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CLINICAL EXPERIENCES WITH RADIOACTIVE MATERIALS*

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PRESENT knowledge of the deleterious effects of internally deposited radioactive materials in humans has been obtained primarily from individuals with accidentally accumulated body burdens of isotopes of radium or thorium.[1,10,11,12] The following report presents a series of cases giving clinical information on several other particularly hazardous radioelements, *i.e.*, plutonium (Pu^{239}), americium (Am^{241}), and polonium (Po^{210}). These are all alpha emitters, the first two artificially produced and relatively recently discovered. Pu^{239}, with a half-life of approximately 24,000 years, is produced and used in considerable quantities and is of interest because of its nuclear power plant and weapon usage. Am^{241}, with a half-life of 500 years, is used primarily in research. Polonium, known for some time, recently has been extensively used as an ingredient in neutron sources. Po^{210}, with a half-life of 138 days, will probably be produced in large quantities as a toxic by-product in Thorium-Bismuth nuclear power plants.

Extensive animal studies have been made to determine body reaction to the presence of these elements. Pathologic effects observed for plutonium and americium are similar to those of radium.[2,14,15] Polonium in high dosage gives a clinical picture similar to "acute radiation syndrome."[4]

To date there has been no report of a human having received a sufficient quantity of any of these isotopes to produce demonstrable injury. The cases described below are reported here because:

1. They illustrate typical situations in which contamination accidents may occur.
2. They provide some of the first human excretion data on these isotopes (to be reported in the literature).
3. They document current techniques for evaluation and care of personnel contaminated by radioactivity.
4. It was possible to test the efficacy of therapeutic agents for hastening excretion of the isotopes in these cases.

REPORT OF CASES

CASE 1. *Americium.* This case involved a skilled radiochemist who, at the time of the accident, was working with a very "hot" mixture of Am^{241}, Am^{242}, Cm^{242} and associated fission products contained in a quartz ampule. A gamma-ray meter held 6 inches from the ampule read 150 r/hr. This mixture had been obtained by irradiating 5 mg. of Am^{241} in a high neutron flux pile. Just as the ampule was about to be opened (for reasons still undetermined), it exploded, forcing the contents over the top of the lead shield in front of the working space and spraying his face and hair. Almost immediately he scrubbed thoroughly with soap and water, but even after thorough washing there remained "hot" spots over his forehead, cheek and upper lip that went off-scale on the alpha meter and that read over 20 mr/hr. on the beta-gamma meter. He was taken to the hospital where physical examination revealed only minor abrasions over his forehead and in the mucous membranes of his mouth and nares.

The first urine sample, obtained approximately three hours after the accident, assayed 2 to 3 d./min./cc. The next urine sample, one to one and one-half hours later, showed an even higher count. This rising count strongly indicated that he had accumulated a body burden of radioactivity, probably through the abraded areas on his skin and mucous membranes and possibly by inhalation. Undoubtedly, some material was swallowed since gastric washings assayed over 1000 d./min./cc.

It was decided to attempt therapy, *i.e.*, to use a means to accelerate the excretion of the radioactive material. Calcium ethylenediaminetetraacetate (Ca EDTA), one of the current drugs recommended for this purpose,[5,6,7,16] was administered intravenously in 2 gm. doses in

* Work performed under the auspices of the United States Atomic Energy Commission.

250 cc. saline solution twice a day for five days, starting eight hours after the accident. A blood sample drawn at the time treatment was started assayed 3 d./min./cc. For the first two days the patient was hospitalized for observation and to assure full collection of urine and feces. He was ambulatory at all times and was able to help with the monitoring and to take full precautions to prevent contamination of hospital equipment. During his hospital stay, the remaining "hot" spots on his skin and hair were removed by repeated scrubbing with a mixture of detergent and Ca EDTA solution.

Shortly after admission to the hospital, a series of laboratory tests were run to serve as a base line against which to compare changes which might result from the radiation exposure or possibly from the use of the drug. These tests included a complete blood cell count with a platelet count, complete urinalysis, serum proteins, serum calcium and phosphorus, serum alkaline phosphatase and prothrombin time. Urinalysis was repeated daily while treatment was going on. Hematologic tests and serum chemistry tests were repeated in a week and after a month. No significant changes were ever noted.

After leaving the hospital, treatment was continued at the same dosage level for three more days on a come-and-go basis in the first-aid room. Following that, Ca EDTA was given only as a diagnostic aid, at times indicated in Figure 1.

The results of urine excretion assays are presented in Figure 1, expressed as disintegrations of americium* per minute per twenty-four hours (d./min./24 hr.) During the first twenty-four hours, urine excretion was about 11,000 d./min., a surprisingly high amount, indicating either a high degree of effectiveness for the treatment or the presence of a dangerously high level of activity in the body. Fortunately, the former turned out to be true. The excretion level remained high in the first few days and dropped abruptly with cessation of treatment, rising again sharply when treatment was re-instituted. One month after the accident, urine excretion levels had fallen to approximately 0.5 d./min./24 hr., the lowest level of significant

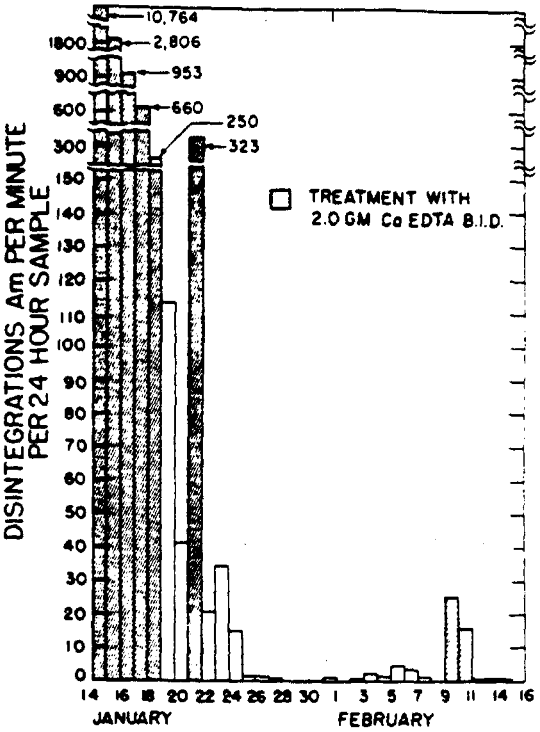

FIG. 1. Effect of Ca EDTA on urinary americium excretion.

detection by the analytical procedure used. Urine samples were assayed monthly from then on. The assays ranged from 0.12 to 0.30 d./min./24 hr., values which would not be taken to indicate with any certainty the presence of any americium internally. One could not distinguish these urine samples from others obtained from individuals who had had no americium exposure. Approximately one year after the accident, he was given an additional trial of Ca EDTA. The urine excretion level rose from a pretreatment level of 0.2 d./min. to 4.2 d./min. on the first day of treatment, then to 2.4 d./min., and 1.6 d./min. on subsequent treatment days and dropped to 0.3 d./min. the day after treatment was stopped. Ca EDTA, used in this fashion, served as a diagnostic aid to demonstrate the presence of a body burden of activity not otherwise detectable.

Fecal samples were collected for the first seven days. The results of assay of these samples are given in Table 1. The very high fecal excretion in the seven days (over 80,000 d./min. of americium) was undoubtedly in a large measure due to material that was swallowed and excreted, rather than material which had

* Because of the short half-lives of most of the isotopes in the contamination mixture, the only appreciable activity detectable in a few days after the accident was that associated with Am^{241} and Cm^{242}. Pulse height analysis of the activity in the urine showed the Am:Cm ratio to be 16 to 1. Since the hazard from curium is almost the same as that from americium, no great error was introduced by considering all of the activity to be americium.

TABLE I

AMERICIUM FECES EXCRETION

Date	Disintegrations per Minute of Americium per Twenty-four Hour Specimen
January 14	14,800
15	41,000
16	19,000
17	1,541
18	2,105
19	1,710
20	438

actually gained entrance into the circulation and was being excreted through the bowel.

With the data at hand, it was possible to estimate the present body burden, the effectiveness of the treatment and the initial dose taken in. The calculation of the body burden was made by using an empirical excretion curve obtained from humans for plutonium and extrapolating to americium by use of a factor. The assumption was made that the treatment did not alter the slope of the excretion curve at times long after the treatment was stopped. The equation of the excretion curve for plutonium as given by Langham[8] is:

$$D_r = 435\ Ut^{0.76}$$

where D_r is the body burden in d./min., U is the urine excretion in d./min., on day t, and t is the time in days after the exposure. The factor for adapting the equation for use with americium was obtained from Carter and Langham's[3] study in animals, wherein it was shown that plutonium and americium urine excretory curves are approximately parallel and that at a given time, *i.e.*, thirty days, after the entrance of the isotope into the body, the urine excretion of americium is twice that of plutonium. With this information adapting the equation for use in americium cases was simple, namely:

$$D_r \text{ (americium)} = 1/2 D_r \text{ (plutonium)}$$
$$= 1/2\ (435\ Ut^{0.76})$$

In the case under discussion, at thirty days the americium urine excretion, U, was 0.45 d./min. Putting this datum into the equation gave a body burden of 1,350 d./min. at thirty days.

The calculation of the amount of activity entering the body was made as follows. Langham (again from human plutonium studies) found the amount of plutonium remaining in the body at thirty days after acute exposure is 96.3 per cent of the initial dose. For americium, using the same factor as above, this would be approximately 92.5 per cent. With a body burden of 1,350 d./min., the corresponding initial dose is 1,460 or approximately 1,500. However, in the present case, treatment resulted in the excretion of an additional 16,000 d./min. (this neglects the 150 or so d./min. which would have been excreted normally, but this is negligible compared to the 16,000), so the actual initial dose must have been 1,500+16,000 or approximately 17,500 d./min.

The efficacy of the treatment can be judged by comparing the present body burden with that which would have resulted had no treatment been given. With an initial dose of 17,500 d./min., the amount remaining in the body at thirty days (without treatment) would be the initial dose (17,500) minus the amount excreted (0.075 ×17,500), namely, 16,200 d./min. This value compared to 1,350 indicates the treatment was decidedly efficacious. As a result of the treatment the body burden is less than one-tenth of what it would have been had treatment not been instituted.

CASE II. *Plutonium.* This case concerns a forty year old woman technician,* who at the time of the accident was working with a plutonium solution in 1 N HNO_3 that assayed approximately 2×10^6 d./min./cc. The flask broke and a jagged edge of the broken contaminated glass cut her across the base of the thumb through a rubber glove. The first-aid treatment

* A preliminary report of this case was presented to the Section on Preventive and Industrial Medicine at the 103rd Annual Meeting of the American Medical Association in San Francisco, 1954, and published in the *A. M. A. Arch. Ind. Hyg. & Occ. Med.*, 1954, *10*, 226.

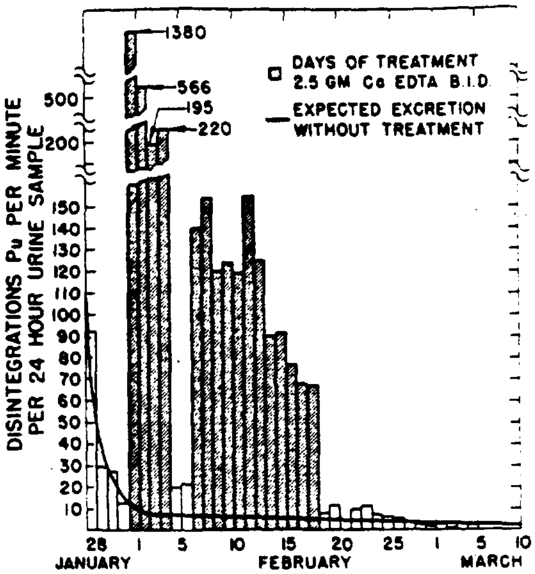

FIG. 2. Effect of Ca EDTA on urinary plutonium excretion.

consisted of cleansing the wound area with soap and water and stopping the profuse bleeding with a couple of sutures and a small pressure dressing.

From the conditions of the accident, it did not seem likely that any appreciable radioactive material had entered the wound. However, an alpha meter passed over the surface of her hand indicated a few "hot" spots as high as 1,000 c./min., after the initial cleansing. It was decided to collect urine in an attempt to learn how much, if any, plutonium had gained entrance into the body. The first day's collection of urine assayed 90 d./min. There was a possibility that this sample was contaminated, as occurs not infrequently in the first urine samples collected after an accident. However, subsequent collections on the following days showed continued excretion of measurable amounts of plutonium. It was apparent that a small amount of plutonium had been absorbed from the wound and, therefore, it was decided to give her Ca EDTA.

Before starting the treatment, the wound area was excised. The excised specimen assayed 1,500 d./min., a very small amount. Ca EDTA was given in 2.5 gm. doses in 500 cc. of saline solution by slow intravenous drip twice a day for four days, stopped for two days, and then given again under the same regimen for twelve days. The first day of treatment brought forth an unusually high excretion; the count jumped from a pretreatment level of 12 up to 1,380. As seen in Figure 2, on subsequent days under treatment, the output continued high. When treatment was stopped, the level dropped sharply and rose again with renewed treatment.

Toward the last of the second course of treatment, the patient began to develop symptoms, first a nonspecific malaise, then a backache and finally urinary frequency and nocturia. It was suspected that the symptoms might be related to the treatment. Treatment was stopped and an attempt was made to learn the cause of her illness. There were no unusual findings on physical examination. The standard blood chemistry and blood morphology studies gave normal values. Urinalysis, however, showed 2+ albumin, many fine granular casts, occasional red blood cells and a few white blood cells. Urine culture was negative. The signs and symptoms cleared quickly with rest. In two or three days, the symptoms were gone and by the fourth day, the urine was entirely clear and the patient appeared well.*

Calculation of the body burden was made similarly to the way in which the body burden was calculated in the americium case described above. Forty days after the accident, the urine excretion level averaged 1.95 d. min. of plutonium per twenty-four hours. At this excretion level, the equation yields a body burden of 14,000 d. min.

As seen from Langham's data, under ordinary conditions, the body burden of plutonium at thirty days is 96.3 per cent of an initial acute dose, which in this case would give

$$\frac{14{,}000}{96.3} = 14{,}540 \text{ d./min.}$$

To obtain the actual initial dose, the amount excreted under treatment must be added to this value, giving 14,540+4,500 = 19,040 d. min. With an initial value of this magnitude, the body burden at thirty days without treatment would have been

* As a result of this case, an extensive toxicology study of Ca EDTA was undertaken in rats. It was found that when the drug is given repeatedly and in sufficiently high doses, a reversible tubular nephrosis could be produced. The results of these studies are reported in the *J.A.M.A.*, 1956, *160*, 1042. These findings make it quite likely that the symptoms seen in the case above were related to the drug.

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19,040 − 3.7 per cent of 19,040 = 18,366 d./min. The actual body burden was 14,000 d./min. or approximately 76 per cent of this. The difference of 24 per cent is an index of the effectiveness of the treatment. It is likely that had the drug been started almost immediately after the accident instead of five days later, the treatment would have been even more efficacious.

Case III. *Plutonium.* This case was a more complicated one. The individual involved had been working with plutonium in various forms for a number of years and had had several minor contamination accidents. He was slowly accumulating plutonium internally as evidenced by a slowly rising urine count over the years. It was just about decided to remove him from his job and place him on work away from plutonium when he had this rather serious accident.

The accident occurred while he was working in a drybox used for processing plutonium residues. He was placing rubber tubing over the outlet of a suction flask when the tip broke and he was cut across the ball of the thumb. The flask was highly contaminated with plutonium in various forms, the nitrate, fluoride, oxide, *etc.* Surface counts of both the glove he was wearing and the skin about the wound were off-scale on the alpha meter.

He was taken to the hospital where the wound area was immediately excised. Analysis of the tissue yielded 850,000 d./min. The removal of this tremendous amount amply justified our practice of excising all potentially contaminated wounds.

Treatment with Ca EDTA was started about one hour after the accident. Results of the urine assays are shown in Figure 3. The urinary excretion of plutonium for the first day (from about 4:30 in the afternoon, when the accident occurred, until the following morning) was 80 d./min. It was expected from the conditions of the accident that there would be a tremendous excretion, but surprisingly enough, the value was low. Then, instead of dropping as had happened in previous cases, the excretion rose on subsequent days. This rising level was interpreted to mean there was still plutonium left at the wound site that was slowly feeding into the blood stream.

After four days, treatment was stopped. The reasoning was as follows. Only a little over 1,000 d./min. had been put out in the four days. If

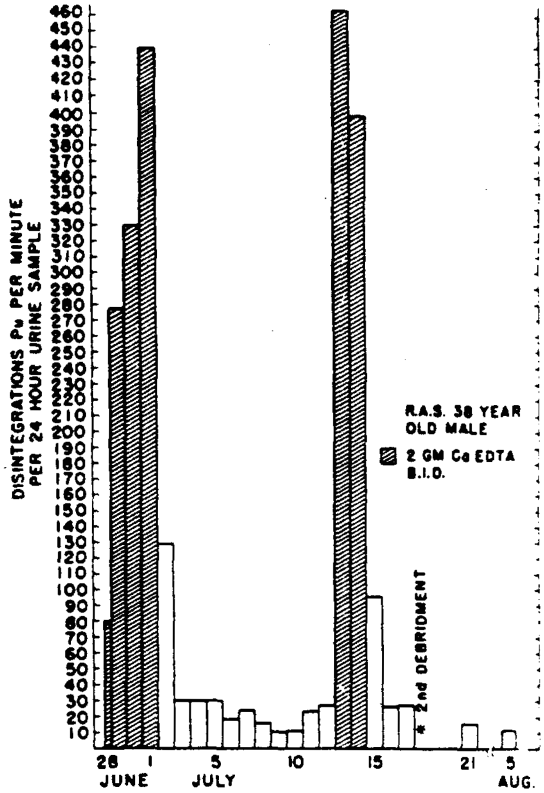

Fig. 3. Effect of Ca EDTA on urinary plutonium excretion.

the treatment was very effective, *i.e.*, this excretion level represented a high percentage of his body burden, then he must not have had much plutonium in him. The other alternative was that the low level of excretion was due to the fact that the treatment was not being very effective. In either case, it was advisable to stop treatment. With the stopping of the drug, the urinary plutonium excretion dropped to 27 d./min./day and stayed about this level for five days. This gave further confirmation to the impression that an intramuscular source was feeding into the blood stream since the excretion level would have been expected to drop sharply at this time had a single acute exposure occurred. Another two days of Ca EDTA treatment was given and again the excretion went up, this time even higher than on the first day. It was decided to excise more of the wound area. The second tissue piece assayed 30,000 d./min. The effect of the excision was immediately manifest in the urine. The excretion began to fall and dropped steadily to a level of 9 d./min./day about one week after the second excision. By one year after the accident, the level had fallen to approximately 4 d./min./day.

At the time the excretion level was on the order of 9 d./min./day, it was possible to do further studies to gain more information about Ca EDTA and plutonium excretion. In one such study, a comparison between orally administered and intravenously administered Ca EDTA was made. A three-day trial of 2 gm. a day of Ca EDTA was made for each mode of administration. The oral treatment produced no change in excretion above the control levels. Intravenous administration resulted in a tenfold increase in urinary plutonium excretion. Fecal excretion assays were also made at these times. Intravenous administration of the drug did not alter the fecal excretion. The feces: urine excretion ratio was approximately 1 to 1 in the control period and did not change during the oral treatment period.

The net increase in excretion brought about by the Ca EDTA was not significant. The administration of the drug was of value primarily because of the diagnostic information it gave, namely, in pointing out the residual intramuscular deposit. The apparent ineffectiveness of Ca EDTA in this case might well have been because of the very low blood levels of plutonium present at any one time, *i.e.*, that small amount of plutonium that was being fed slowly from the intramuscular site into the circulation.

Using the same mode of calculation as described above, it is estimated that the body burden at seventy days after the accident was approximately 50,000 d./min.[9]

Case iv and Case v. *Polonium.* These cases involved two young physicists whose cases are so similar that they can be described together. Both were exposed at the same time in the same accident.

The details of the exposure were as follows. The two men had been working with a 25-curie mock fission neutron source contained in a graphite pile, when it was noticed that the neutron flux was about 5 per cent higher than expected. While they were investigating the cause, the apparently already defective Po-Be source ruptured and sprayed alpha active material over the source room. The cause of the rupture was judged to be a buildup of hydrogen and oxygen which had resulted from irradiation of the moisture collected in the capsule.

The men left the room almost immediately. Essentially all of the exposure to the activity occurred during the few minutes while the men were in the source room right after the accident. On coming out of the room, their clothing and exposed parts of the body, the face, neck and hair had counts ranging up to 20,000 c./min. of alpha activity. After a shower and change of clothing, the only appreciable activity remaining in both cases was on the upper lip. This activity persisted for several days, even after repeated scrubbing with detergent and water. Apparently it was due to the deposition of exhaled polonium.

On physical examination, no cuts, abrasions or any evidence of injury were found. Collection of urine and feces samples was started and a series of laboratory tests was run as a base line against which to measure any possible future changes which might occur from irradiation. The tests included a complete blood cell count, platelet count, sedimentation rate, bleeding and clotting time, serum phosphatase, prothrombin time, nonprotein nitrogen, serum proteins and urinalysis. Tests were repeated on alternate days for the first week, then weekly for the rest of a month and at the end of the second month. No changes from the normal were noted in either case. The men never ceased their normal activities, except that they were kept away from radiation sources for several weeks.

It was possible to follow total excretion (urinary and fecal) in the individual who received the largest dose (as manifested by excretion rates). In the second case, only urinary excretion was closely followed. The results are presented in Figure 4. At the beginning of the third week, a three day course of Ca EDTA, 4 gm. daily in 2 divided doses by slow intravenous drip, was given to one of the men. There was no change in excretion rate.

From simple inspection of the curves, it is immediately apparent in an inhalation exposure such as these that excretion is predominantly via the feces. For the first week after exposure, fecal excretion was 2 to 3 orders of magnitude greater than urinary excretion. At later time periods, urine and feces contribution tended to approach each other, but even at five months, the polonium level in the feces was at least 10 times greater than in the urine. The plot of fecal excretion data on a semi-log scale showed that there are two definite phases of fecal excretion, an early one occurring at a half-time of 0.6 days and a later one at a rate characterized by a half-time of 19.6 days. The first excretion phase

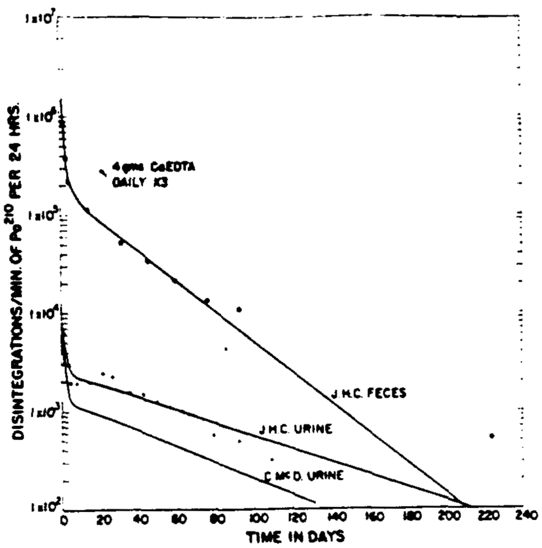

FIG. 4. Effect of Ca EDTA on urinary polonium excretion.

probably represents swallowed activity brought up from the pharynx and major bronchi, plus the polonium that was swallowed initially. The activity appearing in the second phase was probably polonium which was brought up from the lower respiratory tract by ciliary action and swallowed, as well as material which had gained entry into the systemic circulation across the lung alveoli and intestinal wall and was excreted through the bile.

Urinary excretion plotted on a semi-log scale likewise was resolved into two components in both cases, an initial component with an approximate half-time of 0.75 days and a later component with a half-time of 47 days in one case and 37 days in the second. The first phase was probably due to polonium entering the systemic circulation across the alveoli and gastrointestinal tract, and the second phase, material being returned to the blood stream after initial deposition in tissue sites.

Unlike the situation for plutonium and americium, the calculation of body burden at any given time after an acute exposure for polonium is not particularly meaningful because the body burden changes rapidly with time and in a relatively short time becomes insignificant. Of much more importance is the calculation of the initial dose, because from this value and the excretion rates one can obtain an idea of the internal radiation dose received as a result of the exposure.

The length of time for the body burden to fall to essentially zero was estimated by extrapolation of the excretion curves to the time when excretion levels were insignificant, *i.e.*, below 1 d. min. day. In the case where both feces and urine data were available, the feces excretion was calculated to become insignificant at three hundred and forty days and urine excretion about three hundred and seventy days. Actual assays of excreta at one year after exposure verified this. The initial dose received was estimated by summing up the total excretion from time of exposure until one year later. The general equation for the excretion curves is:

$$E_t = D_1 e^{-k_1 t} + D_2 e^{-k_2 t}$$

where E_t is the twenty-four hour excretion at time t, D_1 and D_2 represent the amount of material present initially, and k_1 and k_2 the rate constants for the two different phases of excretion. Integration of this equation from zero to time t sums up the excretion during that time. The expression for the integration is:

$$\int_0^t (D_1 e^{-k_1 t} + D_2 e^{-k_2 t}) = \frac{D_1(1 - e^{-k_1 t})}{k_1} + \frac{D_2(1 - e^{-k_2 t})}{k_2}.$$

Substitution of numerical values from the excretion curves with $t = 365$ days and with appropriate corrections for radioactive decay gives the following:

Total Fecal Excretion

$$= \frac{6.89 \times 10^6(1 - e^{-1.17 \times 365})}{1.17} + \frac{1.74 \times 10^5(1 - e^{-0.04 \times 365})}{0.04}$$

$= 10.24 \times 10^6$ d./min., or 4.65 μc.

Total Urine Excretion

$$= \frac{8.81 \times 10^3(1 - e^{-0.97 \times 365})}{0.97}$$

$$+\frac{2.8\times 10^{3}(1-e^{-0.02\times 365})}{0.02}$$

$$=1.49\times 10^{5}\ \text{d./min., or } 0.067\ \mu c.$$

The total excretion, the sum of the urinary plus fecal excretion, was 4.65+0.067 or 4.72 μc. This essentially represents the amount of activity initially entering the body. The determination of the radiation dose delivered to the various organs in the body following the inhalation of this quantity of Po^{210} was not possible because of lack of information on the distribution of the activity in the body. However, by the use of certain assumptions, it was possible to calculate the maximum possible dose to the organ most likely to have received the largest dose, namely, the lung. The total energy delivered to the lung by the 4.72 μc of Po^{210} in terms of mev., using the fecal excretion data, was:

$$\left[5.89\times 10^{6}\begin{pmatrix}\text{Portion of initial activity}\\ \text{excreted in phase one}\end{pmatrix}\times 1.23\times 10^{3}\begin{pmatrix}\text{Mean life of phase}\\ \text{one in minutes}\end{pmatrix}+4.35\times 10^{6}\begin{pmatrix}\text{Portion of initial activity}\\ \text{excreted in phase two}\end{pmatrix}\times 3.6\times 10^{4}\begin{pmatrix}\text{Mean life of phase}\\ \text{two in minutes}\end{pmatrix}\right]$$

$$5.3\begin{pmatrix}\text{Energy of Po}^{210}\\ \text{alpha in mev.}\end{pmatrix}=8.68\times 10^{11}\ \text{mev.}$$

Converting this to rep, assuming uniform distribution throughout the lung, one obtains:

$$\frac{8.68\times 10^{11}}{10^{3}\ (\text{nominal wt. of lung})\times 5.18\times 10^{7}\ (\text{mev./gm./rep})}=16.6\ \text{rep}^{*}$$

This result does not include the contribution made by the polonium which was eventually excreted in the urine. At most, however, this could be only 1 per cent of the total.

The gastrointestinal tract is the only other system of organs that might have received a radiation dose even approaching that of the lung, but it is not possible to estimate this, except to guess that the overall dose was certainly far less than that to the lung. On the basis that 0.004 of the amount of polonium in the lung reached the spleen (see Handbook 52),[13] the dose to the spleen (the so-called *critical organ*) can be estimated to be negligible, *i.e.*, less than 1 per cent of the dose to the lungs.

In the second case, an estimate of the initial dose and the total radiation dose to the lung can be made by merely comparing the urine polonium output (the only available data) with that of the first case. Results of approximately one-half that of Case IV are obtained.

* This calculation does not include any factor for any unusual RBE (relative biological effectiveness) for the polonium alpha particles, but in all likelihood only a small error is introduced by this simplification.

SUMMARY

Case reports are presented on 1 individual who received an internal dose of Am^{241}, on 2 individuals who accumulated Pu^{239} internally, and on 2 individuals who received a body burden of Po^{210}. The urinary excretion of the isotopes was followed closely over a long period of time in all cases, and the results of the assays are reported. In 2 cases, the assays on feces are also presented. The results of attempts to accelerate excretion of the isotopes are presented. A procedure for evaluating the initial dose, the body burden at given periods of time, and the effect of treatment is given. The technique for estimating the dose received from the polonium exposure is described and the dose received evaluated.

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