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THE UPTAKE, DISTRIBUTION AND EXCRETION OF PROMETHIUM IN HUMANS AND THE EFFECT OF DTPA ON THESE PARAMETERS*

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Abstract—An experiment was performed to study the uptake, retention, distribution, and excretion of promethium in humans. Six volunteers were injected with 0.1 μCi of $^{143}PmCl_3$ and these parameters were studied for a period of one year after injection by whole body counting and excretion measurement techniques. About one-half of the injected ^{143}Pm became deposited in the liver within a few minutes and most of the ^{143}Pm remaining in the blood stream became deposited in the bone within the next 5 hr. This initial distribution between liver and bone appeared to remain unchanged for at least 1 yr. Only 10% of the injected dose was excreted within the first 20 days. The biological half life of the major portion of the dose cannot be accurately determined from this experiment but it is much greater than 1000 days. The initial uptake of ^{143}Pm after ingestion by two volunteers appeared to be not more than 0.001%. The effect of DTPA on the removal of ^{143}Pm after injection was studied in eight volunteers. The effectiveness of this chelating agent decreased rapidly with the length of time between injection of the ^{143}Pm and administration of the DTPA. The DTPA removed 90%, 25%, and 5% of the ^{143}Pm from the body when administered 30 min, 24 hr, and 60 days respectively after injection of the ^{143}Pm. Fecal excretion of the ^{143}Pm is enhanced by DTPA and the total amount excreted in the feces is quite constant and is independent of the time interval between ^{143}Pm and DTPA injection.

1. INTRODUCTION

LARGE scale separation of ^{147}Pm fission product waste and preparation of the material for several applications constitutes a potential source of radiation exposure to workers in this field. Since ^{147}Pm ($T_r = 0.73$ yr) is a low energy beta emitter, and the maximum energy of the beta particle is only 0.22 MeV, internal depositions of ^{147}Pm cannot be directly determined by whole body counting. Therefore, analysis of body excreta must be relied upon to provide a basis for body burden estimates. In order to develop an excretion model for diagnosis of promethium in humans, to form a basis for radiation exposure, and to determine the dose from accidental exposure, the uptake, retention, distribution, and excretion of promethium in humans must be known.

A number of animal studies have been performed at Battelle Northwest Laboratories and elsewhere on the metabolism of promethium in animals.[1–16] While these various reports give values for organ content of promethium at sacrifice and discuss histopathological findings of the dosed animals, very few excretion-retention data are presented from which models may be developed. In instances where excretion data has been obtained, its relationship to excretion of promethium by humans is not clear. An experiment using ^{143}Pm and human volunteer test subjects was performed to help resolve some of these problems and to determine the necessary metabolic parameters. Whole body counting techniques and urinary and fecal measurements were used to study the course of the promethium following both intravenous and oral administration of $^{143}PmCl_3$ to humans. The results provide a correlation between body burden and urinary excretion of promethium which should

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be useful in evaluating cases of accidental exposure to ^{147}Pm.

2. METHODS AND PROCEDURES

Promethium-143 decays by electron capture and subsequent gamma ray emission. The gamma ray energy is 0.74 MeV and is excellent for whole body counting purposes. The ^{143}Pm used in this experiment was prepared by Oak Ridge National Laboratory using high energy proton irradiation of enriched $^{144}Nd_2O_3$ (94.4%).[17] A small amount of ^{144}Pm was also formed. The ^{143}Pm was separated from the irradiated neodymium at Battelle-Northwest by an ion exchange method using Dowex 5-X4 fine mesh resin and eluting the ^{143}Pm essentially carrier free with 0.25 N α-hydroxybutyric acid at a pH of 4.6. The separated ^{143}Pm was sent to a radiopharmaceutical laboratory where it was sterilized, dissolved in isotonic saline solution, made acidic to a pH of 3, and pyrogen tested in rabbits.

Localization and distribution of the ^{143}Pm within the body was followed using a shadow shield whole body counter.[16] A 2-in. wide slit collimator over the 9-3/8 in. dia. NaI(Tl) detector permitted differential scanning of the subject as he traveled under the crystal. Whole body counts were made periodically to determine the total ^{143}Pm remaining in the body and these counts were continued for 1 yr after injection. Urine, feces and blood samples were collected and analyzed for ^{143}Pm for each volunteer for periods up to 85 days after injection of the ^{143}Pm.

The $^{143}PmCl_3$ was administered to a total of fourteen normal human volunteers by physicians of the Hanford Environmental Health Foundation. Six volunteers received approximately 0.1 μCi of ^{143}Pm intravenously and two volunteers received an oral dose of 10 μCi. Another six volunteers were injected with 0.1 μCi of ^{143}Pm and then injected with DTPA at various intervals to study the effect on ^{143}Pm retention. These dose levels were chosen as a balance between enough activity to measure the body burden for at least one year with a whole body counter and the smallest possible dose to the volunteer. The radiation dose using standard man parameters and promethium organ distribution in dogs[11] and pigs[12] was calculated and is shown in Tables 1 and 2. These tabulated doses show that the highest exposed organ, the large intestine, is about 0.5% of the maximum permissible annual limit for occupational exposure. Doses to other organs are even smaller in comparison to their respective limits and insignificant in terms of radiological safety.

Table 1. Total dose to standard man from i.v. injection of 0.1 μCi ^{143}Pm

Organ	Dose (rem)
Whole body	0.005
Bone	0.008
Liver	0.036

Table 2. Total dose to standard man from ingestion of 10 μCi ^{143}Pm

Organ	Dose (rem)
Total body	0.001
Bone	0.001
Liver	0.001
Lower large intestine	0.077
Upper large intestine	0.038
Small intestine	0.009
Stomach	0.005

A gamma ray spectrum of the ^{143}Pm obtained from a whole body count of one of the volunteers is shown in Fig. 1. The smaller peaks at 0.695, 0.615, and 0.474 MeV are from the decay of a small amount of ^{144}Pm which was also present.

3. INJECTION STUDIES

A typical distribution of ^{143}Pm in a human volunteer with time following intravenous administration is shown in Fig. 2. The uptake in the liver is very rapid with most of the liver fraction arriving there within 90 sec. This was determined by placing the collimated detector directly over the liver area of the subject before injection and monitoring the count rate after injection with a count rate meter until it appeared to be constant. A rough measure of the amount in the liver was made from the whole body scan and found to be between 40 and 50% of the injected dose. Whole body scans after 24 hr show that the distribution in the body remains unchanged for a year after injection with the exception that the peak over

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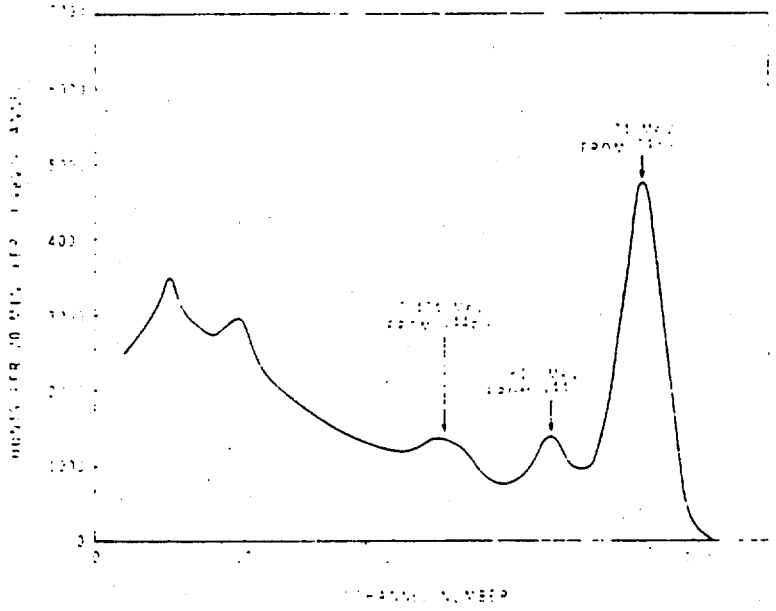

FIG. 1. Gamma ray spectrum of ^{143}Pm *in vivo*.

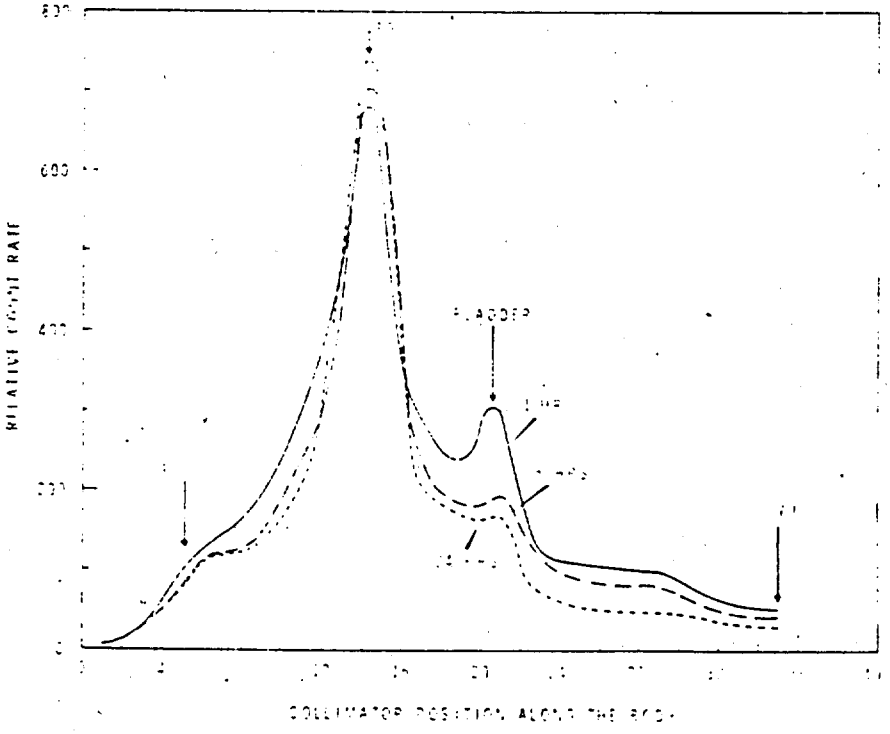

FIG. 2. Differential scan of ^{143}Pm in test subjects at various times after injection.

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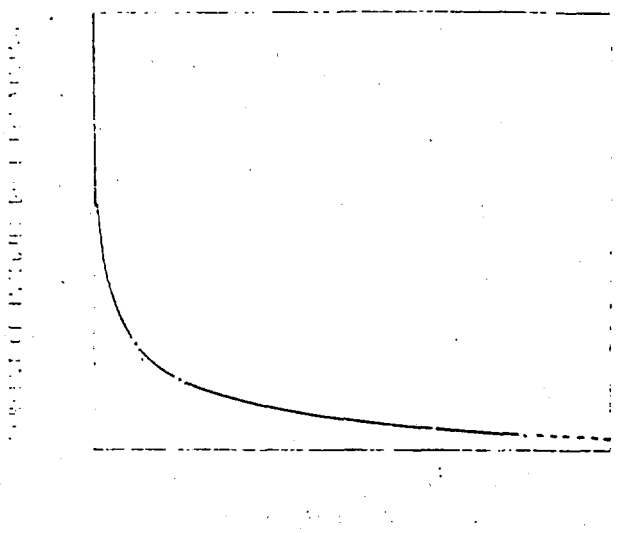

FIG. 3. Percent ^{143}Pm remaining in blood, following intravenous administration.

the bladder area disappears during the second day. The ^{143}Pm which does not go immediately to the liver appears to remain in the blood for a short time and gradually deposits in the bone. The total estimated content of ^{143}Pm in the blood as a function of time was obtained by analyzing periodic blood samples of two volunteers is shown in Fig. 3. The ^{143}Pm activity was not detectable in the blood at 24 hr.

After intravenous injection, promethium excretion occurs by both urinary and fecal routes. Figure 4 shows the daily urinary excretion rate for 50 days and the daily fecal excretion for 7 days after injection. Most of the urinary excretion which occurs during the first two months occurs during the first day and the rate decreases rapidly thereafter. The urinary excretion is greater than the fecal excretion until the seventh day when they become about equal. Daily fecal samples were stopped after the seventh day, however, the average ^{143}Pm in the fecal samples on the 15th day after injection was 0.075% of the injected amount whereas the average urine content was only 0.03%. These excretion rates are quite similar to those obtained with a pig injected with $^{143}PmCl_3$[1] and two dogs[11] injected with $^{147}Pm(ClO_4)_3$ except the first days urine excretion in humans was twice as much as that of the pig and the dogs. Reliable measurements of urinary excretion could not be made after about 50 days after injection because the content in the urine was near or below the detection limit of the counting method.

The retention of the ^{143}Pm was measured by the whole body counter for a period of one year and these results agree with the excretion results and are shown in Fig. 5. An extrapolation of the retention curve between 20 and 365 days indicates the biological half-life of ^{143}Pm in the total body is greater than 1000 days. Any redistribution of the ^{143}Pm between liver, bone, or other organs was not detected in comparing periodic counts over the legs, liver and head of the volunteers; therefore, the whole body counts should provide an accurate measure of the retention.

Most accidental internal exposures to ^{147}Pm occur by inhalation of the material with subsequent gradual transfer of some fraction of ^{147}Pm from the lungs to the blood stream. Therefore, these excretions and retention curves obtained from single injections are not directly applicable for estimating lung and systemic body burdens of promethium after inhalation. However, since each daily transfer of ^{147}Pm from lung to bloodstream can be considered as an injection into the blood stream, these curves provide a basis for the development of mathematical models for use in estimating the systemic burden of ^{143}Pm and the rate of transfer of the ^{147}Pm from the lung to the blood stream. These models are presently being developed and tested and will be published at a later date. The results of these experiments show that the metabolism of promethium in humans is similar to that in large animals such as pigs and dogs but quite different than that in small animals such as the rat. In humans most of the promethium is retained and the excretion rapidly drops to a very low rate. It quickly becomes distributed between liver and bone and remains essentially unchanged for at least a year. The retention in the rat is much lower[14] with the liver gradually losing most of its initial early deposition of promethium and relatively high amounts are excreted in the feces.

The results disagree with the liver uptake parameters listed by the ICRP.[19] The report of ICRP Committee on permissible dose for

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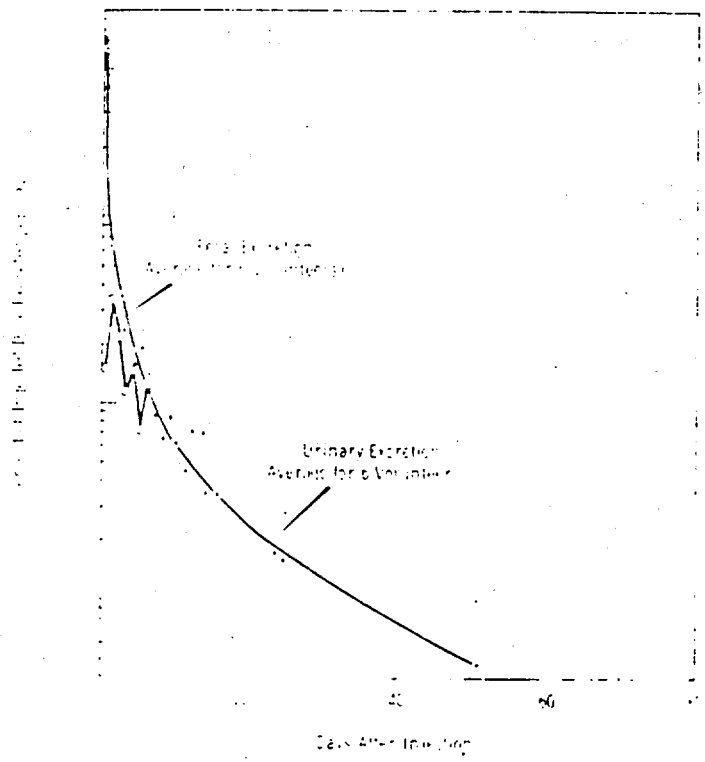

FIG. 4. Daily urinary and fecal excretions of intravenously injected ^{143}Pm.

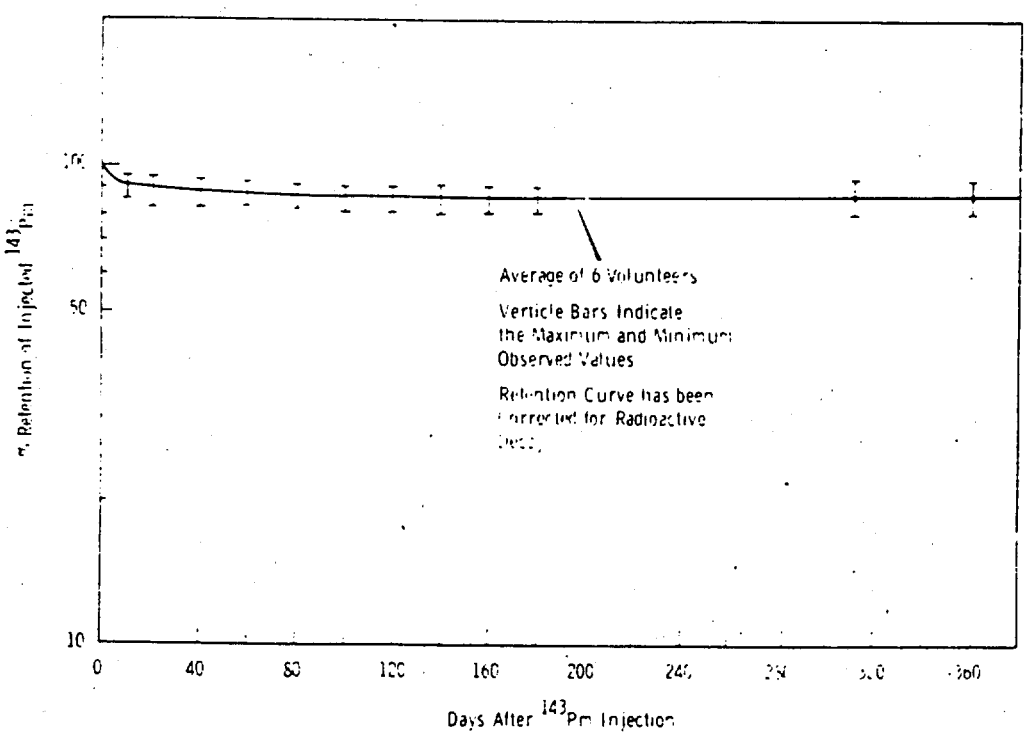

FIG. 5. The retention of ^{143}Pm in humans.

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internal radiation lists the fraction going from blood to liver as 0.06, whereas, this experiment shows this fraction to be between 0.4 and 0.5.

4. INGESTION STUDIES

Two volunteers orally ingested 10 μCi of the $^{143}PmCl_3$ solution mixed with orange juice. Subsequent excretion analysis showed that essentially none of the material was absorbed by the body and all of it was excreted in the feces. No activity was detected in the urine samples. After one week a regular whole body count did not indicate any activity remaining in the body. However, a one hour count directly over the liver of one of the volunteers showed a liver content of about 0.0001 μCi. The ^{143}Pm content in the liver remained constant in subsequent counts up to a month later which confirmed that the activity was actually in the liver and not temporarily lodged in the GI tract. The uptake by this volunteer was estimated to be about 0.001% which agrees with the ICRP[19] estimates of the uptake of promethium from ingestion. Promethium-143 activity was not detectable in the other volunteer and the uptake was probably less than 0.0005%.

5. THE EFFECT OF DTPA ON EXCRETION OF PROMETHIUM IN HUMANS

The effect of calcium trisodium diethylenetriaminepentaacetate (DTPA) on the excretion and retention of ^{143}Pm in humans was studied as a function of the time interval between the injection of ^{143}Pm and the injection of DTPA. One gram of DTPA was given at different times to 8 subjects from 5 min before to 80 days after injection of ^{143}Pm. Figure 6 shows the urinary excretion of ^{143}Pm with time up to 6 days after injection for 6 subjects who were given DTPA according to the schedule shown in Table 3.

The excretion of the injected ^{143}Pm varied from 100% of dose for the case where DTPA was injected for 5 min before the ^{143}Pm injection to only 20% of dose when DTPA was administered 24 hr after the ^{143}Pm injection. In the three cases where DTPA was administered within an hour or less after ^{143}Pm injection, 80% or more of the ^{143}Pm was excreted; however, two of these cases received additional injections of DTPA. These results indicate that DTPA is very effective in significantly reducing the body content of promethium when administered within about an hour after it enters the blood stream. If the DTPA is given 5 hr later, the body burden will decrease by only about 50% and when given 24 hr later only 20% of the ^{143}Pm is excreted which is only 10% more than the amount excreted without DTPA administration.

To study the effect of DTPA on long term internal depositions of promethium, DTPA was given to two subjects 80 days after a previous injection of ^{143}Pm. Urinary excretion measurements indicated that only about 5% of the body content of 143 was excreted during the following week but the whole body counter measurements showed a total body loss of 10%. In following the excretion of ^{143}Pm from the body after DTPA administration, it was found that the whole body counting results always indicated a greater loss than did the excretion results. Since the ^{143}Pm in the liver is counted with a greater efficiency than that in the bones, these results indicate that much more of the ^{143}Pm that is extracted by the DTPA comes from the liver than from the bone. Further studies are needed to more accurately determine the relative excretion rates from liver and bone.

Table 3 also shows the total ^{143}Pm excreted in each volunteer in both urine and feces during the six-day period after injection of the ^{143}Pm. Both the urine and fecal excretion of ^{143}Pm are enhanced by DTPA administration, and it is interesting that although the urinary excretion depends upon the interval of time between the ^{143}Pm and DTPA injection, the fecal excretion is quite constant except in the case where DTPA was administered before the ^{143}Pm. A possible explanation for this constant fecal excretion is the fact that most of the liver deposition of ^{143}Pm occurs immediately (within 90 sec) after injection. LAFUMA[20] has suggested the injected fraction of ^{143}Pm which hydrolyzes into colloids and deposits in the liver, breaks down and becomes protein bound, and is removed by the hepatic cells into the bile and feces. It appears that DTPA enhances this mechanism and a rather constant fraction of the liver deposition is excreted in this manner. The urine excretion results largely from the DTPA complexing of the ^{143}Pm still in the blood stream

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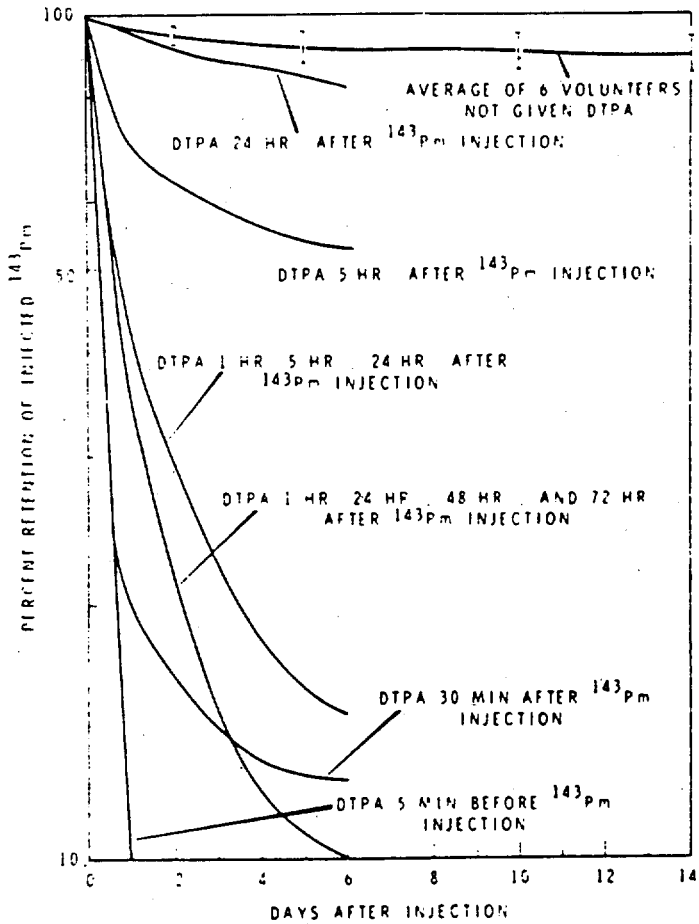

FIG. 6. The effect of DTPA on ^{143}Pm retention in humans.

Table 3. Schedule of DTPA administration and total urinary and fecal excretion during first 6 days

Subject	Time of administration of 1 g DTPA relative to time of injection of ^{143}Pm	Per cent lost in urine	Per cent lost in feces
1	5 min before	100	0
2	30 min after	80	7.4
3	1 hr, 5 hr and 24 hr after	76	9.1
4	1 hr, 24 hr, 48 hr, 72 hr after	81	8.5
5	5 hr after	38	8.2
6	24 hr after	12	8.7

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and of course should decrease with longer time intervals between ^{143}Pm and DTPA injection. Unfortunately, fecal samples were not collected from the volunteers who received one gram of DTPA after 80 days so the fecal excretion from long-term burdens of promethium in humans is not known. The whole body counts indicate that up to half the excretion could have occurred by the fecal route, however, this estimate needs to be corrected by the difference in counting efficiency of the liver vs. the total body.

It should be noted that if DTPA is given after the ^{143}Pm has essentially all left the blood stream, for instance at 24 hr, the fecal excretion is enhanced much more than the urinary excretion. In the case of subject 6 in Table 3, the urinary excretion without DTPA during the first 6 days would normally be about 7–10% of the initial body burden. The DTPA only caused an additional 2–5% to be excreted. The normal fecal excretion for the first 6 days is only 1.3% of the initial dose but DTPA caused an additional 7.4% to be excreted. In terms of percentage increase the urine excretion was increased by 41% whereas the fecal excretion was increased by about 570% with DTPA administration. Therefore, to assess the results of the removal of promethium and probably other rare earth isotopes from the body by DTPA administration, it is very important that both urinary and fecal excretions be carefully collected and analyzed.

Since only one volunteer was studied in each variation of DTPA administration, further conclusions are not warranted. Studies of the effect of DTPA on ^{143}Pm retention in a much greater number of miniature swine is presently under way at Battelle Northwest Biology Laboratory and these should indicate the variability of results to be expected between individuals.

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