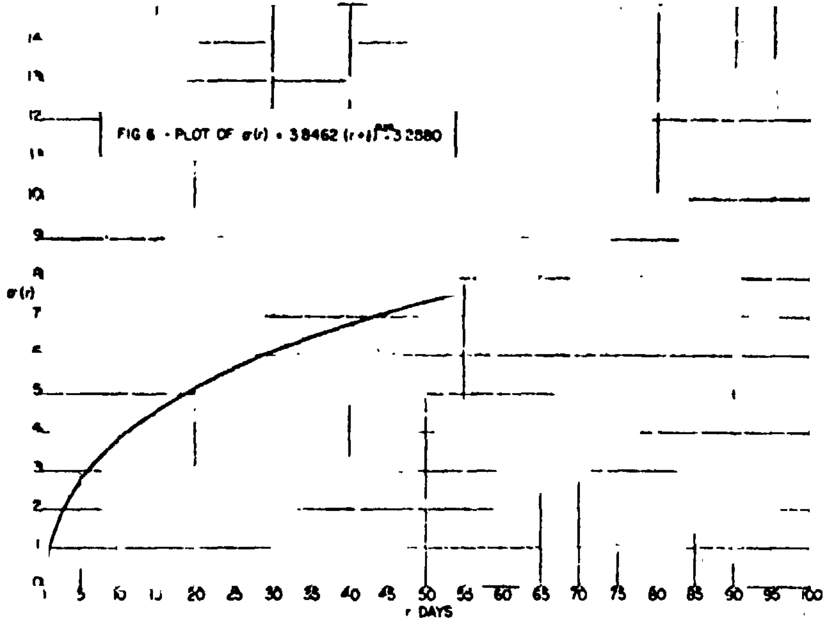
FIG 6 - PLOT OF $\sigma(r) = 3.8462\,(r+\frac{1}{2})^{0.26} - 3.2880$

Hence:

$$D_j = \frac{Y_n}{0.002\left\{\left[\sigma(n) - \sigma(n-m)\right] - \left[(n-6)^{-0.74} + (n-13)^{-0.74} + (n-20)^{-0.74} + \ldots\ldots + (n-7a+1)^{-0.74}\right]\right\}}$$

And designating the total exposure dose for the six day week as $T_{D_{m_6}}$ then

$$T_{D_{m_6}} = \frac{500\,mY_n}{3.8462\left[(n+1/2)^{0.26} - (n-m+1/2)^{0.26}\right] - \left[(n-6)^{-0.74} + (n-13)^{-0.74} + (n-20)^{-0.74} + \ldots\ldots + (n-7a+1)^{-0.74}\right]} \qquad [18]$$

Similarly for 5 exposure days per week

$$D_6 = D_7 = D_{13} = D_{14} = D_{20} = D_{21} = \ldots\ldots D_{7a-1} = D_{7a} = 0$$

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The total exposure dose $T_{D_{m5}}$ =

$$T_{D_{m5}} = \frac{500\, m Y_n}{3.8462\left[(n+1/2)^{0.26} - (n-m+1/2)^{0.26}\right] - \left[(n-5)^{-0.74} + (n-6)^{-0.74} + (n-12)^{-0.74} + (n-13)^{-0.74} + \dots + (n-7a+2)^{-0.74} + (n-7a+1)^{-0.74}\right]}$$

In the preceding formulae exposure conditions were assumed to consist of an equal and constant daily exposure dose D_1 equivalent to a single injected dose. Also, the constants 0.0020 and -0.74 were empirically established on the basis of data available at the time of this report. These values may change as more data become available.

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 we 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 (Y_n) = 2 c/m
The total body dose T_{D_m} may be calculated from the formula:

$$T_{D_m} = \frac{130 \times m \times Y_n}{\left[(n-1/2)^{0.26} - (n-m-1/2)^{0.26}\right]}$$

On substitution:

$$T_{D_m} = \frac{130 \times 330 \times 2}{\left[(360.5)^{0.26} - (30.5)^{0.26}\right]} = \frac{8.58 \times 10^4}{2.19} = 3.9 \times 10^4 \text{ c/m}$$

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

$$T_{D_m} = 0.56\ \mu g$$

V. SUMMARY

The distribution and excretion of plutonium administered intravenously to man has been studied. The data from twelve subjects have been correlated with similar data collected by other investigators, making a total of sixteen cases considered. The data have been supplemented further with observations made on three Los Alamos Laboratory personnel who absorbed measurable amounts of plutonium in the course of their work. The results of these studies may be summarized as follows:

1. Clinical observations and clinical data collected on the various subjects indicate that the intravenous injection of a single dose of 5 to 100 µg of plutonium is without acute subjective or objective clinical effects.
2. The analysis of tissues following the intravenous injection of plutonium showed that there was little difference in the mode of deposition of plutonium in man and in the common laboratory animals. As in the case of rats and other laboratory animals the skeletal system was the major site of plutonium deposition. Retention of plutonium by the liver of man seemed to be higher and the "biological half-time" in liver longer than for the more common laboratory animals.
3. Concentration of plutonium in the blood following intravenous injection drops very rapidly; only 0.3 per cent of the total injected dose was fixed in the total blood volume thirty days after injection.
4. The urinary excretion of intravenously administered plutonium was not exponential. Curvilinear regression line fitting showed that the urinary excretion through 138 days was best expressed by the fractional logarithmic function

   $$Y_u = 0.23\, X^{-0.77}$$

   In this expression Y_u is the per cent of the injected dose excreted in a single day and X is the time of observation in days post-injection. The standard error of estimate is 32%.
5. The above expression for the urinary excretion through 138 days was adjusted by including data collected on Los Alamos Laboratory personnel. This adjustment permitted the development of an expression for the urinary excretion of plutonium through 1750 days. The adjusted expression is:

   $$Y_{ua} = 0.20\, X^{-0.74}$$

   The standard error of estimate of the adjusted expression is 42 per cent.
6. The excretion of plutonium in the feces likewise was not exponential. Application of the method of least squares showed the best curve of fit for the fecal excretion of plutonium through 138 days was:

   $$Y_f = 0.63\, X^{-1.09}$$

   In this expression Y_f is the per cent of the injected dose excreted on a specific day and X is the time of measurement in days post-injection. The standard error of estimate of the above expression is 28 per cent.
7. The urinary to fecal plutonium excretion ratio obtained by solution of the above expressions for urinary and fecal excretion showed the urinary to fecal ratio was not constant. It was essentially 1:1 at 30 days and approached 4:1 at approximately five years.
8. The total (urine and fecal excretion) through 138 days was best expressed by the equation:

   $$Y_{u+f} = 0.79\, X^{-0.94}$$

9. The total urine plus fecal excretion through 1750 days could be approximated by adding the expression for the fecal excretion through 138 days and the adjusted expression for the urinary excretion through 1750 days. The expression for the combined excretion is:

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$$Y_{ua+f} = 0.20\, X^{-0.74} + 0.83\, X^{-1.09}$$

in which Y_{ua+f} represents the per cent of the injected dose excreted in the urine plus feces on a specific day, and X designates the time of observation in days post-injection.

10. Integration of the above expression between the limits of 1/2 and n+1/2 days post-injection gives the following expression:

$$A_{ua+f} = 0.77\,(n+1/2)^{0.26} - 7.00\,(n+1/2)^{0.09} + 6.81$$

which represents the integrated amount of plutonium in per cent of the injected dose (A_{ua+f}) excreted up to and including the nth day after injection. Substitution in this expression showed that only 8.7 per cent of a single injected dose was excreted in approximately five years.

11. Application of the data of this report to the calculation of the "biological half-time" of plutonium in man gives a mean minimal "biological half-time" estimate of 118 years, with a variation of from 84 to 175 years.

12. The urinary excretion data of this report were applied to the diagnosis of exposure of personnel to plutonium. Three sets of exposure conditions were considered:

(a) The application of plutonium urine analysis to estimate the total body dose following a single acute exposure occurring at a known time,

(b) The application of plutonium urine analysis to estimate the total body burden of plutonium following variable chronic or sub-acute exposure with only the total exposure time being known and,

(c) The application of urine analysis to estimate the total body burden following chronic invariant exposure (such as may occur in a carefully controlled routine plant process) with time of exposure known.

Expressions for the calculation of body dose under the conditions set forth in (a), (b) and (c) are included in this report.

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