

## Interpretation of Enhanced Fecal and Urinary Plutonium Excretion Data under a 2-y Regular DTPA Treatment Started Months after Intake

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**Abstract**—In a worker who had internalized plutonium, most likely through inhalation of a somewhat soluble compound, an extensive diethylenetriaminepentaacetate (DTPA) treatment regimen was initiated several months after contamination. Numerous radiotoxicological analyses were performed in both fecal and urinary specimens collected, sometimes for three consecutive days after DTPA administration. Activity measurements showed the continued effectiveness of DTPA intravenous infusions in removing plutonium from tissues of retention even if the treatment regimen started very belatedly after contamination. In the present case, the activity excreted through urine within the first 24-h after a DTPA infusion contributed only about half of that activity excreted within the first three days (i.e., the cumulative activity of the first three 24-h urine collections). In addition, the careful study of the data revealed that DTPA-induced excretion of plutonium via fecal pathway significantly contributed to the overall decorporation. The intracellular chelation of plutonium may be responsible for this enhanced excretion of activity in feces as well as for the delayed and sustained increased clearance of activity in urine. The authors would suggest that the occupational physicians offer to individuals who internalized moderately soluble or soluble plutonium compounds undergo a long-term DTPA treatment, especially when it is not initiated promptly after intake. Under this scenario, measurements of plutonium in successive urine and fecal collections after treatment should be required to get a better estimate of the therapeutic benefit. Also, intracellular chelation and fecal route should be taken into account for better interpretation of radiotoxicological data and modeling of plutonium kinetics under delayed DTPA treatment. *Health Phys.* 121(5):494–505; 2021

**Key words:** chelation; DTPA; exposure, occupational; plutonium

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The authors declare no conflicts of interest.

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### INTRODUCTION

THE DECORPORATION of accidentally-internalized transuranics such as plutonium is the requisite treatment to reduce the cumulative radiation dose, thus lowering the associated risk. Thus, plutonium-contaminated individuals are commonly treated with the chelator diethylenetriaminepentaacetate (DTPA) to minimize plutonium retention in tissues and promote its elimination from the body (Bhattacharyya et al. 1992; Ménétrier et al. 2005; NCRP 2010). This case report presents a follow-up study of a plutonium exposure in a worker who underwent multiple intravenous infusions of DTPA. The various aspects of interest of this particular case are: (1) treatment was initiated probably several months after the assumed date of plutonium intake, (2) decorporation therapy was prolonged for almost 2 y, (3) radiotoxicological analyses were performed throughout the course of treatment resulting in a large and complete data set, (4) DTPA-induced alteration of plutonium elimination was assessed by measuring the activity recovered not only in urine samples but also in many stool specimens, and (5) on several occasions, fecal and urinary clearance of plutonium was measured for several days after DTPA treatment. The objective of the present communication is to provide, discuss, and propose biological interpretations of the radiotoxicological data collected in a worker who underwent a protracted DTPA treatment started late following a soluble plutonium intake. A careful study has been made about fecal excretion of plutonium under DTPA therapy, which is to date very poorly documented in the literature.

### MATERIALS AND METHODS

#### Description of the case

An unsuspected radiocontamination with plutonium was detected in the feces of a worker in the context of routine annual medical follow-up as part of his employment. Following this discovery, a 24-h urine specimen was found to contain a few mBq of <sup>238</sup>Pu (99.6% of the total alpha activity). A direct external chest monitoring by gamma spectrometry did not reveal any measurable activity in the lungs. The exact scenario

of the internal contamination and the time of incorporation are not known. Based on the interview with the worker, his occupational activities, the isotopic composition, and alpha activity measurements, the preferred scenario was a low-level inhalation of a soluble compound of plutonium that occurred several months before detection of the contamination. It should be noted that the worker usually handles plutonium in fume hoods in rooms with equipment for airborne particulate radioactivity monitoring, which did not detect any air contamination. However, a liquid aerosol with low plutonium level generated too close to the edge of the hood that would have given off from the hood when handling might be the source of plutonium exposure through airways. The hypothesis of a wound was ruled out as the worker does not use sharp or pointed tools/objects. According to the worksite's exposure records, the individual had no other confirmed intake during his employment.

Decorporation therapy was then initiated late after the presumed incident date. In view of the effectiveness of first DTPA administrations in promoting plutonium excretion, the worker agreed to pursue the treatment. Thus, the worker underwent a long-term chelation treatment consisting of 40 intravenous infusions of DTPA. Overall, the subject received 26.5 g DTPA divided into  $29 \times 0.5\text{-g}$  doses and  $11 \times 1.0\text{-g}$  doses, over a period of nearly 2 y. The time elapsing between two consecutive DTPA treatments was often 1 or 2 wk and sometimes 3 or even 4 wk. During the 707-d therapy schedule, two breaks from medication were made. DTPA treatments were suspended from d 137 (just after the 12th DTPA administration; 72-d period) to d 208 and from d 523 (just after the 33rd DTPA administration; 51-d period) to d 573 following the start of therapy.

DTPA was given only as the calcium salt complex ( $\text{Na}_3\text{Ca-DTPA}$ ) purchased from the French Army Central Pharmacy (Pharmacie Centrale des Armées, Orléans, France). No adverse clinical health effects were reported by the subject, and no depletion of divalent cations was identified in blood samples collected on three occasions during the DTPA treatment schedule.

### Radiotoxicological data

The worker accepted that radiotoxicological data will be published on the sole condition that a maximum anonymization is ensured. In response to the request, authors decided not to disclose any detailed identifiable information in the paper such as demographic and workplace information. As to the issue of data anonymization, all the data were multiplied by the same factor that will still be known by authors but not by readers. The authors would like to stress the fact that the "transformation" of the data did not change at all the analyses and conclusions presented in the paper.

Numerous measurements of  $^{238}\text{Pu}$  activity in excreta specimens were performed throughout the course of the decorporation therapy schedule. The subject provided more than 300 urine

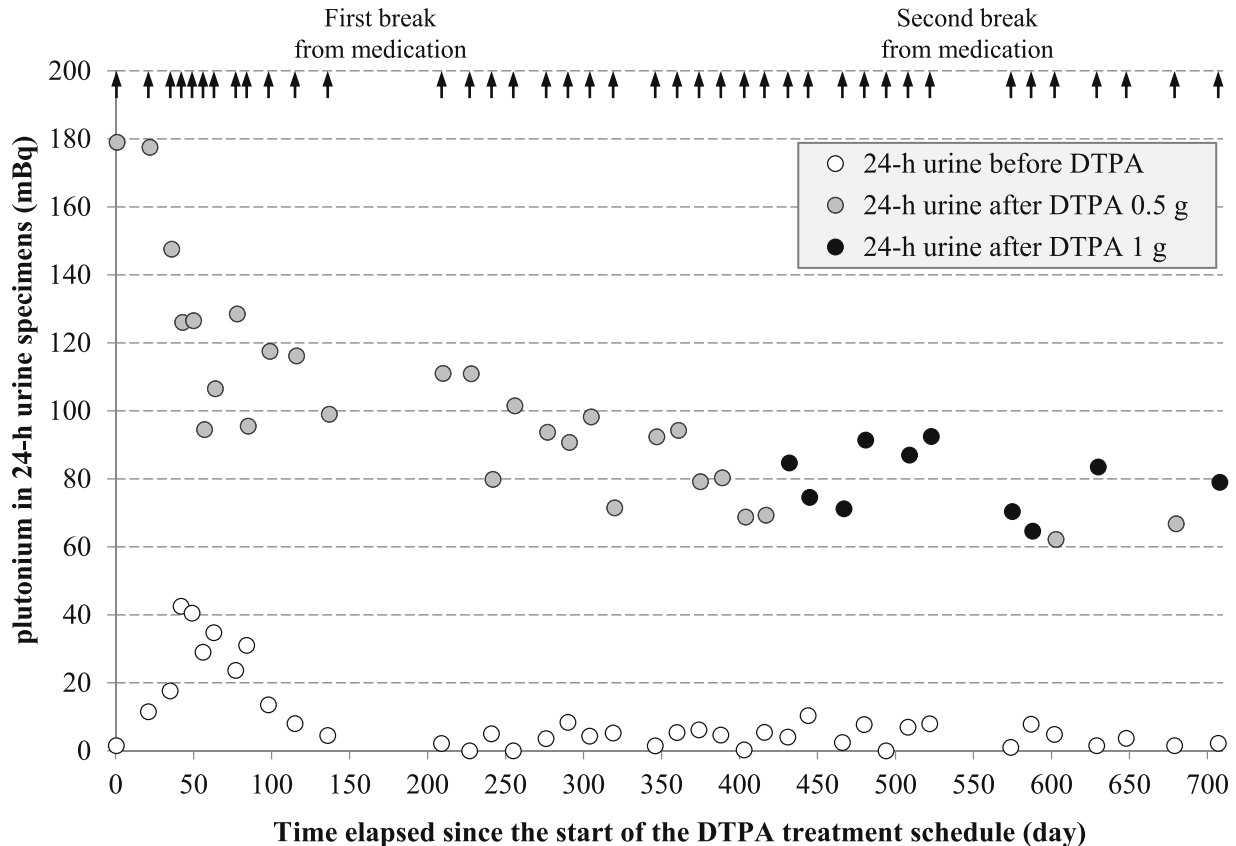
samples and more than 110 fecal samples based on 24-h collections. One urine specimen was almost always collected during the 24-h period prior to and after DTPA treatment. For 13 treatments, two 24-h urine samples were collected for 2 d consecutively after treatment. For 19 treatments, three 24-h urine samples were collected for 3 d consecutively after treatment. As for feces, one specimen was collected during the 24-h period prior to DTPA treatment, and one or several 24-h fecal specimens were collected after DTPA treatment for 35 treatments. In addition, three consecutive 24-h fecal samples after treatment were measured for 13 of these treatments. Some fecal specimens were collected sporadically. Radiotoxicological analyses of both urine and fecal samples were performed by an accredited medical analysis laboratory using standard radiochemical separations followed by alpha spectrometry (detection limit = 1 mBq per sample).

## RESULTS AND DISCUSSION

### A long-term delayed DTPA therapy after plutonium internalization is efficient

As shown in Fig. 1, where daily urinary  $^{238}\text{Pu}$  excretion during the delayed protracted therapy is plotted, each intravenous infusion of DTPA significantly enhanced the amount of plutonium in the 24-h urine collected after treatment in comparison with that collected prior to treatment. Thus, the long-term treatment regimen undergone by the present human case decorporated plutonium material even though it started late after plutonium internalization. Several previous studies of human cases have already reported an effectiveness of late DTPA therapies begun (or started again) several months or years after exposure to plutonium or americium [americium inhalation case (Roedler et al. 1989); USTUR plutonium inhalation case 0269 (James et al. 2007; Konzen et al. 2016; Dumit et al. 2019a); USTUR americium inhalation case 0846 (Breustedt et al. 2019); and USTUR plutonium inhalation/wound case 0785 (Dumit et al. 2019b)]. In the present case, the late chelation treatments with 1-g DTPA did not appear more efficient than those with 0.5-g DTPA (Fig. 1 and Table 1), probably because the order of magnitude of the ratio of DTPA to plutonium available for chelation did not change significantly.

The efficacy of a given DTPA administration is usually estimated by calculating the enhancement factor in urinary activity elimination, which is the ratio of the activity excreted in urine during the day following treatment to the activity that should have been excreted during the same day if the treatment had not been given. As this activity unaffected by DTPA cannot be available, it is then assumed to be identical to that cleared during the day prior to the therapy start, which can be considered as the baseline activity excretion rate. Thus, the enhancement factor induced by the first DTPA infusion received by the present case is 122, which is within the range of values already published (Dumit et al. 2020a).



**Fig. 1.** Plot of  $^{238}\text{Pu}$  excretion in urine during the 24 h before (white circles) or after DTPA administration of 0.5 g (light grey circles) or 1 g of DTPA (black circles) vs. time after the start of the long-term chelating treatment regimen. Little arrows at the top of the graph represent DTPA intravenous infusions. Only the white circle before the first DTPA treatment is non-affected by DTPA and can be considered as the baseline rate of plutonium urinary excretion. Those after the breaks from medication could be assumed as no longer affected by the previous DTPA treatment and hence also considered as the baseline rate.

### What are the various sources of decorporated plutonium?

The  $^{238}\text{Pu}$  inhaled by the individual is presumed to be somewhat soluble according to his typical professional activities. Accordingly, a significant part of the activity initially deposited within lungs would be expected to be already absorbed and retained in the two main organs of secondary deposition for plutonium, namely the liver and bone, when chelating therapy was initiated several months after contamination. Thus in the present case, the liver and parts of the skeleton may be potential sources of plutonium available for chelation and, therefore, of the plutonium eliminated from the body after DTPA injections (Fig. 1 and Table 1). Even though plutonium deposits established in bone tissue are usually considered to be retained tenaciously (Chipperfield and Taylor 1970, 1972) and hence not easily removable by DTPA (Guilmette et al. 2003) in humans, James et al. observed an ability of multiple DTPA treatments to reduce skeletal plutonium level, predominantly from trabecular bone surfaces (James et al. 2007). With regard to the liver, a chelation of hepatic transuranic deposits in animals (Bhattacharyya et al. 1978; Grémy et al. 2016) and humans (Roedler et al. 1989; James et al. 2007) has

been reported by several authors. More recently, Dumit et al. (2019c and 2020b) considered also that plutonium chelation can take place in systemic soft tissues including the liver and parts of skeleton.

Animal studies have demonstrated that intravenously-administered DTPA was able to attain lung compartments and to reduce the pulmonary burden of plutonium when given repeatedly, even when treatment was delayed (Grémy et al. 2017). Provided that DTPA succeeds in reaching pulmonary compartments in man, some plutonium trapped in the lungs might contribute to the activity eliminated through urine in this DTPA-treated worker. However, this contribution would probably be small, as the amount of plutonium still present in the lungs several months after inhalation of plutonium as soluble form is expected to be very low.

### The DTPA-induced increase of plutonium elimination slowly diminishes as the number of treatments increases

The efficacy of DTPA appeared to be maintained throughout the therapy period of 40 intravenous infusions, as each additional administration of DTPA increased excretion of plutonium (Table 1 and Fig. 1). Nevertheless, the

**Table 1.** Data of urinary  $^{238}\text{Pu}$  excretion after DTPA administration.

DTPA treatment			$^{238}\text{Pu}$ in 24-h urine samples after DTPA <sup>a</sup> (mBq)			DTPA treatment			$^{238}\text{Pu}$ in 24-h urine samples after DTPA <sup>a</sup> (mBq)		
Number <sup>b</sup>	Dose (g)	Time <sup>c</sup> (d)	U1 <sup>d</sup>	U2 <sup>d</sup>	U3 <sup>d</sup>	Number <sup>b</sup>	Dose (g)	Time <sup>c</sup> (day)	U1 <sup>d</sup>	U2 <sup>d</sup>	U3 <sup>d</sup>
1	0.5	0	179	<i>nc</i>	<i>nc</i>	21	0.5	346	92	40	<i>nc</i>
2	0.5	21	178	109	109	22	0.5	360	94	38	<i>nc</i>
3	0.5	35	148	88	78	23	0.5	374	79	45	<i>nc</i>
4	0.5	42	126	76	28	24	0.5	388	80	30	<i>nc</i>
5	0.5	49	127	84	55	25	0.5	403	69	42	<i>nc</i>
6	0.5	56	95	67	45	26	0.5	416	69	32	<i>nc</i>
7	0.5	63	107	76	47	27	1	431	85	45	30
8	0.5	77	129	48	55	28	1	444	75	38	39
9	0.5	84	96	58	60	29	1	466	71	33	36
10	0.5	98	118	59	60	30	1	480	91	40	37
11	0.5	115	116	44	45	31	1	494	<i>nc</i>	26	<i>nc</i>
12	0.5	136	99	56	42	32	1	508	87	26	<i>nc</i>
13	0.5	209	111	69	61	33	1	522	92	29	34
14	0.5	227	111	46	<i>nc</i>	34	1	574	70	38	<i>nc</i>
15	0.5	241	80	<i>nc</i> <sup>e</sup>	<i>nc</i>	35	1	587	65	26	31
16	0.5	255	102	<i>nc</i>	<i>nc</i>	36	0.5	602	62	14	<i>nc</i>
17	0.5	276	94	<i>nc</i>	<i>nc</i>	37	1	629	84	33	<i>nc</i>
18	0.5	290	91	<i>nc</i>	<i>nc</i>	38	0.5	648	<i>nc</i>	<i>nc</i>	<i>nc</i>
19	0.5	304	98	<i>nc</i>	<i>nc</i>	39	0.5	679	67	28	23
20	0.5	319	71	<i>nc</i>	<i>nc</i>	40	1	707	79	31	<i>nc</i>

<sup>a</sup>Alpha activities from  $^{238}\text{Pu}$  are given in mBq, values being rounded to the closest unit.

<sup>b</sup>The number corresponds to the nth treatment.

<sup>c</sup>The time is the time elapsed since the therapy start.

<sup>d</sup>U1, U2, and U3 correspond to the 24-h urine sample collected over the first, the second, and the third day following DTPA administration, respectively.

<sup>e</sup>*nc*: sample not collected. Note: Dotted lines indicate breaks from medication.

activity level cleared in urine following DTPA administration diminished with therapy progression. This has already been observed in previously reported cases that received a prolonged chelation treatment regimen, regardless of when therapy was started and the radiocompound concerned [americium oxide, early treatment (Fasiska et al. 1971); plutonium nitrate, early treatment (Jolly et al. 1972); americium oxide, early treatment (Breustedt et al. 2019); plutonium nitrate, delayed treatment (Jech et al. 1972); americium nitrate, delayed treatment (Roedler et al. 1989); plutonium nitrate, delayed treatment (James et al. 2007; Konzen et al. 2016; Dumit et al. 2019a); insoluble plutonium, delayed treatment (Dumit et al. 2019b)].

It is noteworthy that the decline in excreted plutonium between the first and the fourth treatment spread out over about 50 d was of the same order of magnitude as that observed between the fourth and the 40th treatment that was given > 600 d later. In other words, this loss of efficacy was rapid during the first DTPA administrations, whereas it became very slow during the following ones. This difference cannot be related to the level of plutonium present in blood and interstitial fluid compartments because the base

level of circulating plutonium is expected to be constant and minimal at late times following plutonium intake. Besides, the activity eliminated at the resumption of DTPA treatments after either of the two breaks from medication was again markedly enhanced but was no higher than that eliminated by the DTPA treatment preceding the corresponding breaks. Accordingly, and assuming that DTPA removed plutonium predominantly from solid tissues (i.e., not blood) of long-term plutonium retention, the first treatments might have mobilized the fraction of plutonium most available for chelation in some retention compartments that have not been refilled or refilled only extremely slowly by new deposits afterward. Consequently, the plutonium pool in lungs most likely to be transferable might have been decorporated as a result of the first DTPA administrations of the therapy schedule. Afterward, the residual plutonium still retained in lung compartments might have been very low and poorly soluble and transferable, thus explaining that other compartments may not have been refilled. Thus, the later treatments could promote a mobilization of plutonium mainly among established, more firmly bound deposits in the liver and bones and therefore much more difficult to remove.

### Each DTPA administration induces a delayed and sustained increased elimination of plutonium

The daily urinary excretion of plutonium between two successive DTPA intravenous infusions did not return to the baseline level measured before therapy began, except during the two breaks from medication (52- and 73-d periods) and when the time elapsed between treatments was at least 3 wk (Fig. 1). This observation indicates that DTPA-induced enhancement of urinary excretion in plutonium persisted for at least several weeks. This slow fading of the DTPA effect on activity excretion was already reported in the first case of plutonium contamination treated with DTPA (Norwood 1960). It has been seen in other cases. For example, Alderhout (1972) described a plutonium inhalation case who received two delayed DTPA intravenous injections separated by a long time interval. Both treatments significantly increased plutonium urinary excretion, which remained elevated above the levels prior to treatment for around 40 d. In addition, other authors have reported an enhancement effect for periods up to 100 d following chelator administration (Jech et al. 1972; Jolly et al. 1972; Schofield et al. 1974; Hall et al. 1978). A small fraction of injected DTPA and/or that of transuranic-DTPA chelates that persist in the body must be responsible for this sustained elimination of activity.

### The analysis of only the first 24-h urine after DTPA treatment underestimates the total plutonium eliminated through urinary route

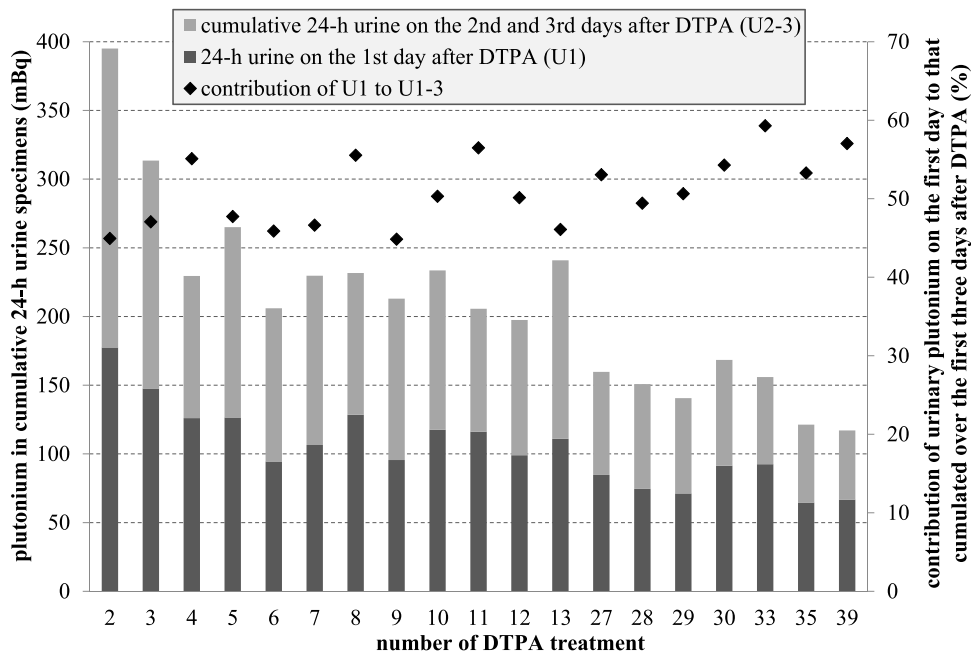
In the present case study, 24-h urine samples were provided during the two or three successive days after DTPA

infusion for many treatments (Table 1). The stacked bar chart in Fig. 2 represents the cumulative urinary plutonium recovered on the second and third day (U2-3) as well as the plutonium measured in the first 24-h urine after DTPA administration (U1) for 19 treatments for which data were available. This highlights the contribution of the first collection time (U1) to the 3-d cumulative urinary excretion of activity (U1-3). Calculation of the average U1-to-(U1-3) ratio was  $49.8 \pm 4.6\%$  for 0.5-g DTPA treatments and  $53.3 \pm 3.4\%$  for 1-g DTPA treatments (Fig. 2), revealing that the combined urinary plutonium of second and third day post-DTPA was approximately as high as that cleared within the first 24 h.

Based on these data and the hypothesis that the DTPA-increased urinary plutonium elimination follows a downward curve described by a sum of two exponentials, the common idea that this enhancement may last for several days but that most of this plutonium decorporation occurs during the first day is not a general rule for all DTPA-treated cases. In the present case, it is clear that an assessment of DTPA-enhanced plutonium excretion based solely on the first 24-h urine collection would be misleading and could entail a large underestimation of treatment effectiveness and consequently of the potential averted dose.

### The slow fading of the increase of plutonium urinary elimination is in accordance with a contribution of intracellular chelation to the overall decorporation

DTPA is a negatively charged hydrophilic molecule that is very rapidly eliminated from the body. These properties



**Fig. 2.** Stacked bar chart of cumulative  $^{238}\text{Pu}$  in 24-h urine specimens of d 2 and 3 (U2-3; light grey bars) and  $^{238}\text{Pu}$  in 24-h urine specimen of d 1 (U1; dark grey bars) following DTPA administration, for 19 treatments for which data were available. The contribution of plutonium excreted during the first day (U1) to the cumulative plutonium excreted over the 3 d (U1-3) following DTPA treatment is also plotted. The number in the x-axis corresponds to the nth treatment.

favor a distribution in plasma and extracellular fluids rather than intracellular accumulation. This is why the possibility of an intracellular chelation of transuranics is commonly rejected or considered to be negligible. It should be noted, however, that the idea is beginning to be accepted. Indeed, the fitting of radiotoxicological data from humans exposed to plutonium and treated with DTPA has been improved by a new chelation model that assumes both extracellular and intracellular chelation (Dumit et al. 2020b). Of course, in respect to DTPA properties, the fraction of administered DTPA accessing intracellular compartments is expected to be very low.

Stather et al. (1983) pointed out a measurable accumulation of  $^{14}\text{C}$ -labeled DTPA in soft tissues of rat and dog for the first 2 d following intravenous injection, suggesting that 2-3% of injected DTPA could penetrate cells and then be retained. In particular in the rat, the ratio of DTPA in liver to that in plasma is  $>1$  as soon as 2 h after injection, reaches a maximum of 4 at 4 h, and is still  $>3$  at 48 h (Stevens et al. 1978). These data showed a slight accumulation of DTPA in the liver, which is more easily explained by cell penetration and then retention of chelator molecules rather than a persistence within extracellular fluids and/or binding to cell membranes. Thus, even though the fraction of DTPA entering hepatic cells is expected to be very small, it is probably sufficient to mobilize intracellular transuranics, as chelation in a given biological compartment depends mainly on the DTPA-to-transuranic molar ratio attained in this compartment, as discussed in greater detail elsewhere (Grémy et al. 2016).

In addition, new evidence exists for the existence of hepatic intracellular chelation of plutonium and americium in the rat (Grémy et al. 2016), and there is no biological reason why this should be different in other mammals including humans. Transuranic-DTPA chelates that are formed in intracellular compartments are expected to be slowly released from cells into the bloodstream prior to elimination from the body, which was also taken into consideration by Dumit et al. (2020b) for chelation model improvement. Furthermore, a prolonged residence of DTPA molecules in cell compartments will increase the likelihood of chelation of transuranics already present in cells as well as those arriving later (defined as delayed intracellular chelation; Grémy et al. 2016), which may contribute to the prolonged intracellular chelation of DTPA treatment. In addition, a slow translocation of free DTPA from cells to the bloodstream cannot be excluded, which may enable a delayed and prolonged mobilization of transuranics in certain extracellular compartments. These possible mechanisms of action for DTPA (i.e., a persistent action of DTPA and the slow release of chelates from cells following intracellular chelation), are in accordance with the slow decline of urinary plutonium excretion observed after treatment in the

present case and in others (Alderhout 1972; Jech et al. 1972; Jolly et al. 1972).

The sustained effect of DTPA has been much more pronounced than that of ethylenediaminetetraacetate (EDTA) (Norwood 1960). By using labeled chelating agents, Foreman (1959) demonstrated that a small fraction of administered DTPA was retained for long periods and that this fraction was substantially greater than the fraction of EDTA (Foreman 1959). This reinforces the assumption that the persistence of increased urinary activity for some days after treatment may be due mainly to intracellular chelation. Indeed, in addition to the stronger affinity of DTPA for plutonium than EDTA, a greater cell penetration may result in a higher intracellular chelation and hence a longer sustained activity elimination.

We assume that the enhanced excretion of transuranics following DTPA administration results from both chelation of extracellular (in circulation as complexes with plasma ligands or loosely bound to tissue surfaces) and intracellular (bound to intracellular ligands) transuranics. Nonetheless, the respective contribution of extracellular and intracellular chelation to the decorporation may depend on the treatment regimen. When DTPA therapy is initiated promptly after contamination, plutonium is still predominantly within the extracellular space, and so intracellular chelation is expected to be very low as compared to extracellular chelation. Since in most cases of transuranic-exposed individuals only a single or a few DTPA treatments are administered as soon as possible after the contamination event, it is therefore quite understandable that only the urinary excretion on the day after treatment is said to be influenced significantly (Grappin et al. 2007). Such treatment regimens will involve mainly a chelation of extracellular transuranics resulting in the formation of transuranic-DTPA chelates that are rapidly eliminated through glomerular filtration (Fritsch et al. 2009). When the initial treatment is started a long time after contamination, the decorporation efficacy is undoubtedly lower. But at the same time, the contribution of intracellular chelation may increase with time since transuranics present in the extracellular space and available for chelation during the short residence time of DTPA in fluids becomes very small, and those deposited and then stored inside cells become larger. Thus, the success of a delayed protracted chelation therapy may result, at least in part, from the contribution of successive minimal intracellular chelation of cell-internalized plutonium over time (Grémy et al. 2016).

All cells retaining plutonium at the time of DTPA injection would be potentially sources of DTPA-induced excreted activity from the body. This cellular contribution is expected to vary broadly depending first on the ability of DTPA molecules to penetrate in sufficient quantities the cells involved and second on the quantity and the availability for chelation of plutonium present in these cells. An example of cell type

is alveolar macrophages, which have an important role in pulmonary plutonium retention uptake and retention (Van der Meeren et al. 2012). Injected DTPA may have limited access to this compartment, thus probably limiting its action (Grémy et al. 2017). Phagocytic cells of bone tissue such as bone marrow macrophages and osteoblasts also sequester plutonium (Priest 1981). The two main cell types of the liver (i.e. hepatocytes and the phagocytic cells named Kupffer cells) are responsible for hepatic plutonium retention, but the former sequester more plutonium than the latter (Grube et al. 1978; Fouillit et al. 2004). Thus decorporated plutonium may result from the sum of the intracellular chelation taking place in these cells as well as in other cells such as those of testes, spleen, and striated skeletal muscle as previously suggested (Grémy and Miccoli 2019; unpublished data). With the exception of hepatocytes, as discussed later, plutonium-DTPA chelates formed in cells are likely to be slowly translocated to the bloodstream prior to urinary excretion, thereby contributing to the sustained urinary elimination of plutonium observed after DTPA treatment.

### A DTPA-induced increase of plutonium elimination through fecal route is identified

The monitoring of chelation therapy effectiveness is generally based on measurements of alpha activity recovered in urine samples, since glomerular filtration is the major pathway of clearance for stable plutonium/amercurium-DTPA chelates. Excretion of activity in feces during chelation treatment is very poorly documented in the literature, as stools of DTPA-treated individuals have been infrequently collected. This is probably due to difficult individual cooperation for fecal sampling and also because the fecal route is commonly regarded as negligible in relation to the urinary route for DTPA-induced activity elimination, which is indeed often the case.

In the present case of plutonium contamination, more than 100 feces samples have been measured during the treatment schedule with collections before and after DTPA administration. The results of  $^{238}\text{Pu}$ -in-feces measurements are listed in Table 2. For around 50% of the treatments, at least one 24-h stool specimen among those collected after DTPA infusion (F1, F2 or F3) had a plutonium amount higher than that measured prior to treatment (F0) (Table 2).

**Table 2.** Data of fecal  $^{238}\text{Pu}$  excretion after DTPA administration.

DTPA treatment			$^{238}\text{Pu}$ in 24-h feces samples <sup>a</sup> (mBq)				DTPA treatment			$^{238}\text{Pu}$ in 24-h feces samples <sup>a</sup> (mBq)			
			Before	After DTPA						Before	After DTPA		
Number <sup>b</sup>	Dose (g)	Time <sup>c</sup> (day)	F0 <sup>d</sup>	F1 <sup>e</sup>	F2 <sup>e</sup>	F3 <sup>e</sup>	Number <sup>b</sup>	Dose (g)	Time <sup>c</sup> (day)	F0 <sup>d</sup>	F1 <sup>e</sup>	F2 <sup>e</sup>	F3 <sup>e</sup>
1	0.5	0	4.3	3.3	25	99	21	0.5	346	<i>nc</i>	<i>nc</i>	<i>nc</i>	<i>nc</i>
2	0.5	21	5.8	16	14	40	22	0.5	360	9.4	4.1	10	<i>nc</i>
3	0.5	35	10	19	37	139 <sup>f</sup>	23	0.5	374	6.2	8.1	<i>nc</i>	<i>nc</i>
4	0.5	42	118	30	69	40	24	0.5	388	12	13	12	<i>nc</i>
5	0.5	49	42	44	110	36	25	0.5	403	33	3.9	12	<i>nc</i>
6	0.5	56	16	39	125	<i>nc</i>	26	0.5	416	11	9.2	13	<i>nc</i>
7	0.5	63	22	53	70	31	27	1	431	3.4	4.8	11	52
8	0.5	77	15	36	30	52	28	1	444	25	14	10	<i>nc</i>
9	0.5	84	<i>nc</i> <sup>g</sup>	34	48	<i>nc</i>	29	1	466	3.9	3.2	52 <sup>f</sup>	54
10	0.5	98	8.3	19	24	65	30	1	480	5.0	13	24	<i>nc</i>
11	0.5	115	10	6.9	12	44	31	1	494	12	22	27	<i>nc</i>
12	0.5	136	10	14	77	96 <sup>f</sup>	32	1	508	11	<i>nc</i>	26	24
13	0.5	209	0.8	27	<i>nc</i>	<i>nc</i>	33	1	522	10	42	48	<i>nc</i>
14	0.5	227	<i>nc</i>	2.4	7.4	<i>nc</i>	34	1	574	<i>nc</i>	1.1	16	<i>nc</i>
15	0.5	241	25	<i>nc</i>	<i>nc</i>	<i>nc</i>	35	1	587	10	15	11	<i>nc</i>
16	0.5	255	16	21	<i>nc</i>	<i>nc</i>	36	0.5	602	7.1	22	15	<i>nc</i>
17	0.5	276	4.2	24	<i>nc</i>	<i>nc</i>	37	1	629	1.7	4.0	31	<i>nc</i>
18	0.5	290	17	9.0	<i>nc</i>	<i>nc</i>	38	0.5	648	4.5	5.9	<i>nc</i>	<i>nc</i>
19	0.5	304	27	10	<i>nc</i>	<i>nc</i>	39	0.5	679	1.0	6.6	8.0	<i>nc</i>
20	0.5	319	9.3	3.9	<i>nc</i>	<i>nc</i>	40	1	707	1.2	6.5	<i>nc</i>	<i>nc</i>

<sup>a</sup>Alpha activities from  $^{238}\text{Pu}$  are given in mBq, values being rounded to the closest unit as soon as they exceeded 10.

<sup>b</sup>The number corresponds to the nth treatment.

<sup>c</sup>The time is the time elapsed since the therapy started.

<sup>d</sup>F0 corresponds to the 24-h feces sample collected the day before DTPA administration.

<sup>e</sup>F1, F2, and F3 correspond to the first, the second, and the third 24-h feces sample collected after DTPA administration, respectively.

<sup>f</sup>It is possible that this stool specimen is the fourth and not the third produced after the treatment, according to the patient.

<sup>g</sup>*nc*: sample not collected. Note: Dotted lines indicate breaks from medication.

This shows that DTPA is able to increase plutonium excretion not only in urine but also in feces. Such an enhanced fecal elimination of activity in DTPA-treated contamination cases has been reported previously (Norwood 1960; Roedler et al. 1989; Piechowski et al. 2003; James et al. 2007). For example, a USTUR registrant who inhaled a liquid aerosol of plutonium nitrate received a DTPA treatment regimen that was started 2 y after the end of a previous intermittent chelation therapy with EDTA for 6 to 7 mo. These later DTPA administrations significantly increased fecal excretion of activity (USTUR plutonium case 0269; James et al. 2007). Roedler et al. (1989) also observed an increased activity clearance via fecal route under a DTPA therapy started several months after americium nitrate exposure. The effect of DTPA administrations on plutonium fecal excretion has already been the subject of scientific discussions in the literature as evidenced by the exchange of letters to the editor between Grémy and Dumit (Grémy and Miccoli 2019; Dumit et al. 2019d). Besides, the most recent model of plutonium chelation by DTPA that was developed by Dumit et al. (2020b) includes the possibility of fecal excretion for Pu-DTPA chelates.

In the present case, the treatments for which  $^{238}\text{Pu}$  amounts have been assessed in three consecutive 24-h feces samples obtained after DTPA administrations are shown in Table 2. The patterns of DTPA-induced activity fecal excretion are shown in Fig. 3a for five treatments as illustrative examples. It can be noted that these patterns are uneven and highly variable from one treatment to another (Fig. 3a), contrary to data for plutonium urinary excretion (Fig. 3b). Indeed, increased plutonium fecal clearance was not consistently

observed in the first 24-h fecal specimen, and the peak appears either in the second or the third fecal specimen (Table 2 and Fig. 3a). The DTPA-induced fecal excretion of activity is delayed and unpredictable because of its dependence on gastrointestinal transit and food, of course. This may be especially true in this individual, who has an irregular and slow intestinal transit according to the interview. These factors make identification and extent assessment of fecal activity excretion very difficult where only the first 24-h feces specimen after DTPA treatment is collected. Only multiple and successive collections of fecal specimens after treatment were the most informative. From Table 2, it is indeed noteworthy that no fecal excretion enhancement of plutonium was observed for some treatments where only one or two fecal samples were collected after DTPA, whereas there is no reason why it should not exist for those treatments, given they were also efficient according to urinary plutonium excretion data (Table 1). Also, the overall increase in fecal clearance of plutonium is difficult to highlight from only the plutonium-in-feces measurements recovered just before and just after DTPA injections (Table 2, J0 vs. J1).

Prior to the decision to start decorporation therapy, four 24-h feces specimens were collected over a period of weeks and then measured: 0.8, 1.0, 2.9 mBq (not listed in the Table 2), and 4.3 mBq (obtained just prior the first DTPA administration; Table 2). In addition, during the break from medication covering a 73-d period, four 24-h feces samples were collected on the 167th, 173rd, 180th, and 208th days (corresponding to the 31th, 37th, 44th, and 73th day following the 12th DTPA administration). These samples contained 0.7, 2.7, 2.0, and 0.8 mBq, respectively. The last value corresponds to the

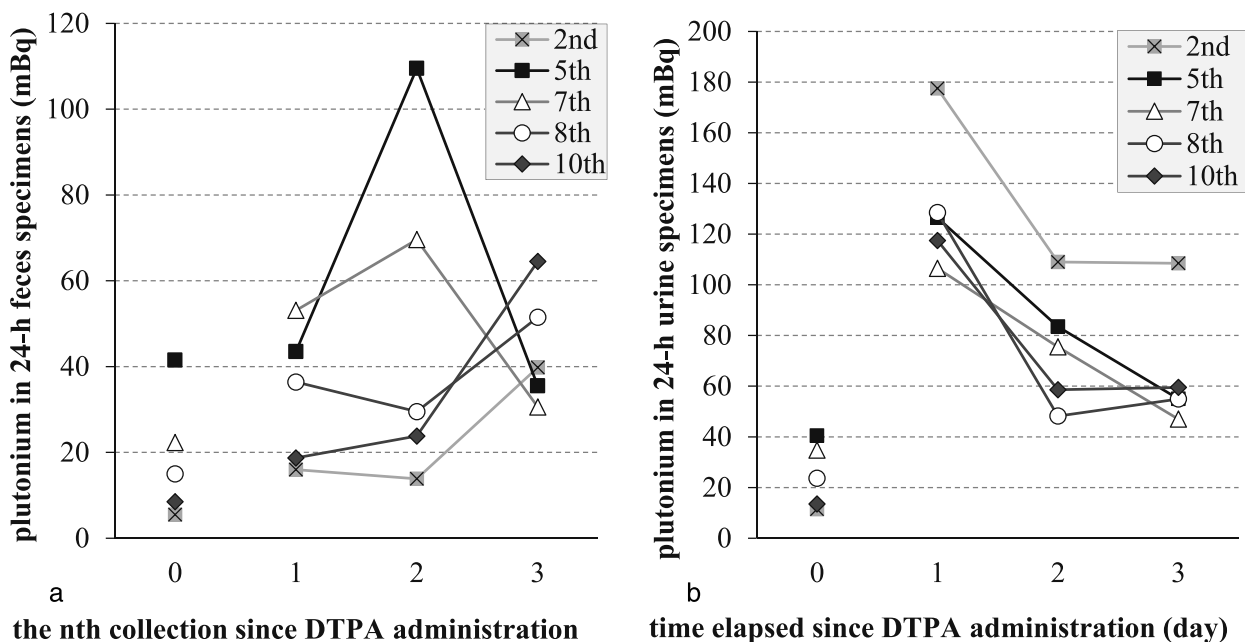


Fig. 3. Plot of  $^{238}\text{Pu}$  excretion in the 24-h feces (a) or urine collection (b) before DTPA (0) and the three consecutive ones after DTPA (1, 2, and 3) for 5 treatments chosen as illustration (the 2nd, 5th, 7th, 8th, and 10th treatment).



activity measured in feces obtained just prior to the resumption of the therapy. These values, not yet affected by DTPA or assumed to be no longer affected by the previous DTPA infusion, were of the same order of magnitude and so could be considered as the baseline level for daily fecal plutonium excretion. During the periods of repeated treatments, plutonium amounts very rarely returned to values lower or equal to the highest value (4.3 mBq). Except after the 72-d period of break from medication, values of about 2-3 mBq were observed only just before treatments 37, 39 and 40 (Table 2) where the time elapsed from the previous treatment was approximately 1 mo. This observation therefore indicates that a DTPA administration can influence the fecal excretion of internalized transuranics for several weeks.

### The DTPA-induced increase of plutonium elimination through fecal route is not negligible

For eight out of the 40 treatments,  $^{238}\text{Pu}$  activities were measured in both three consecutive 24-h urine and feces samples collected after DTPA administration (Table 3). The 3-d cumulative fecal contribution represented from 15% to 42% of the 3-d cumulative total DTPA-induced excretion of plutonium (total means urine plus feces) (Table 3). The three treatments (4th, 5th, and 7th) with the highest fecal contributions (38, 40, and 42%, respectively) were also those with the peak of plutonium excretion occurring in the second stool specimen after treatment (Fig. 3a and Table 3). For other treatments, the peak of activity appeared only in the third feces specimen and was lower. This could suggest that the significant part of the plutonium fecal excretion for these treatments may be not only more delayed but also spread over

a longer period, thus lowering the estimation of fecal contribution by considering only the third feces specimens. In addition, this expected variation in distribution of the main fraction of fecal activity over more than 3 d probably explains the variation in fecal contribution rate observed between these treatments, as well as why there is no direct relationship between the 3-d cumulative activity in feces and that in urine (Table 3). Norwood (1960) had already pointed out that “large numbers of tests will be needed since fecal elimination varies greatly from day to day” (Norwood 1960).

These results show primarily that increased fecal activity by a DTPA treatment regimen in man can, in certain circumstances (such as the form of internalized plutonium and the DTPA treatment initiation), significantly contribute to the overall decorporation.

### The DTPA-induced increase of plutonium elimination through fecal route results from a chelation of hepatocyte-internalized plutonium

The only way to recover increased plutonium level in stools resulting from DTPA action is its clearance via the biliary route as shown in the rat (Ballou and Hess 1972; Bhattacharyya et al. 1978; Bhattacharyya and Peterson 1979) and the pig (Smith et al. 1961). In other words, transuranic-DTPA chelates localized inside hepatocytes translocate into the intestinal lumen when mixed with the bile produced and secreted by this hepatic cell type. As a consequence, the variations noticed between profiles of DTPA-induced plutonium fecal excretion can result from several physiological parameters, including the quantity of bile produced, then the rate of its release into the biliary ducts, the fraction of the bile stored in the gallbladder, and its residence time. Finally, there is the rate of intestinal transit, which can itself depend on parameters such as the amount and the nature of foods consumed.

Such quantities of plutonium eliminated in feces after DTPA treatment that are observed in the present case cannot be explained by the diversion of  $^{238}\text{Pu}$ -DTPA chelates from the extracellular space toward hepatocytes, as only some percentages are expected to be eliminated through the fecal pathway. Thus, the increased activity eliminated via the biliary route after DTPA injection results from a mobilization of plutonium localized inside hepatocytes, i.e., from an intracellular chelation followed by transuranic-DTPA chelate release. Intracellular chelation implies a penetration of DTPA molecules into these cells, and as already mentioned, biokinetic and biodistribution data from previous works showed a retention of DTPA in tissues of the rat and the dog, particularly in the liver (Stevens et al. 1978; Stather et al. 1983). In addition, Bhattacharyya and Peterson (1979) evidenced that 0.12% of the injected DTPA is eliminated into rat bile over 24 h, thus indicating a prior uptake of at least this amount by hepatocytes. If this is the case in man, around  $1 \times 10^{-6}$  mol could reach hepatocytes following an injection

**Table 3.** Data of cumulative  $^{238}\text{Pu}$  in three consecutive 24-h urine (U1-3) or fecal (F1-3) samples after DTPA administration.

DTPA treatment			$^{238}\text{Pu}$ in three excreta samples after DTPA <sup>a</sup> (mBq)		
Number <sup>b</sup>	Dose (g)	Time <sup>c</sup> (d)	U1-3 <sup>d</sup>	F1-3 <sup>e</sup>	Fecal part <sup>f</sup> (%)
2	0.5	21	395	70	15
4	0.5	42	230	139	38
5	0.5	49	265	189	42
7	0.5	63	229	153	40
8	0.5	77	232	117	34
10	0.5	98	236	107	31
11	0.5	115	206	62	23
27	1	431	160	68	30

<sup>a</sup>Alpha activities from  $^{238}\text{Pu}$  are given in mBq, values being rounded to the closest unit.

<sup>b</sup>The number corresponds to the nth treatment.

<sup>c</sup>The time is the time elapsed since the therapy start.

<sup>d</sup>U1-3 corresponds to the 3-d cumulative activity in urine.

<sup>e</sup>F1-3 corresponds to the 3-d cumulative activity in feces.

<sup>f</sup>Fecal part corresponds to the fecal contribution to the overall plutonium excretion (urine plus feces) over 3 days after DTPA treatments.

of 0.5 g Na<sub>3</sub>Ca-DTPA. This amount of DTPA may be several orders of magnitude greater than the plutonium expected to be present in this cell type at the time of treatment, which would favor a successful shift of plutonium from endogenous ligands to DTPA.

A further point is that an enhanced fecal excretion of activity also implies a significant presence of plutonium internalized within hepatocytes when DTPA administration occurs. It is therefore quite understandable that prompt treatment does not increase activity excretion via the biliary route because no or negligible transuranic amount is likely to be already deposited inside hepatocytes. When the initial treatment is followed by others, the enhancement in fecal activity will probably also be negligible as repeated DTPA administrations will prevent transuranic hepatic accumulation. This should be particularly true in respect to frequent DTPA injections and/or low soluble internalized compounds where the blood absorption rate of transuranic from the primary site of contamination, wound site, or lungs is very slow. Besides, in case of exposure through airways, the potential DTPA-induced enhancement in fecal transuranic will be masked as long as daily activity cleared by feces due to the mucociliary transport is not much lower than that eliminated by feces due to DTPA action in hepatocytes.

Finally, DTPA-induced enhancement in fecal activity has been observed rarely in man, either because feces have been collected sporadically or too soon after DTPA injection or because this increase has been non-existent or negligible for the reasons already mentioned: (1) occupational internal contaminations have involved slightly soluble forms of transuranics, i.e., oxide forms; and (2) DTPA therapy was started rapidly. Both these factors will limit transuranic deposition drastically in systemic target tissues, including the liver. In the present and other contamination cases [americium nitrate, delayed treatment (Roedler et al. 1989); plutonium nitrate, delayed DTPA treatment (James et al. 2007; Konzen et al. 2016; Dumit et al. 2019a)], individuals internalized moderately soluble forms of plutonium (nitrate) or americium (oxide), and the chelation treatment regimen was initiated belatedly. In these cases, because of the non-negligible fraction of the radiocompound quickly dissolved at the primary site of contamination and absorbed into the bloodstream, the amount of activity deposited in the liver, and hence in hepatocytes, should be sufficient enough to observe a treatment-induced increased fecal activity following DTPA treatment.

A last point is that the high contribution of fecal pathway to plutonium decorporation observed in the present case probably implies that extensive DTPA therapy has had a substantial effect on hepatic plutonium, and this organ was probably a large source of plutonium available for chelation and hence of decorporated plutonium.

## CONCLUSION

It is well known that DTPA chelation therapy is more effective if it is initiated as soon as possible after accidental transuranic intake. In accordance with previous studies of DTPA-treated human cases, the present report confirms that a long-term regimen can remove internalized plutonium even when it is started several months after the time of contamination. In addition, the effectiveness of DTPA has continued throughout the therapy schedule that lasted almost 2 y.

A careful analysis of the large collection of stool specimens highlighted an increased fecal excretion of plutonium. The follow-up of fecal plutonium over several days after some of the DTPA treatments demonstrated a great variability in excretory patterns of plutonium in the successive 24-h feces specimens from one DTPA administration to another. Furthermore, even if DTPA-induced fecal clearance of plutonium was lower than that via urine, it was nonetheless significant. Indeed, it accounted for up to 40% of the total excretion (urinary plus fecal excretion) of activity over three cumulative consecutive 24-h samples in the DTPA-treated present case.

Enhanced fecal excretion of plutonium showed the ability for DTPA to join hepatocytes, trap some plutonium stored within, and afterward decorporate plutonium as plutonium-DTPA chelates via the biliary route. More generally, DTPA can presumably even penetrate various type cells in small quantities but in sufficient amounts to attain a DTPA-to-plutonium molar ratio that favors cell-internalized plutonium removal. This intracellular chelation of activity in cell types other than hepatocytes probably contributes mainly to the sustained increased urinary excretion observed in the present case and others given the expected slow transfer of plutonium-DTPA chelates from cells to the bloodstream.

Thus, the present case in particular demonstrates the persistent elimination of plutonium via urine and the enhanced excretion of plutonium in feces after DTPA treatment. This conclusion is drawn from the fact that the therapy was initiated at a delayed time after an inhalation of a somewhat soluble form of plutonium, which suggests that a significant amount of plutonium had migrated from lungs to the systemic compartment and, therefore, significant deposits were already established in cells, including hepatocytes.

Especially in view of the very low incidence of side effects from DTPA, an extensive long-term chelation therapy regimen should be advised when internal contamination with transuranics involves a moderately to highly soluble compound. Such a strategy with multiple treatments given over a long time would be especially justified where the initiation of the treatment is unfortunately delayed in order to mobilize transuranics established in tissues, particularly in the

liver. Accordingly, a good estimation of a delayed long-term therapy efficacy should require measurements of transuranic levels excreted over several successive 24-h urine and fecal samples collected after treatment. However, for the well-being and the compliance of the individual, a series of collections should be performed periodically but not systematically so as to ensure a useful radiotoxicological follow-up.

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