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A Study on the Short-term Metabolism of Curium and Its Removal with DTPA in the Rat

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Abstract

The contents of ^{242}Cm in the plasma, liver, skeleton and kidneys were determined from 22.5 minutes to 16 days after the intravenous injection of ^{242}Cm citrate to the rat. The ^{242}Cm injected disappeared from the plasma rapidly and deposited mainly in the liver and skeleton. By analyzing the relationship between the disappearance from the plasma and the accumulation in the organs of injected curium, the initial distribution space, or the actual site of transfer compartment used for dose calculation in the ICRP Publ.30, of curium was identified as the extracellular fluid (ECF). The calculation showed that the difference between the radiation dose to bone surface or red bone marrow from short-lived curium isotopes evaluated under the current ICRP assumption, on one hand, and the same radiation dose, evaluated under the assumption that the actual site of transfer compartment is ECF, on the other, is not negligible.

The effect of administration of CaDTPA or ZnDTPA on the retention of ^{242}Cm in organs was studied by changing the time interval between the ^{242}Cm injection and DTPA administration and the amount of DTPA administered. The results obtained showed that 1) DTPA treatment of a person who has incorporated curium into the body should be started as early as possible, 2) the first single prompt DTPA should be administered as Ca salt, and the following multiple delayed DTPA, as the less toxic Zn salt, and 3) the dose of first CaDTPA should be as large as possible within the range not producing its side effect.

The study on the mixture of ^{242}Cm and ^{238}Pu showed that these two radioelements are metabolized and removed with DTPA independently.

Keywords: Curium, Plutonium, Metabolism, Rat, Initial Distribution Space, Transfer Compartment, Extracellular Fluid, Dosimetry, Removal, CaDTPA, ZnDTPA, Plasma, Liver, Skeleton, Kidneys

ラットにおけるキュリウムの初期代謝および DTPAによるその除去に関する研究

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高 田 和 夫

1983年6月3日受理

要 旨

ラットの静脈内にクエン酸塩として注射した ^{242}Cm の，血漿，肝臓，骨格および腎臓中含有量を，注射22.5分後から16日後まで測定した．注射後の ^{242}Cm は血漿から速やかに消失し，主として，肝臓および骨格に沈着した．^{242}Cm の血漿からの消失と臓器への蓄積との間の関係をしらべ，血液中に取り込まれた ^{242}Cm の初期分布域，すなわち，ICRP Publ. 30 において線量計算のために使われている通過コンパートメントに相当する部位が細胞外液であることを明らかにした．同部位を全身均等分布とした場合（現行の ICRP の仮定）と細胞外液とした場合について，短寿命キュリウム同位体からの骨表面などに対する線量評価値を計算し，両者の差が無視できないことを認めた．

^{242}Cm の臓器中残留におよぼす Ca DTPA あるいは Zn DTPA 投与の効果を，^{242}Cm 注射と DTPA 注射との間の時間間隔および DTPA の投与量を変化させてしらべた．これらの実験結果から，キュリウムによる体内汚染が生じた場合，汚染者に対する DTPA 投与はできるだけ速やかに行うべきであること，また，汚染後最初の DTPA 投与には Ca 塩を用いるべきであるが，その後のくり返し投与には副作用の少ない Zn 塩を用いるべきであることが明らかになった．なお，最初の1回の Ca 塩投与のみは，副作用の生じない範囲で，できるだけ多量投与することが望ましいこともわかった．

本研究では，^{242}Cm が ^{238}Pu との混合物として体内に取り込まれた場合についてもしらべた．その結果，これら両元素の代謝およびその DTPA による除去が互いに独立に行われることが判明した．

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1. Introduction

Curium, atomic number 96, was found by Seaborg, James and Ghiroso in 1944[1]. Therefore, only four decades has elapsed since its discovery. Nevertheless, a number of curium isotopes are presently known, as shown in **Table 1**. It can be seen from **Table 1** that all of the isotopes of curium are radioactive, and that many of them emit α radiations which are, if emitted in the body, far more harmful than β, γ or X radiations, due to their high LET values. Actual biological effects, namely, lethal[3] and carcinogenic[4,5] ones, of curium taken into the body have also been observed by animal experiments.

In a light water nuclear reactor for electric generation, great amounts of curium are produced by multiple neutron capture from fuel elements, ^{238}U and ^{239}Pu. Although many other kinds of transuranium elements are generated in the light water reactor, according to Pigford et al.[6], eighty percent of alpha-activities of all the transuranium elements generated are those of curium (cooling time, 150 days*1). The amounts of curium produced yearly in a 1000 MW_e uranium-fueled light water reactor are 1.9×10^{10} MBq ($= 5.15 \times 10^5$ Ci (α))[6]. In the other field of industry, curium isotopes are used as energy sources in thermoelectric generator[7,8], α-sources for neutron production[8], sources of monoenergetic photons[9], and

Table 1 Curium isotopes

Isotope	Half-life[2)a]	Mass (g) per 10^{10} Bq	Principal radiation[2)] : energy (MeV) and intensities
^{238}Cm	2.3 hr	4.73×10^{-8}	α6.52 (>10%), EC (<90%)
^{239}Cm	2.9 hr	5.98×10^{-8}	EC, γ0.188
^{240}Cm	26.8 d (1.9×10^6 y)	1.33×10^{-5}	α6.29 (71%), 6.25 (29%)
^{241}Cm	32.8 d	1.64×10^{-5}	EC (99%), α5.94 (1%), γ
^{242}Cm	162.8 d (6.09×10^6 y)	8.16×10^{-5}	α6.11 (74%), 6.07 (26%), γ
^{243}Cm	28.5 y	5.24×10^{-3}	α6.06 (5%), 6.00 (6%), 5.79 (74%), 5.74 (11%), others, γ
^{244}Cm	18.1 y (1.35×10^7 y)	3.34×10^{-3}	α5.81 (77%), 5.76 (23%), γ
^{245}Cm	8537 y	1.58	α5.36 (93%), 5.30 (5%), others, γ
^{246}Cm	4713 y (1.80×10^7 y)	8.77×10^{-1}	α5.39 (79%), 5.34 (21%), γ
^{247}Cm	1.56×10^7 y	2.91×10^3	α5.27 (14%), 5.21 (6%), 4.87 (71%), 4.82 (5%), others, γ
^{248}Cm	3.40×10^5 y	6.38×10	α5.08 (75%), 5.03 (17%), SF (8%)
^{249}Cm	65.4 m	2.34×10^{-8}	β0.86, γ
^{250}Cm	1.13×10^4 y	2.14	SF
^{251}Cm	16.8 m	6.07×10^{-9}	β1.42, γ
^{252}Cm	<2 d	$<1.04 \times 10^{-6}$	?

a The values in bracket show the half-lives of spontaneous fission (SF).

*1 Ordinary cooling time for reprocessing of spent fuel[6].

sources for producing transplutonic elements[10]. **Table 2** shows Annual Limits on Intake (ALI) for the curium isotopes, given by International Commission on Radiological Protection (ICRP)[11], for occupational persons. Taking into account the extremely small amounts*2 of ALI of curium shown in **Table 2** and the great amounts of curium encountered in industry, it goes without saying that sure preventive measures against internal contamination with curium must be established. However, perfect control of handling of radionuclides is usually very difficult. This can be seen from the fact that several cases of curium incorporation by humans were already reported in USA[12,13,14] and West Germany[15]. When the internal contamination with curium occurrs, the evaluation of radiation dose from the incorporated curium and the treatment to remove the curium from the body become necessary.

The ICRP gives a method for the evaluation of radiation dose to organs and tissues from the incorporated radionuclides[11]. However, this method involves many simplifications, especially, of the behavior of radionuclides in the body. These simplifications should be improved in the future, as stated by the ICRP itself.

It is known that the organ retention of curium in animals is decreased by administration of DTPA (diethylenetriaminepentaacetic acid)[16,17] (see **Fig. 1**). However, these experiments were performed under the limited conditions. Namely, the object of the experiment by Nenot et al.[16] was focussed on the treatment with DTPA of local contamination, and they studied the effect of intramuscularly injected DTPA on the migration and organ retention of intramuscularly injected ^{242}Cm. Seidel et al.[17] studied the effect of intraperitoneally injected DTPA on the organ retention of intravenously injected ^{242}Cm, as in the present experiment. However, their experiment was performed only in delayed treatment and with high DTPA dose.

In the present paper, with the object of contributing to the improvement of the current ICRP method of evaluation of radiation dose from internal curium and also to the development of a reasonable method of DTPA administration for the removal of internal curium from the body, the metabolism of curium and its removal with DTPA were studied using rats.

The behavior of curium in the body was first studied by Scott et al.[18] soon after the

Table 2 Annual Limits on Intake, ALI (Bq) for Isotopes of Curium[11]

Radionuclides	Route of entry	
	Oral	Inhalation
^{238}Cm	6×10^{8}	4×10^{7}
^{240}Cm	4×10^{6}	2×10^{4}
^{241}Cm	5×10^{7}	9×10^{5}
^{242}Cm	2×10^{6}	1×10^{4}
^{243}Cm	7×10^{4}	3×10^{2}
^{244}Cm	9×10^{4}	4×10^{2}
^{245}Cm	5×10^{4}	2×10^{2}
^{246}Cm	5×10^{4}	2×10^{2}
^{247}Cm	5×10^{4}	2×10^{2}
^{248}Cm	1×10^{4}	5×10^{1}
^{249}Cm	2×10^{9}	5×10^{8}

*2 For the masses of these "Limits", see the third column of **Table 1**.

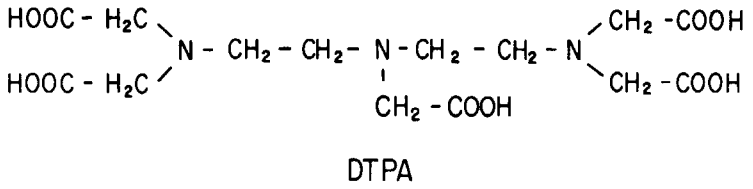

Fig. 1 Constitutional formula of diethylenetriaminepentaacetic acid (DTPA). For decorporation of radiometals from the body, the DTPA is used as trisodium calcium (or zinc) salt.

discovery of curium. They observed the tissue distribution and retention of intramuscularly injected curium (chloride) in the rat, and found that the curium absorbed from the injection site was predominantly deposited in the liver and skeleton. They also found that the curium deposited in the latter remained there for a long time. Thereafter, successive experiments on the metabolism of curium in mammals were performed in various laboratories using various kinds of animals. These results, most of them was compiled in the reviews by ICRP[19], Durbin[9] and Nenot et al.[20], have made contribution to the development of the current ICRP's metabolic model of curium which is used for the calculation of the internal radiation dose. It is quite reasonable that the main interest in these studies has been taken in the long-term behavior of curium in the body, because the curium incorporated into the body remains there for a long time and determination of the retention half-time in the organs such as liver or skeleton is an important factor for the evaluation of radiation dose from internal curium. In the present paper, to the contrary, early behavior of intravenously injected curium was studied in detail. As the results of the study, the initial distribution space (IDS), namely, the actual site corresponding to transfer compartment in the ICRP dose evaluation model[11], of systemic curium was identified as the extracellular fluid (ECF). In the ICRP model, the transfer compartment of all the elements is assumed to be quite homogeneously distributed in the total body. However, it is obvious that this assumption is an unrealistic one. The calculation showed that the difference between the radiation dose to bone surface or red bone marrow from short-lived curium isotopes evaluated under the current ICRP assumption, on one hand, and the same radiation dose, evaluated under the assumption that the actual site of transfer compartment is ECF, on the other, is not negligible. Furthermore, it was found, by comparing the metabolic data obtained in the present experiment with the literature values obtained under various experimental conditions, that the behavior of curium in the rat was virtually independent on whether the chemical form injected was citrate or simple salts such as chloride or nitrate. The knowledge should be useful when determining the biological parameters of curium for dose evaluation from the various metabolic data obtained under various experimental conditions.

A chelating agent, DTPA is a well-known agent for removing lanthanide or actinide radioelements from the body[21,22,23]. Therefore, it seems quite appropriate to apply this agent to the removal of curium from the body. In fact, as mentioned before, the experiments to enhance the excretion of curium from rats by DTPA administration were performed by Nenot et al.[16] and Seidel et al.[17]. Moreover, administrations of DTPA to humans who accidentally incorporated curium were also performed[13]. However, these observations were carried out under limited conditions. Therefore, in order to establish a reasonable method of DTPA administration for removing curium from the body, further research must be carried out. In the present paper, the effectiveness of DTPA to decrease the organ retention of intravenously injected curium was studied in rats by widely changing the time interval between curium injection and DTPA administration and by widely changing the amount of DTPA

administered. One of the disadvantages of DTPA as a decorporating agent is the elimination of essential metals from the body. Therefore, in order to avoid this deleterious side-effect of DTPA, the agent is usually administered as its calcium salt ($Na_3CaDTPA$)[24]. However, it was found by Catsch et al.[25,21] that zinc salt of DTPA ($Na_3ZnDTPA$) is less toxic than this calcium salt, and, according to a preliminary study by his group[17], efficacy of both the salts to remove curium from the body was almost equal. In the present study, the DTPA experiments mentioned above were performed for both the calcium salt and the zinc salt. From the results of the experiments, an effective and weakly toxic regimen of DTPA administration for removing curium from the body was derived.

In practice, humans may be exposed to mixtures of radionuclides. However, little work on the metabolism and removal of such mixtures from the body has been carried out. The method of evaluation of internal dose by ICRP assumes that any radionuclide incorporated into the body as mixture behaves there independently. In the present study, for verifying the ICRP's assumption mentioned above and for testing whether such radionuclide is removed by DTPA independently or not, the study when curium was accompanied by plutonium was also performed. As the result, it was found that the metabolism of these two elements and their removal with DTPA in rats were not influenced with each other.

2. Experimental

The animals used in this study were female albino rats of the Heiligenberg strain of about 3 months of age weighing from 180 to 200 g. Four or five rats per group were kept in one cage, with free access to "altromin" standard food pellets and tap water. ^{242}Cm (III) in 3 N HNO_3 ($\sim 3.7 \times 10^6$ Bq (= 100 μCi)/mℓ) was purchased from the Radiochemical Centre, Amersham, England. Before preparation of the injection solution of ^{242}Cm, ^{242}Cm was separated from its decay product, ^{238}Pu, by ion exchange chromatography. The purified ^{242}Cm solution was tested by α-spectrometry and found to contain less than 1% of ^{238}Pu activity (see **Fig. 2(a)**). Injection solution of ^{242}Cm was prepared in 1% trisodium citrate solution, neutralized with sodium bicarbonate powder, allowed to stand overnight, and ultrafiltered with Millipore filter (25 nm)[26]. Most of the rats were, under ether anaesthesia, injected with approx. 1.1×10^4 Bq (= 0.3 μCi) ^{242}Cm in 0.25 mℓ into the tail vein. However, the rats sacrificed 4, 8 or 16 days after the injection in the metabolic study were injected with approx. 7.4×10^4 Bq (= 2.0

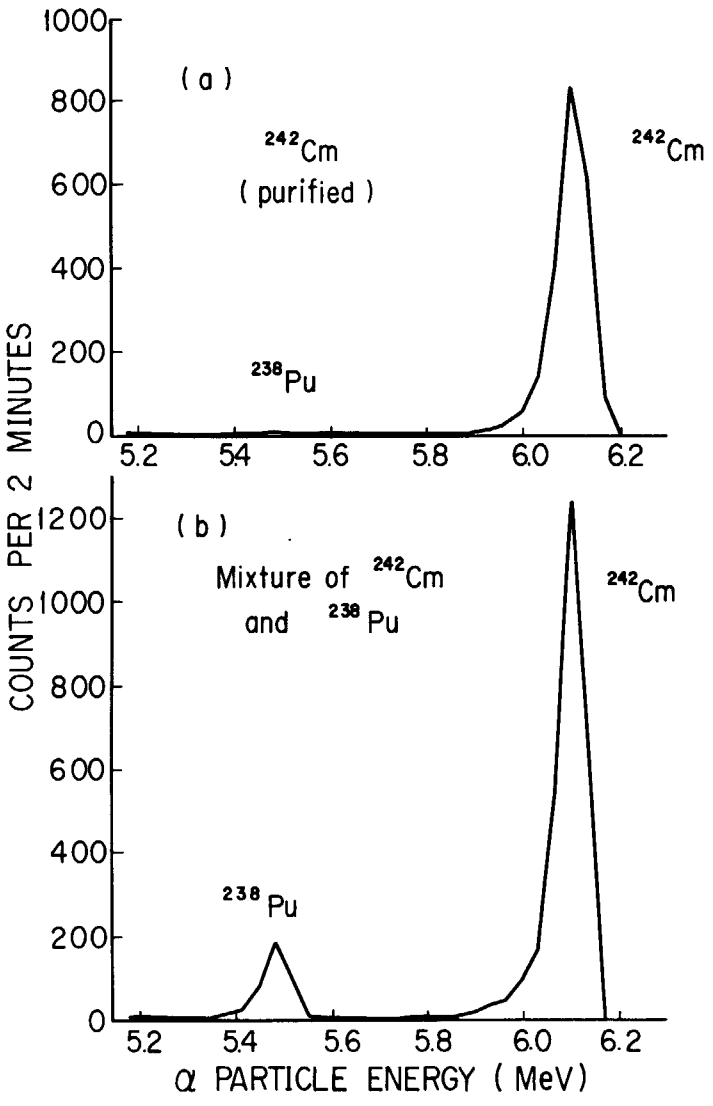

Fig. 2 Alpha-spectra of the ^{242}Cm and the mixture of ^{242}Cm and ^{238}Pu used.

μCi) in 0.25 mℓ. All the injections were performed in a few hours after the preparation of the solution. Sacrifice took place under ether anaesthesia by exsanguination. The blood (3-5 mℓ) was collected into a centrifuge tube, when the exsanguination was made by cutting the aorta with scissors. The plasma was obtained by ordinary centrifugation of the blood. Two parts of the plasma (each was 0.5 mℓ), the right femur*3, three parts of the liver (each was 0.2-0.4 g), and the right kidney*3 were collected into plastic vials, solubilized with 1 mℓ of 1 : 1 mixture solution of perchloric acid (70%) and hydrogen peroxide (30%), and their contents of ^{242}Cm were assayed by liquid scintillation counting[27]. The volume of the whole plasma was taken as 3% of the body weight[28]. The whole skeletal content of ^{242}Cm was estimated by multiplying the activity of one femur by 20. The validity of this factor was verified by Seidel for americium and californium, chemically analogous elements to curium, in rats[29]. The activity of ^{242}Cm in the liver was calculated by multiplying the radioactivity in the partial samples by the ratio of the weight of the whole organ to that of the samples.

As shown in **Table 1**, ^{242}Cm decays, emitting an alpha particle, to ^{238}Pu with half-life of 163 days. Therefore, an aged "^{242}Cm" inevitably contains ^{238}Pu in itself. The experiments on a mixture of curium and plutonium were performed using an aged "^{242}Cm". An alpha-ray spectrum of the aged "^{242}Cm" used is shown in **Fig. 2(b)**. Activity composition was 15% of ^{238}Pu and 85% of ^{242}Cm. The half-life of ^{238}Pu (87.7 years) is much longer than that of ^{242}Cm (163 days). Therefore, the mass ratio of ^{238}Pu to ^{242}Cm of the mixture is 34 : 1. The injection solution of the mixture was prepared in a similar manner as the ^{242}Cm injection solution described above and the same amount, 1.1×10^4 Bq (= 0.3 μCi)/0.25 mℓ, as that of the ^{242}Cm injection solution was injected into the tail vein.

In the study of metabolism, the contents of ^{242}Cm in the plasma, liver, skeleton and kidneys were determined at 22.5, 45 minutes, 1.5, 3, 6, 12 hours, 1, 2, 4, 8 and 16 days after the intravenous injection of ^{242}Cm citrate, and the contents of mixture of ^{242}Cm and ^{238}Pu in the same organs were determined at 22.5, 45 minutes, 1.5, 3, 6 hours, 1, 2, 4 and 8 days after the intravenous injection of mixture of ^{242}Cm and ^{238}Pu citrate.

$Na_3CaDTPA$ and $Na_3ZnDTPA$ were prepared from H_5DTPA, plus NaOH and $CaCl_2$ or ZnO. The concentrations of the solutions ranged from 2 to 200 μmole/mℓ (pH 7.4). Rats received intraperitoneal injection of 1 mℓ of chelate solution per 200 g body weight. The control rats were intraperitoneally injected with physiological saline. In the study of removal of ^{242}Cm with DTPA, A) the effect of time interval between ^{242}Cm injection and DTPA administration, and B) the effect of the amount of DTPA administered, on the retention of ^{242}Cm in organs were investigated. In experiment A), single intraperitoneal injection of 30 μmole of CaDTPA or ZnDTPA per kg body weight which corresponds to about 1.0 g for 70 kg human (= a dose recommended for human[23,24]) was given to rats at 1.5 minutes, 1.5 hours, 1, 2, 3 or 4 days after the intravenous injection of ^{242}Cm citrate. In experiment B), single intraperitoneal injection of 10, 30, 100 or 1000 μmole of CaDTPA or ZnDTPA per kg body weight was given to rats at 1.5 minutes or 1 day after the intravenous injection of ^{242}Cm citrate. In the study of removal of mixture of ^{242}Cm and ^{238}Pu with DTPA, C) the effect of the amount of DTPA administered and D) the effect of delayed and repeated administration of DTPA, on the retention of the mixture in organs were investigated. In experiment C), single intraperitoneal injection of 10, 30, 100, (300) or 1000 μmole of CaDTPA or ZnDTPA per kg body weight was given to rats at 1.5 minutes or 1 day after the intravenous injection of mixture of ^{242}Cm and ^{238}Pu citrate. In experiment D), six weekly intraperitoneal injections of 30 μmole of CaDTPA or ZnDTPA per kg body weight were given to rats at 4, 11, 18, 25, 32

*3 These samples were divided into two parts and taken into two vials separately.

and 39 days after the intravenous injection of mixture of ^{242}Cm and ^{238}Pu citrate. In all the experiments, the contents of ^{242}Cm, or mixture of ^{242}Cm and ^{238}Pu, in the organs were determined at 7 days after the DTPA administration*4, and compared with corresponding control values. This is because the effectiveness of singly administered DTPA to decrease the organ retention of americium, a chemically analogous element to curium, is sustained during about 7 days after its administration[30].

*4 In experiment D), the determination was made at 7 days after the last DTPA administration.

3. Results and Discussion

3.1 Metabolism

3.1.1 Curium

(1) Tissue Distribution and Retention

The contents of ^{242}Cm in the plasma following an intravenous injection of ^{242}Cm citrate to the rat are shown in **Fig. 3**, and those in the liver, skeleton and kidneys are shown in **Fig. 4**. As shown in **Fig. 3**, the intravenously injected ^{242}Cm disappeared from the plasma quite rapidly. For example, the plasma retention of the ^{242}Cm at 1.5 hours (= 0.063 days) post-injection was less than 1% of the injected dose. Turner and Taylor studied[31] the early clearance from the rat plasma of ^{242}Cm injected intravenously as nitrate and obtained the

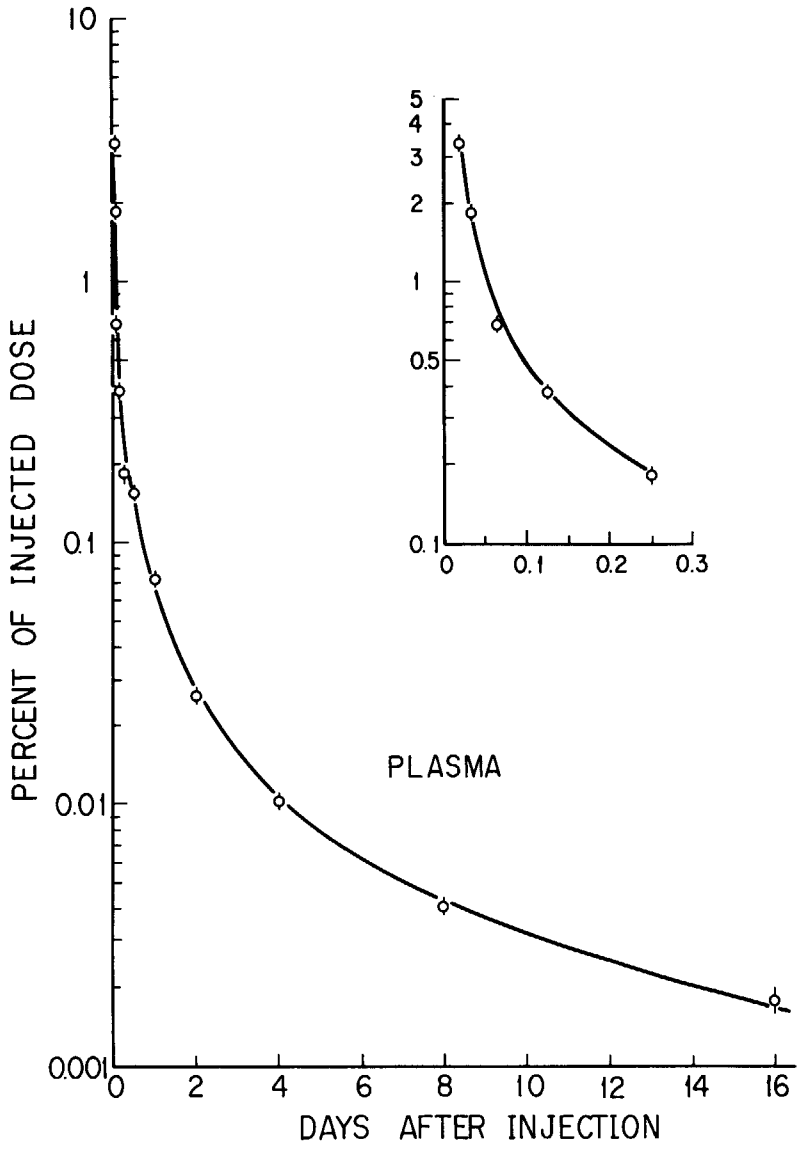

Fig. 3 The contents of ^{242}Cm in the plasma following an intravenous injection of ^{242}Cm citrate to the rat. Mean values and standard errors for groups of four to five animals.

similar results to the present ones. **Fig. 4** shows that the ^{242}Cm cleared from the plasma was deposited mainly in the liver and skeleton. The deposition of ^{242}Cm in the former was about 60% of injected dose, and that in the latter 20-25%. Although the contents of ^{242}Cm in the skeleton did not decrease within the observation period (16 days), the contents of ^{242}Cm in the liver, after reaching a maximum at 0.25-0.5 days postinjection, decreased with a half-time of 9.5 days. These results agree fairly well with the results obtained by Scott et al.[18] who observed the tissue distribution and retention of intramuscularly injected curium (chloride) in the rat from 1 to 256 days postinjection. According to their results, the deposition of curium in the liver and skeleton were 61 and 28% of the absorbed amount, respectively, and the half-time of disappearance from the former organ was 8.5 days. Semenov studied[32] the organ distribution of intravenously injected ^{244}Cm (chloride) in the rat. Although some longer retention of ^{244}Cm in the blood than the present ones was observed in his experiment, the deposition and retention of ^{244}Cm in the liver and skeleton were almost identical to the present ones. The results observed in rats by other authors, namely, the liver and skeletal contents of curium at 1 day after the intravenous injection of ^{242}Cm citrate[33], ^{242}Cm chlo-

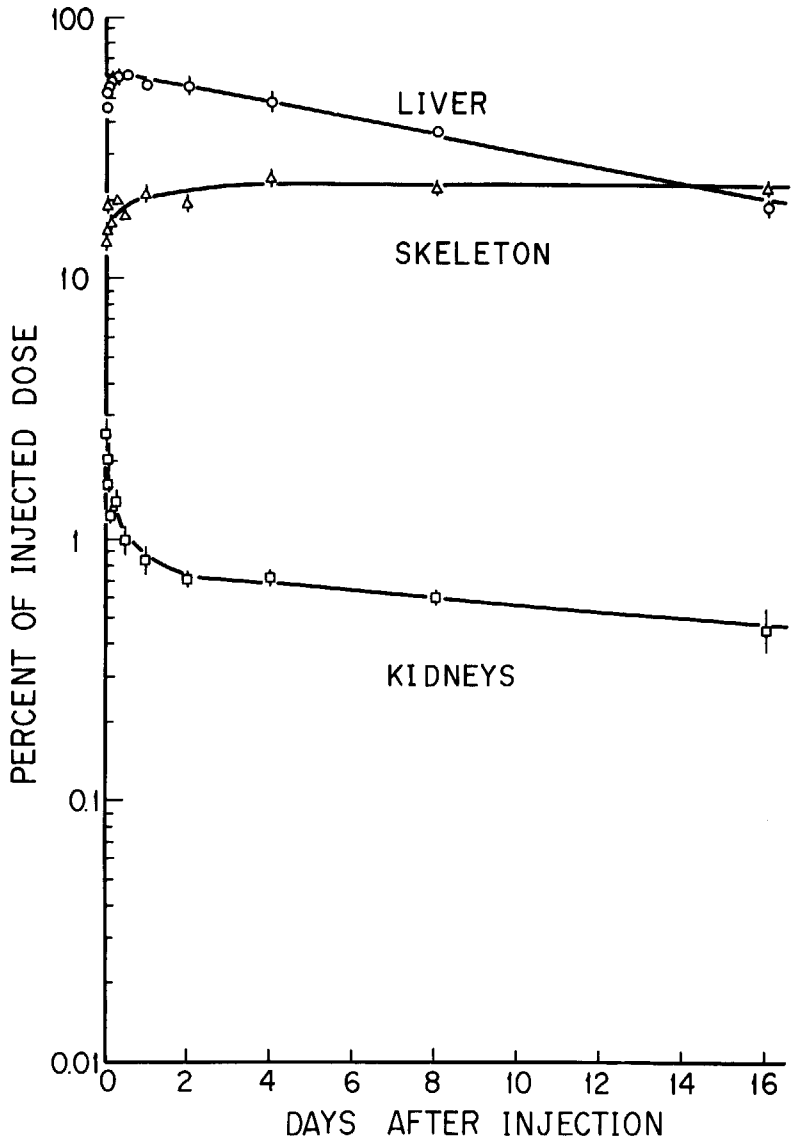

Fig. 4 The contents of ^{242}Cm in the liver, skeleton and kidneys following an intravenous injection of ^{242}Cm citrate to the rat. Mean values and standard errors for groups of four to five animals.

ride[33] or ^{242}Cm nitrate[16], or after the intramuscular injection of ^{242}Cm nitrate[16] also agree fairly well with the present ones. Taylor observed[19] a smaller deposition of curium in the liver and a larger deposition of curium in the skeleton than the present ones, after the intravenous injection of ^{242}Cm citrate to the rat. However, this seems to have resulted from the fact that young and probably male rats were used in his experiments[34], because the liver/skeleton uptake ratio of lanthanide or actinide elements is greatly influenced by the age and sex of the rats[35,36].

The results mentioned above indicate that the metabolism of curium injected intravenously as citrate is virtually identical to that injected intravenously as chloride or nitrate, and identical to that absorbed from the intramuscular site after the intramuscular injection as chloride. Many experiments of the metabolism of lanthanide or actinide elements in animals have been, as in the present ones, performed using citrate[19], because there has been a fear that some aggregation might occur in the blood after the intravenous injection of its simple salt. However, the above-mentioned comparison of the present data with the literature ones obtained under various experimental conditions shows that this might not be the case. The present author compared[37], using rats, the metabolic behavior of ^{144}Ce, one of the lanthanide elements which are chemically similar to actinide elements, injected intravenously as chloride with that of the ^{144}Ce absorbed slowly from the wound site after contamination as chloride, and found that the tissue distribution and excretion of both the ^{144}Ce was identical. This result also suggests that the formation of insoluble aggregate in the blood after the intravenous injection of simple salts of lanthanide or actinide is unlikely, if the mass injected is small enough as in the case of ^{144}Ce or curium referred here. Anyway, the knowledge that the metabolic behavior of systemic curium in the body is virtually independent on whether the chemical form injected is citrate or simple salts, should be useful when determining the biological parameters of curium for dose evaluation from the various metabolic data obtained under various experimental conditions.

The metabolism of curium has been studied in other animal species, too, as mentioned in Introduction. According to Lloyd et al.[38], the deposition of intravenously injected curium (citrate) in the liver and skeleton of beagles were 39.4 and 36.5% of injected dose at 6 days postinjection, and 34.4 and 42.7% of injected dose at 20 days postinjection, respectively. In beagles, the fraction of curium deposited in the skeleton was larger than that in rats, and the fraction deposited in the liver remained longer than that in rats. Recently, Lo Sasso et al. studied[39] the metabolic behavior of curium in baboons, and found that the deposition of intravenously injected curium (citrate) in the liver and skeleton were 20 and 70% of injected dose, respectively. It is surprising that the fractions of the curium deposited in the two organs were quite opposite to those in rats. The biological half-times for the retention of the curium in these two organs were 45 and 2500 days, respectively. The marked dependence of metabolism of curium on animal species shows the difficulty of estimation of metabolic parameter for human from the results of animal experiments. In the current metabolic model[11] of curium by ICRP, it is assumed that, of curium entering the transfer compartment, 0.45 is translocated to the liver and 0.45 to the skeleton. However, it is obvious, if the data shown above are taken into account, that these figures are not final ones. In order to obtain more reliable values, further studies including autopsy of curium-contaminated person must be performed.

(2) Initial Distribution Space (IDS)

For any radioelement, there has been no approach to identify the IDS, namely, the actual site of transfer compartment in the ICRP dose evaluation model. In the following, an analysis to identify the IDS of curium in rats was performed using the data mentioned above.

Hollins et al. could well describe[40] the time course of accumulation of intravenously injected plutonium (citrate) in rat organs by a kinetic model in which a constant fraction of the measured rate of loss of plutonium from the blood was used as the input term for the rate of uptake of plutonium by an organ. In their model, although the purpose of their study was not to identify the IDS of injected ^{239}Pu but to obtain a mathematical model to describe the metabolic data of ^{239}Pu, the blood is treated as the IDS or the actual site of transfer compartment in the ICRP dose evaluation model. Therefore, if the relationship between the disappearance of curium from the blood or plasma*5 and its accumulation in organs is described by their model, it can be said that the IDS of intravenously injected curium is the vascular space, like that of plutonium. However, as shown in **Fig. 3**, the disappearance of curium from the circulation is far more rapid than that of plutonium (see Section 3.1.2), and the retention of curium in the plasma decreases to virtually zero in relatively short time, while the accumulation of curium in the organ is still great. In fact, as shown in **Fig. 5**, the amount of curium which was taken up by the liver was greater than that lost from the plasma. It is obvious from this figure that the vascular space is not the IDS of intravenously injected curium. According to McClellan et al.[42], the plasma clearance of curium resembles that of calcium. Since the rapid diffusion of intravenously injected calcium into the extravascular space is well known[43], this suggests that curium may also be rapidly diffused into the extracellular fluid (ECF). Durbin compared, in her review[9], the tissue distribution of ^{45}Ca, ^{241}Am, ^{239}Pu and other radionuclides 5 minutes after intravenous injection in the rat, and suggested the high degree of leakage of trivalent actinide into the ECF. In the following, to determine whether the ECF is really the IDS of intravenously injected ^{242}Cm citrate or not, the relationship between the disappearance of curium from the ECF and its accumulation in the organs was analyzed by the revised model of Hollins et al., assuming that the intravenously injected ^{242}Cm citrate distributes homogeneously throughout the whole ECF in the body shortly after the injection, and that the concentration of ^{242}Cm in the plasma is identical to that in the whole ECF.

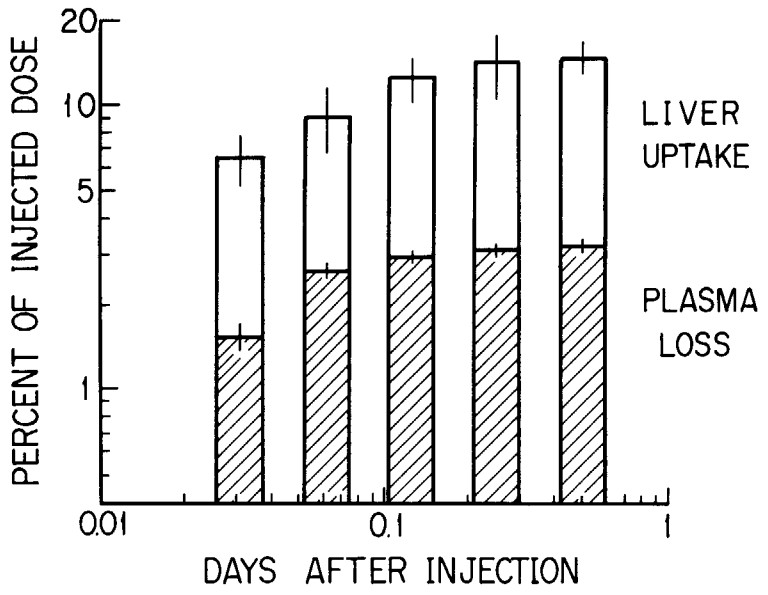

Fig. 5 Loss from the plasma and uptake by the liver of ^{242}Cm after 22.5 minutes (=0.0156 days) postinjection. Bars indicate standard errors.

*5 The transfer of intravenously injected curium to the blood cell is negligibly small[41]. Therefore, the contents of curium in the blood and in the plasma can be assumed to be equal.

Now, the amount of curium in an organ t days after a single intravenous injection, $Q(t)$, can be expressed as follows,

$$Q(t)=q_{ex}(t)+q_{in}(t) \tag{1}$$

where $q_{ex}(t)$ = the amount of curium in the ECF of the organ,
$q_{in}(t)$ = the amount of curium taken up by the cells of the organ,

and

$$q_{ex}(t)=f\cdot R_{ex}(t) \tag{2}$$

where f = the fraction of the total body ECF which is located in the organ,
$R_{ex}(t)$ = the retention of curium in the total volume of ECF in the body,

and

$$q_{in}(t)=\int_0^t -c\cdot\frac{dR_{ex}(s)}{ds}\cdot R(t-s)\,ds \tag{3}$$

where c = the fraction of the curium leaving the ECF that is transferred to the cells of the organ,
$R(t)$ = the retention of a single instantaneous uptake of unit amount of curium in the cells of the organ.

If the experimental data on the contents of curium in the ECF and organs are fitted by the relationships of equations (2), (3) and (1), the ECF can be regarded as the IDS of curium. However, because of markedly rapid initial clearance of curium from the circulation, an exact determination of the contents of curium in the plasma and organs in the very early postinjection time is very difficult. In the present experiment, the observation of organ contents started 22.5 minutes (= 0.0156 days) after injection. Therefore, the calculation of $q_{in}(t)$ was carried out not by equation (3) but by the following equation,

$$q_{in}(t)=q_{in}(t_0)\cdot R(t-t_0)+\int_{t_0}^t -c\cdot\frac{dR_{ex}(s)}{ds}\cdot R(t-s)ds, \qquad t>t_0 \tag{4}$$

where t_0 is the time when the observation began, namely, 22.5 minutes (= 0.0156 days). The first term in the right side of equation (4) shows the amount of curium in the cells of organ at the beginning of observation and its decrease with time. Change of equation (3) to equation (4) does not significantly affect the present purpose, because the amount of curium retained in the ECF at $t=t_0$ was large enough to permit analysis between the disappearance of curium from the ECF and its accumulation in organs.

The contents of ^{242}Cm in the liver and skeleton were calculated by equations (2), (4) and (1), using the experimentally derived equation for the retention of ^{242}Cm in the ECF:

$$R_{ex}(t)^{*6}=0.113e^{-0.138t}+2.41e^{-1.608t}+44.43e^{-44.10t} \quad (\%\text{ of injected dose}),$$

$$t>0.0156 \text{ days},$$

and other necessary values shown below (see Appendix),

$$f_{liver}=0.030$$
$$f_{skeleton}=0.055$$
$$R(t)_{liver}=e^{-(0.693/9.5)t}$$
$$R(t)_{skeleton}=1$$

*6 The equation was derived by multiplying the retention equation of ^{242}Cm in the plasma, which was obtained by the least-squares method from the experimental data shown in the previous section, by the volume ratio[44] of ECF to plasma, 7.43.

Retention of ^{242}Cm in the kidneys, $R(t)_{kidney}$, was too short, as shown in **Fig. 4**, to analyze the relationship between the disappearance of ^{242}Cm from the ECF and its accumulation in this organ. The analysis for the kidneys was, therefore, omitted.

The results calculated are presented graphically together with the observed values in **Fig. 6**. As shown in **Fig. 6**, the observed contents of ^{242}Cm in these organs are well fitted by the calculated ones, and therefore, it can be said from these results that the IDS of curium in rats is ECF. In these calculations, the values of c were chosen to fit best the calculated values to the observed ones. It should be noted that the values of c thus obtained, 0.68 ± 0.07 for the liver and 0.31 ± 0.07 for the skeleton, agree fairly well with the fractions of overall depositions*7 of ^{242}Cm in these organs: 0.63 ± 0.03 for the liver and 0.21 ± 0.03 for the skeleton, respectively, although the values of c were derived from the data only after 22.5 minutes (= 0.0156 days) postinjection and indicate the fractions of transfer only in this period.

(3) Dosimetric Meaning of Identification of IDS

In the foregoing section, the IDS of ^{242}Cm, namely, the actual site of transfer compartment of ^{242}Cm, was identified as the ECF. In this section, the dosimetric meaning of the result is discussed.

According to ICRP Publ. 30[11], the number of transformations of a radionuclide in an organ is the sum of two components: a) the number of transformations in the organ calculated from the metabolic model of the radionuclide, and b) a fraction (U_1) of the transformations in the transfer compartment, given by $U_1=(M/70000)\times U_{transfer}$, where M is the mass of the organ in grams, $U_{transfer}$ is the total number of transformations in the transfer compartment,

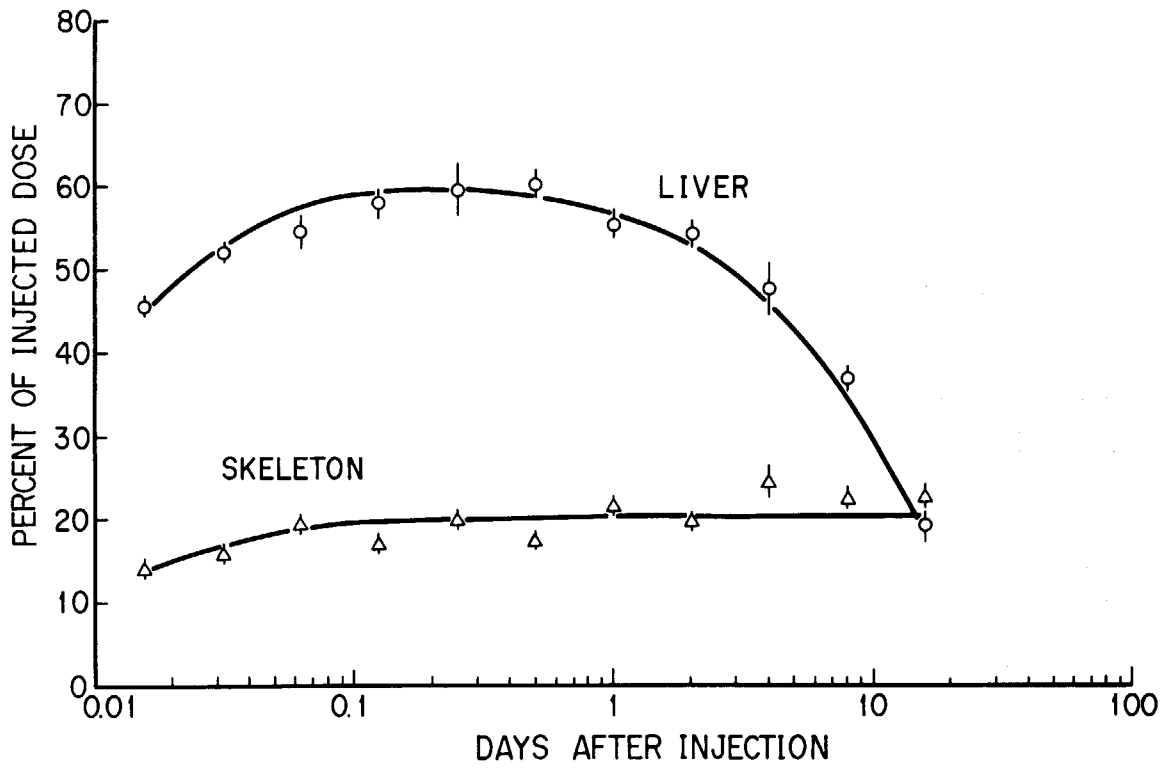

Fig. 6 The contents of ^{242}Cm in the liver and skeleton, fitted by the kinetic model. Open circle and triangle: observed data. Solid line: values calculated by the model.

*7 The overall depositions were obtained as the averages of the organ contents of ^{242}Cm observed from 1 to 16 days postinjection, in which the biological decay of the contents of ^{242}Cm in the liver was corrected.

and 70000 g is the mass of the whole body. It is clear from the equation shown above that, in the calculation of component b), the completely homogeneous distribution of the transfer compartment in the body is assumed. Therefore, for example, if the actual site of transfer compartment of the radionuclide is ECF, the component b) calculated by the above equation will be overestimated in an organ whose content of ECF is smaller than the mean content in the total body and underestimated in an organ whose ECF content is larger than that. As described above, the actual site of transfer compartment of curium is ECF. Then, how much does the radiation dose evaluated by the current ICRP assumption deviate from the one evaluated by assuming that the actual site of transfer compartment is ECF? The content of ECF in the liver is 24.6%[45], and is almost identical to that, 25.7%[45], in the total body. Therefore, the component b) for the liver evaluated by the two methods also is almost identical. No literature information can be obtained on the contents of ECF in the trabecular and cortical bones. However, the contents of total water in these bones are, according to ICRP Publ. 23[45], 23 and 15%, respectively. If the ratios of the amount of ECF to the amount of total water in these bones are presumed to be indetical to that (18000/ 42000 = 0.43) in the total body, the contents of ECF in these bones become 9.9 and 6.4%, respectively. Based on these values, the component b) for the trabecular and cortical bones were calculated, and shown in **Table 3** together with that for the liver. However, since the validity of the presumption made above is unknown, another components b) for the two bones also were calculated under the presumption that the total water in the bones was ECF, although it was very unlikely. The values thus obtained are shown in bracket in **Table 3**. In **Table 3**, the components

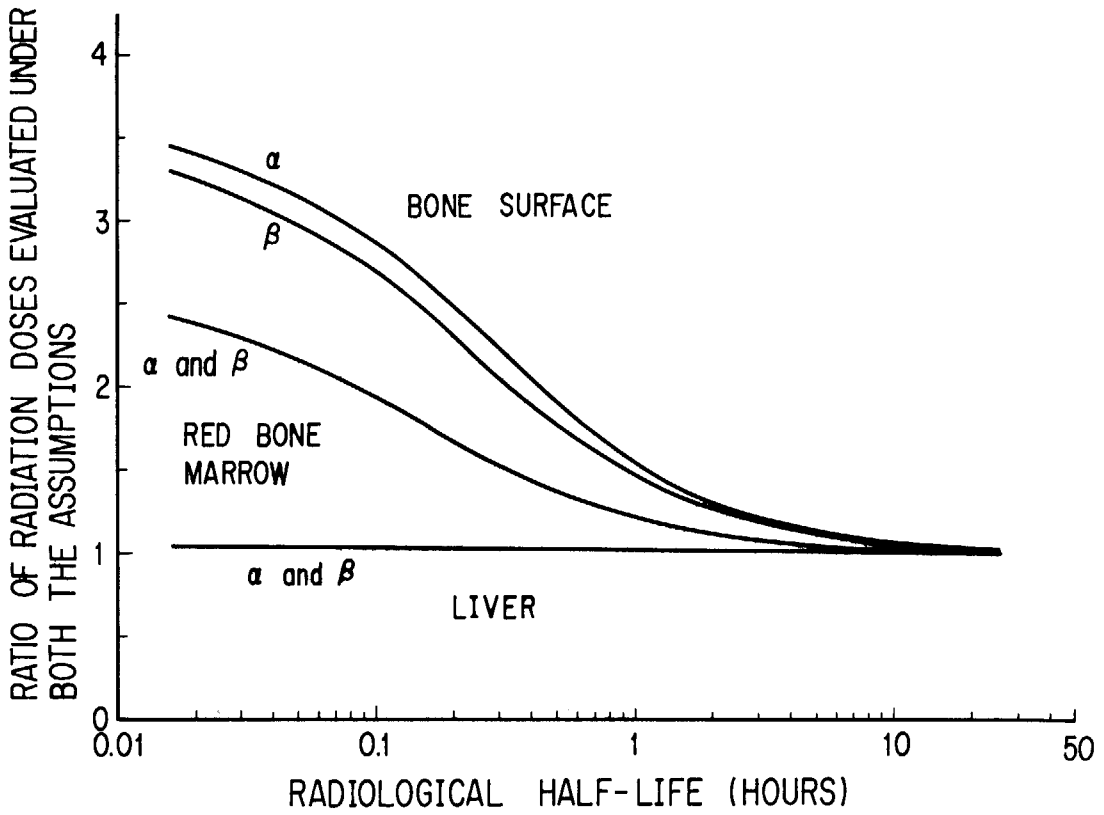

Fig. 7(a) The ratio of radiation dose evaluated under the current ICRP assumption to that evaluated under the assumption that the actual site of transfer compartment is ECF, as a function of radiological half-life of curium isotopes. The ratio of the amount of ECF to that of the total water in the bones was presumed to be identical to that in the total body. α and β indicate the kind of radiations emitted from curium isotopes.

b) calculated under the current ICRP assumption also are given. It is seen from **Table 3** that the components b) for the trabecular and cortical bones evaluated by the current ICRP assumption are 1.1-2.6 and 1.7-4.0 times overestimated. However, as described above, the

Table 3 A fraction (U_1) of the transformations in the transfer compartment (= component b)) for the liver, trabecular bone and cortical bone

Organ	Transfer compartment	
	ECF assumption	ICRP assumption
Liver	$0.0246 \times U_{transfer}$ [a]	$0.0257 \times U_{transfer}$
Trabecular bone	$0.0055 \times U_{transfer}$ ($0.0128 \times U_{transfer}$)[b]	$0.0143 \times U_{transfer}$
Cortical bone	$0.0143 \times U_{transfer}$ ($0.0333 \times U_{transfer}$)	$0.0571 \times U_{transfer}$

a The number of transformations in the transfer compartment. This number is identical in both the transfer compartments, because the half-time of disappearance of curium from both the transfer compartments is assumed to be identical.

b The value in bracket shows the component b) calculated under the presumption that the total water in the bones is ECF.

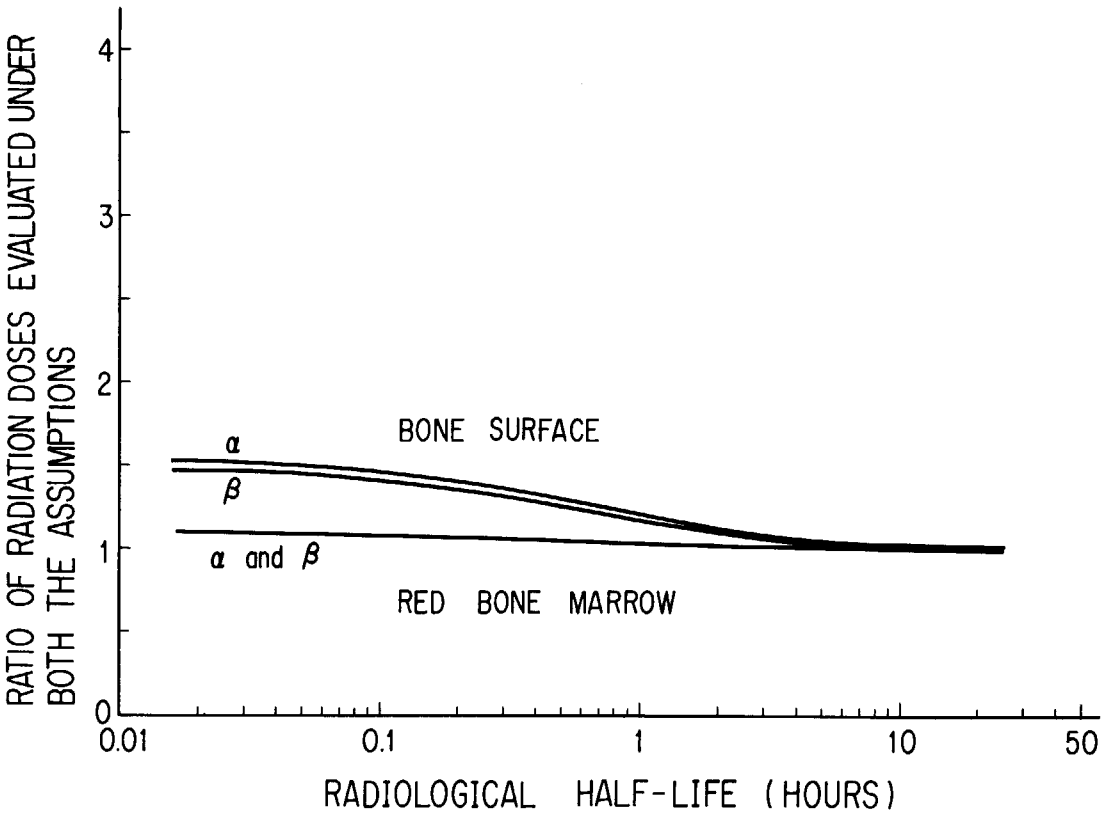

Fig. 7(b) The ratio of radiation dose evaluated under the current ICRP assumption to that evaluated under the assumption that the actual site of transfer compartment is ECF, as a function of radiological half-life of curium isotopes. The total water in the bones was presumed to be ECF. α and β indicate the kind of radiations emitted from curium isotopes.

radiation dose to organs is not only from component b), but also from component a). Therefore, the degree of overestimation must be examined by the radiation dose evaluated. The radiation doses from curium to bone surface, bone marrow and liver following a unit uptake were calculated[11], as a function of radiological half-life of curium isotopes, under the current ICRP assumption and under the assumption that the actual site of transfer compartment is ECF, in which curium isotopes were assumed to emit α or β particle only and have no daughters. Ratio of the former to the latter is shown in **Figs. 7(a)** and **(b)**. It is seen from the **Figs. 7(a)** and **(b)** that the radiation doses to bone surface or red bone marrow from short-lived curium isotopes evaluated under the current ICRP assumption are overestimated even under the unlikely presumption that the total water in the bones is ECF. These results show that difference of the radiation doses to these organs from short-lived curium isotopes evaluated under both the assumptions cannot be neglected.

The ratio between the radiation doses evaluated under the two assumptions, shown in **Fig. 7**, was calculated for the isotopes of curium. However, it also is valid for all the other

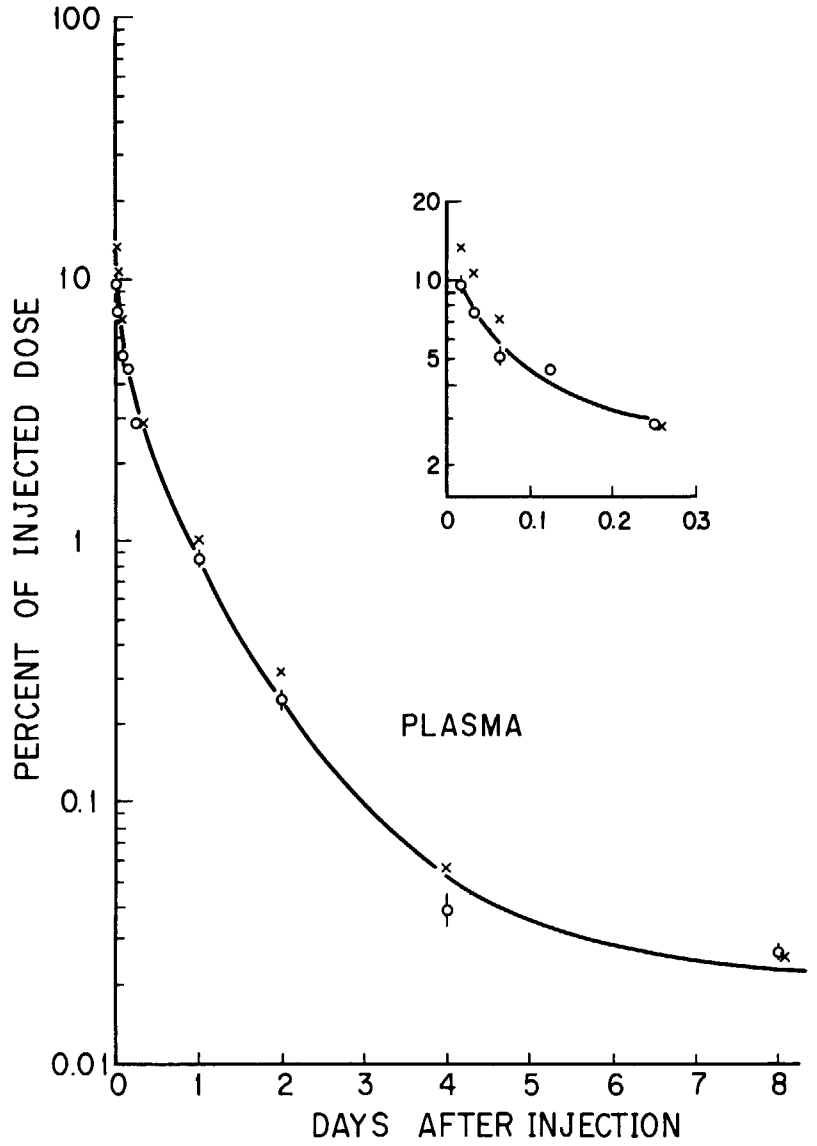

Fig. 8 The contents of mixture of ^{242}Cm and ^{238}Pu in the plasma following an intravenous injection of mixture of ^{242}Cm and ^{238}Pu citrate to the rat (open circle). Mean values and standard errors for groups of four to five animals. For the mark, ×, see the text.

transuranium elements whose IDS are ECF. As mentioned before, there has been no approach to identify the IDS of any radioelement including non-transuranium elements. It is hoped that the IDS of a radioelement whose short-lived isotopes are practically more important than those of curium will be identified.

3.1.2 Mixture of Curium and Plutonium

The contents of mixture of ^{242}Cm and ^{238}Pu in the plasma, liver, skeleton and kidneys following an intravenous injection of mixture of ^{242}Cm (85%) and ^{238}Pu (15%) citrate to the rat are shown in **Figs. 8** and **9**. The disappearance of the mixture from the plasma is slower than that of the ^{242}Cm. For example, the plasma retentions of the mixture and the ^{242}Cm at 1.5 hours (= 0.063 days) postinjection are 5.1 and 0.69% of injected dose, and those at 2 days postinjection are 0.25 and 0.026% of injected dose, respectively. Furthermore, the deposition of the mixture in the skeleton is somewhat larger but that in the liver is somewhat smaller than those of the ^{242}Cm. However, such different metabolism of the mixture from that of the ^{242}Cm can be expected, because curium and plutonium behave in the body fairly differently. Volf studied[46] the plasma clearance and organ deposition of intravenously injected ^{239}Pu citrate in the rat, in the same laboratory as the present experiment was performed. The experimental conditions, except for the kind of radionuclide, were identical to the present ones. Assuming that 15% of the total activity of the mixture was metabolized like the ^{239}Pu in Volf's study and the remaining 85% activity was metabolized like the ^{242}Cm mentioned above, the amounts of mixture in the plasma, liver, skeleton and kidneys following an intra-

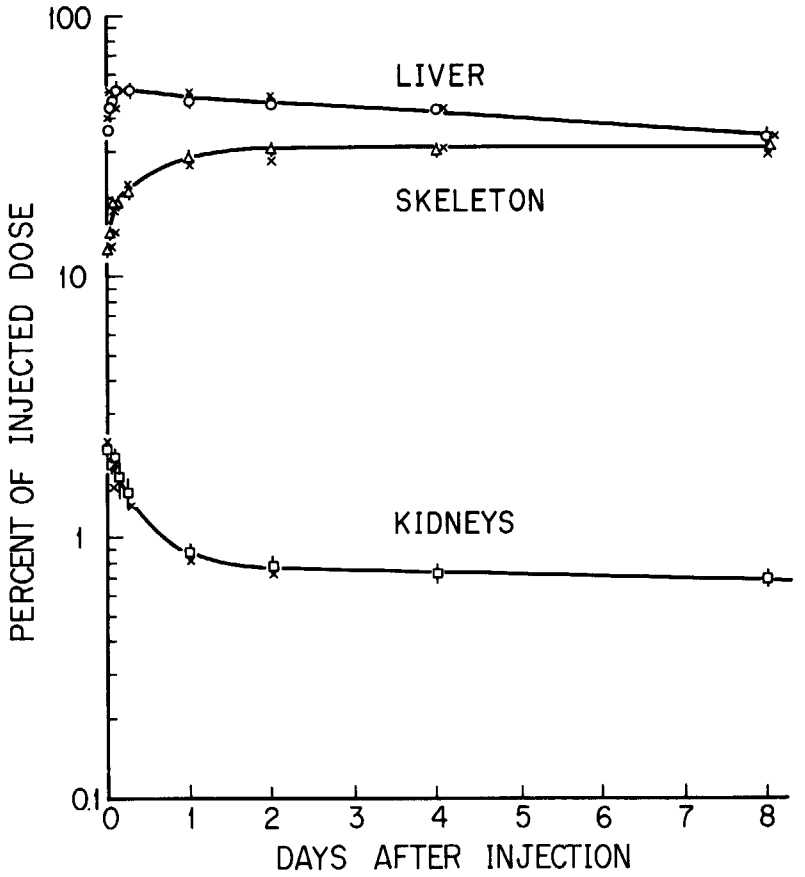

Fig. 9 The contents of mixture of ^{242}Cm and ^{238}Pu in the liver, skeleton and kidneys following an intravenous injection of mixture of ^{242}Cm and ^{238}Pu citrate to the rat (open marks). Mean values and standard errors for groups of four to five animals. For the mark, ×, see the text.

venous injection were calculated. The results are shown in **Figs. 8** and **9** by the mark, X. It can be seen from the figures that the calculated values agree fairly well with the observed ones. This result indicates that the curium and plutonium injected intravenously as mixture behaved in the body independently. Although detailed comparison of the experimental values with the calculated ones shows that the former are somewhat smaller in the plasma and liver, and somewhat larger in the skeleton than the latter, this also is a reasonable result, because the retention of lanthanide or actinide element in the plasma and liver tends to decrease and that in the skeleton tends to increase as the mass of the element adminstered decreases[47,48,49]. The amounts of plutonium administered in the present observation and Volf's one were 1.4×10^{-2} and 24 μg per kg body weight, respectively.

According to Nenot et al.[20], the retention of actinide elements in the lung after the inhalation of mixture of insoluble actinide elements is influenced by the species present in greatest mass and its chemical form. However, it is not surprising that the characteristic of the behavior of insoluble actinide elements deposited in the lung is different from that of soluble actinide elements incorporated into the blood. The present result gives a support for the ICRP assumption that the radionuclides incorporated into the body as mixture behave there independently.

3.2 Removal with DTPA

3.2.1 Curium

Nenot et al.[16] studied the effect of intramuscular injection of CaDTPA on the organ retention of intramuscularly injected ^{242}Cm (nitrate) in the rat. The purpose of their study

Table 4 The effect of the time-interval between ^{242}Cm injection (intravenous) and DTPA administration (intraperitoneal) on the retention of ^{242}Cm in the organs of the rat

Time of treatment	Treatment	Number of rats	Percent of injected dose[a]		
			Skeleton	Liver	Kidneys
1.5 min	NaCl	10	23.1 ± 0.7	38.2 ± 1.5	0.65 ± 0.04
	CaDTPA	5	4.9 ± 0.3	4.7 ± 0.7	0.16 ± 0.02
	ZnDTPA	4	8.8 ± 0.8	10.2 ± 1.5	0.21 ± 0.003
1.5 hr[b]	CaDTPA	4	14.1 ± 0.6	12.5 ± 1.0	0.33 ± 0.03
	ZnDTPA	4	17.2 ± 0.8	16.9 ± 0.8	0.38 ± 0.03
1 day	NaCl	10	22.1 ± 0.8	33.3 ± 1.7	0.59 ± 0.03
	CaDTPA	4	18.9 ± 0.8	17.4 ± 0.9	0.51 ± 0.03
	ZnDTPA	5	18.8 ± 1.1	15.3 ± 1.9	0.38 ± 0.02
2 days	NaCl	5	20.8 ± 0.6	22.2 ± 1.6	0.48 ± 0.04
	CaDTPA	5	14.4 ± 0.7	9.4 ± 1.1	0.35 ± 0.03
	ZnDTPA	5	15.8 ± 0.4	10.4 ± 0.6	0.36 ± 0.02
3 days	NaCl	5	18.0 ± 0.2	21.9 ± 1.9	0.51 ± 0.03
	CaDTPA	5	16.0 ± 0.8	10.6 ± 0.8	0.39 ± 0.03
	ZnDTPA	5	15.8 ± 0.7	11.7 ± 0.7	0.38 ± 0.03
4 days	NaCl	5	22.0 ± 0.6	26.9 ± 0.5	0.59 ± 0.02
	CaDTPA	5	18.8 ± 0.6	12.5 ± 0.5	0.40 ± 0.01
	ZnDTPA	5	21.2 ± 0.8	16.3 ± 1.5	0.38 ± 0.01

a Mean values and standard errors. The rats were sacrificed 7 days after DTPA administration.

b The rats treated with DTPA at 1.5 min and 1.5 hr after the ^{242}Cm injection were sacrificed on the same day and a common NaCl-treated control group was used with these two groups.

was to test the effectiveness of DTPA for removing ^{242}Cm contamination due to a wound. It was verified by their study that the ^{242}Cm in the body could be removed with DTPA. Seidel et al.[17] studied the effect of treatment of CaDTPA or ZnDTPA on the retention of intravenously injected ^{242}Cm (citrate) in the rat, and found that the effectiveness of both the chelates to decrease the ^{242}Cm retention was virtually identical. However, their study was performed only in delayed treatment and only with a high DTPA dose (1 mmole/kg body weight). In order to determine a reasonable method of DTPA administration for removing curium from the body, further study must be performed.

The effect of the time interval between the ^{242}Cm injection (intravenous) and DTPA administration (intraperitoneal) on the retention of ^{242}Cm in the organs of the rat (Experiment A) is shown in **Table 4**. Furthermore, these data have been expressed as percentage of the corresponding controls and plotted in **Fig. 10**. As shown in **Table 4** and **Fig. 10**, the retention of ^{242}Cm in all the organs observed was decreased by administration of DTPA. However, the effect of DTPA to decrease the organ retention of ^{242}Cm decreased rapidly as the time interval between ^{242}Cm injection and DTPA administration increased. Using ^{241}Am, a chemically analogous element to curium, Seidel observed[30] the similar decrease of DTPA effectiveness with increasing time interval between the radionuclide and DTPA injection. The rapid fall of effectiveness of DTPA with increasing time interval is, as pointed

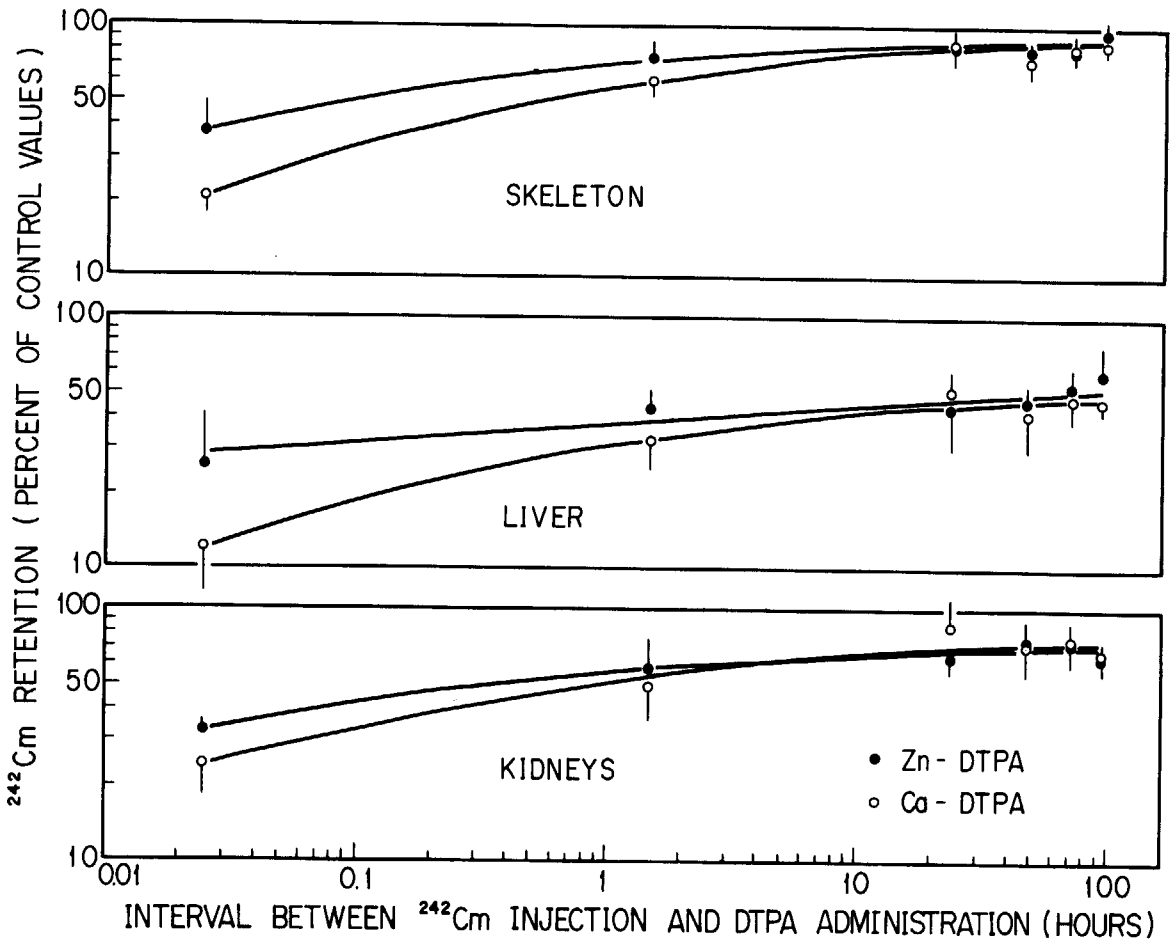

Fig. 10 The effect of the time-interval between ^{242}Cm injection (intravenous) and DTPA administration (30 μmole/kg body weight, intraperitoneal) on the retention of ^{242}Cm in the organs of the rat. The rats were sacrificed 7 days after DTPA administration. Mean values and standard errors for groups of four to five animals (for the sake of clarity, one-tailed standard errors are presented).

out[30] for ^{241}Am by Seidel, clearly associated with the rapid clearance of ^{242}Cm from the plasma or ECF mentioned in Section 3.1.1. According to Bohne et al.[44], the virtual distribution of systemically injected DTPA is restricted in the ECF. Furthermore, the curium deposited in organ cells is in a bound state[50], which is supposed to be more resistant to DTPA action than that in the ECF. However, the ^{242}Cm removed with DTPA is not only that remaining in the ECF when the DTPA is administered. Namely, some part of the ^{242}Cm already deposited in the cells of the organs when the DTPA is administered is also removed with DTPA. This can be seen from the fact that the amounts of ^{242}Cm removed from the skeleton and liver with the DTPA injected, for example, 1 day after ^{242}Cm injection were 3.2-3.3 and 15.9-18.0% of dose, respectively, in total 19.1-21.3% of dose (see **Table 4**), while at this time less than 1% of the ^{242}Cm injected remained in the ECF (see **3.1.1 (2)**). The removal with DTPA of the ^{242}Cm already deposited in the organ cells will be probably caused[21,30] by the disturbance with DTPA of equilibrium of distribution of ^{242}Cm between the organ cell and the ECF. However, some authors considered[51,52,53] that removal with DTPA of plutonium deposited in the liver was brought about by penetration of a small fraction of DTPA into the liver cell. The fact that the amount of plutonium removed with DTPA

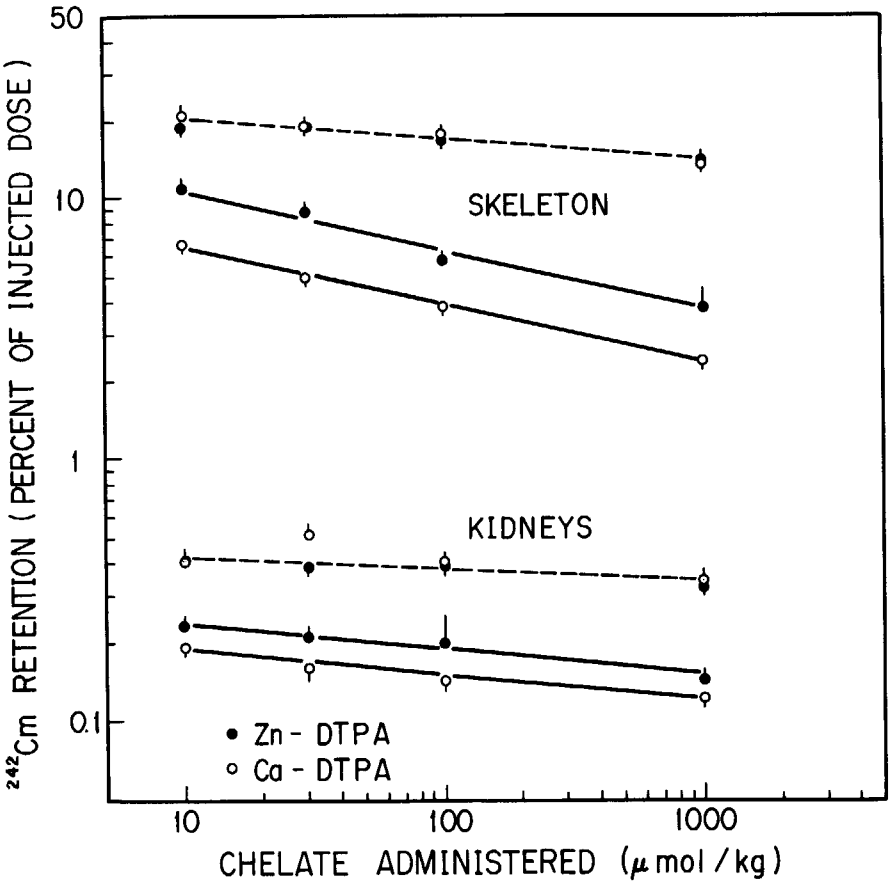

Fig. 11 The effect of the amount of DTPA administered on the retention of ^{242}Cm in the skeleton and kidneys of the rat. DTPAs were injected either 1.5 minutes (full line) or 24 hours (dashed line) after ^{242}Cm citrate. Rats were sacrificed 7 days after DTPA administration. Mean values and standard errors for groups of four to five animals (for the sake of clarity, one-tailed standard errors are presented). The ^{242}Cm retention in the skeleton of control rats on day 7 and 8 was 23.1± 0.7 and 22.1±0.8, respectively, that in the kidneys was 0.65±0.04 and 0.59±0.03, respectively (means ± standard errors from 9 and 10 animals).

from the liver is equal to that excreted via bile[54] supports this idea. The curium also may be removed from the liver by such a mechamism. As shown later, the slope of the dose-effectiveness curves for the liver is far steeper than that for the other organs (see **Figs. 11** and **12**). The mechanism of removal of ^{242}Cm with DTPA from the liver seems to be different from that from the other organs.

As shown in **Fig. 10**, effectiveness of Ca- and ZnDTPA was virtually identical when administered later than 1 day after ^{242}Cm injection. However, when the DTPA was administered earlier than this time, effectiveness of CaDTPA was greater than that of ZnDTPA.

According to Schubert[55], the effectiveness of a chelating agent (Ca or Zn salt) to remove a radiometal from the body, E, can be expressed by the following formula:

$$E=\frac{(M_1L)}{(M_1)}=\frac{K^{M_1}_{M_1L}(L)_{tot}}{K^{M_2}_{M_2L}(M_2)} \quad ,$$

where (M_1) = Concentration of a radiometal in the plasma or ECF,
(M_1L) = Concentration of a radiometal chelate in the plasma or ECF,
$(L)_{tot}$ = Total concentration of a chelating agent in the plasma or ECF,
(M_2) = Concentration of Ca or Zn ion in the plasma or ECF,
$K^{M_1}_{M_1L}$ = Stability constant of a radiometal chelate,
$K^{M_2}_{M_2L}$ = Stability constant of Ca or Zn chelate.

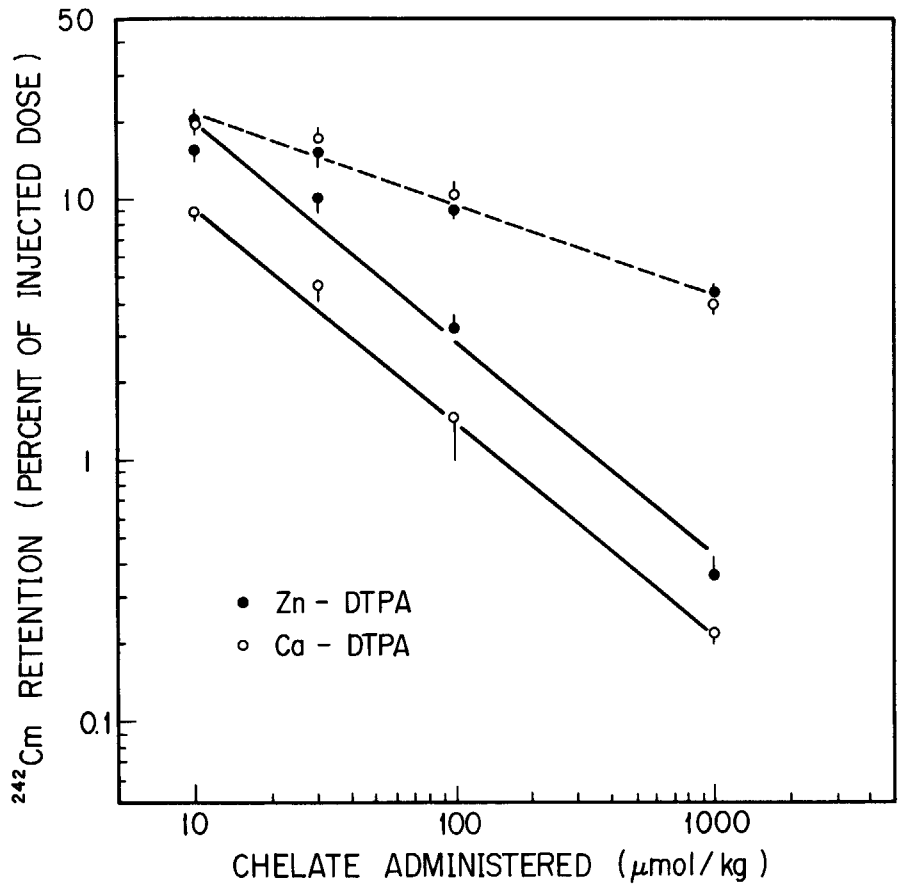

Fig. 12 The effect of the amount of DTPA administered on the retention of ^{242}Cm in the liver of the rat. The ^{242}Cm retention by control rats on days 7 and 8 was 38.2±1.5 and 33.3±1.7, respectively (means ± standard errors from 9 and 10 animals). See also the caption of **Fig. 11**.

The values relevant to the present case are as follows. The stability constants of Ca- and ZnDTPA, K^{Ca}_{CaDTPA} and K^{Zn}_{ZnDTPA}, are 10^{11} [56] and 10^{18} [56], respectively, and the concentration of calcium ion in the plasma is $\sim 10^{-3}$ mole/ℓ[57]. If the same amounts of Ca- and ZnDTPA respectively are administered, the total concentrations in the plasma or ECF of the two are the same, because their behaviors in the body are the same[44,58]. The values mentioned above mean that the concentration of Zn ion in the plasma must be equal to 10^{-10} moles/ℓ for the effectiveness of ZnDTPA to be equal to that of CaDTPA. The Zn ion concentration in the plasma can not be found in the literature. However, such an extremely low concentration of Zn ion in the plasma is very unlikely when the relatively high total (= free and protein-bound) concentration of Zn in the plasma, $1\text{-}2 \times 10^{-5}$ mole/ℓ[59], is taken into account. Therefore, the superiority of CaDTPA to ZnDTPA observed in the early treatment is not a surprising result. The reason why the difference in the effectiveness of both the chelates disappears when the administration is delayed is not yet known. However, according to Seidel[30] who, using ^{241}Am, obtained the similar result to the present one, this phenomenon is due to a "saturation" effect. He states "... in the case of rather low plasma concentration of ^{241}Am, i.e. $>$ 1 day, and with a high surplus of the chelate, the mobilized fraction of ^{241}Am will already be chelated by low DTPA dose. Thus, an increase in dosage does not lead to a correspondingly higher effect (see **Figs. 11** and **12**). Likewise, difference in the effectiveness of different chelates may be abolished. Such a "saturation" effect ..."[30]. His idea is based on the fact that the decrease of the slope of the dose-effect curves resulting from delayed treatment (see **Figs. 11** and **12**) is paralleled by a corresponding decrease of the relative effectiveness of CaDTPA to ZnDTPA. Mays et al., who studied the comparative effectiveness of Ca- and ZnDTPA in removing ^{241}Am from the dog more recently than the present DTPA study[60] was performed, proposed[53] another explanation for the similarity of effectiveness of Ca- and ZnDTPA in delayed treatment. They say "... cells can engulf extracellular material and fluid by the process of pinocytosis. Pinocytosis occurs in all cells, ... Once inside the cell, the DTPA may remain for days. This gives abundant time for the calcium in CaDTPA to be replaced by other metals, such as zinc, and this may account for the similarity in effectiveness of CaDTPA and ZnDTPA ..."[53]. Although the real reason is not yet known, this result, firstly found by Seidel on ^{241}Am in rats, has an important practical meaning for the removal of ^{242}Cm from the body, too, because, except the first CaDTPA administered within a day after ^{242}Cm incorporation all the other CaDTPA administered thereafter can be replaced by the less toxic ZnDTPA without decrease of the effectiveness.

The effect of the amount of DTPA on the retention of ^{242}Cm in the organs of the rat is shown in **Figs. 11** and **12**. Calcium or zinc salt of DTPA was injected 1.5 minutes (full line) or 24 hours (dashed line) after ^{242}Cm injection. The contents of ^{242}Cm in all the organs decreased as the amount of DTPA increased, although the amount of decrease depended on the organ studied and on the time of chelate treatment. The relationships between the amounts of chelate administered and those of the ^{242}Cm retained in the organs can be fitted by a power function, and in all the organs observed, the slope of the curves in delayed treatment was less steeper than that in prompt one. The idea of "saturation" effect proposed by Seidel is, as mentioned above, based on this decrease of the slope of the dose-effect curve in delayed treatment. Since there is no significant difference between the slopes of the curves obtained for CaDTPA and ZnDTPA, the so-called relative potency[21] (i.e., the ratio of equally effective ZnDTPA/CaDTPA molar quantities in removing ^{242}Cm) at a specific time can be expressed by a single value for the whole dose range studied (**Table 5**). It is notable that, irrespective of the kind of chelate and time of treatment, the slopes of the curves characterizing the liver retention are much steeper than those for the other two organs, suggesting, as described

Table 5 Ratio of equally effective ZnDTPA and CaDTPA molar quantities in removing ^{242}Cm from the rat

	Skeleton	Liver	Kidneys
ZnDTPA/CaDTPA[a]	9.5 (8.5–10.5)	2.3 (1.7–3.3)	11.9 (10.8–13.2)

a Calculation of the molar ratios is based on data presented in **Figs. 11** and **12**; values in bracket indicate the fiducial limits (P=0.05). Single DTPA injections were administered 1.5 min after ^{242}Cm citrate.

before, a peculiar mechanism of removal of ^{242}Cm with DTPA from this organ.

The practical implications of the present experiment can be summarized as follows. The effect of chelate therapy depends decisively on the time interval between ^{242}Cm incorporation and DTPA administration. Therefore, the treatment with DTPA of a person who has incorporated curium into the body should be initiated as early as possible. The relative potency of Ca- and ZnDTPA indicates that early after incorporation of ^{242}Cm approximately 10 times the molar amount of DTPA would be necessary, when using ZnDTPA instead of CaDTPA, to remove an equal fraction of ^{242}Cm from the skeleton and kidneys, while about twice as much ZnDTPA would be sufficient to remove ^{242}Cm from the liver. However, the superiority of CaDTPA to ZnDTPA is transient, and the effect of both the chelates in delayed treatment is virtually identical, which suggest preferenital use of CaDTPA for the first treatment after incorporation of ^{242}Cm, while for the prolonged therapy CaDTPA should be replaced by the less toxic ZnDTPA. Since the dependence of chelate effectiveness on the administered amount is much more pronounced early after incorporation of ^{242}Cm, the dose of the first CaDTPA should be as high as possible within the range not producing its side effect.

3.2.2 Mixture of Curium and Plutonium

The effect of the amount of Ca- and ZnDTPA on the retention of mixture of ^{242}Cm and ^{238}Pu in the organs of the rat is shown in **Figs. 13** and **14**. On the whole, the content of the mixture in the skeleton after DTPA treatment was somewhat larger than that of the ^{242}Cm mentioned above and that in the liver was somewhat smaller than that of the ^{242}Cm, reflecting those in the control rats. However, difference of the organ contents of the mixture after Ca- and ZnDTPA treatments was larger than that in the case of the ^{242}Cm, as especially seen in prompt treatment. Volf studied[61] the effect of amount of Ca- and ZnDTPA on the organ retention of ^{239}Pu in the rat, and found that the effectiveness of ZnDTPA administered 1.5 minutes after ^{239}Pu intravenous injection in decreasing the organ contents of ^{239}Pu was much smaller than that of CaDTPA. Furthermore, according to his results, the relationship between the amount of chelate and the content of ^{239}Pu in the liver and skeleton could not be fitted by a power function. The results obtained in the present experiment, therefore, can be expected if it is assumed that the ^{238}Pu contained in the mixture responded to DTPA as ^{239}Pu. Assuming that 15% of the total activity of the mixture responded to DTPA like the ^{239}Pu in Volf's study and the remaining 85% activity like the ^{242}Cm mentioned above, the amounts of mixture in the liver, skeleton and kidneys after the prompt DTPA treatment were calculated, and plotted by the mark, X, in **Figs. 13** and **14**. The values calculated agree well with those observed, except those in the liver. This indicates that curium and plutonium responded to DTPA independently. The reason why the observed contents of mixture in the liver was somewhat smaller than that of the calculated ones might be explained by the assumption that the smaller mass of actinide element tends to be more easily removed from the liver with DTPA than the

larger one, as shown for a chemically similar lanthanide element[62,48]. As described before, the ratio of the amount of plutonium injected in Volf's experiment to that in the present one is ca. 1700.

In the foregoing experiments, the effect of singly administered DTPA on the organ retention of ^{242}Cm or mixture of ^{242}Cm and ^{238}Pu was studied. However, in the actual treatment of contaminated person with DTPA, the drug is repeatedly administered to obtain as large effect as possible. As already described, the results obtained on ^{242}Cm in the present experiment that the difference of effectiveness of Ca- and ZnDTPA disappears when the treatment is delayed are practically very important, because all the CaDTPA administered for the treatment of curium-contaminated person can be replaced by the less toxic ZnDTPA except that administered on the first day. However, when the delayed treatment is repeated, whether the decrease of ^{242}Cm content of the organ by treatment with ZnDTPA is really identical with that with CaDTPA has not yet been confirmed. In experiment D), the comparative effectiveness of Ca- and ZnDTPA in removing mixture of ^{242}Cm and ^{238}Pu from the rat organs after the delayed and multiple administration of the chelates was studied. Three groups of rats were intra-

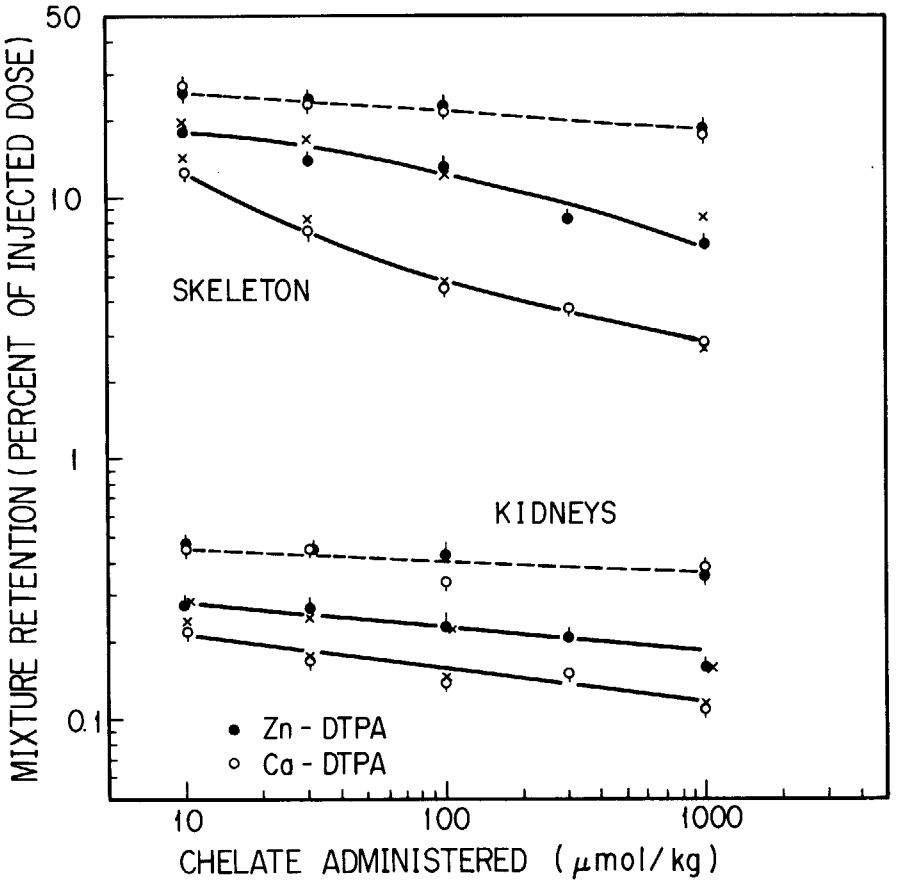

Fig. 13 The effect of the amount of DTPA administered on the retention of mixture of ^{242}Cm and ^{238}Pu in the skeleton and kidneys of the rat. DTPAs were injected either 1.5 minutes (full line) or 24 hours (dashed line) after ^{242}Cm citrate. Rats were sacrificed 7 days after DTPA administration. Mean values and standard errors for groups of four to five animals (for the sake of clarity, one-tailed standard errors are presented). The mixture retention in the skeleton of control rats on days 7 and 8 was 30.4±0.7 and 29.0±1.0, respectively, that in the kidneys was 0.71±0.04 and 0.63±0.03, respectively (means ± standard errors from 25 and 10 animals). For the mark, ×, see the text.

peritoneally administered saline, CaDTPA or ZnDTPA, 6 times, once a week, starting at 4 days after intravenous injection of mixture of ^{242}Cm and ^{238}Pu citrate to the rat, and the contents of the mixture in the skeleton, liver and kidneys 7 days after the last DTPA administration, namely, at 46 days after the intravenous injection of mixture of ^{242}Cm and ^{238}Pu, were determined. The results are shown in **Table 6**. The contents of mixture of ^{242}Cm and ^{238}Pu in the organs observed were clearly decreased by the multiple administration of Ca- or ZnDTPA. The ratios of the contents in the liver, skeleton and kidneys to the corresponding

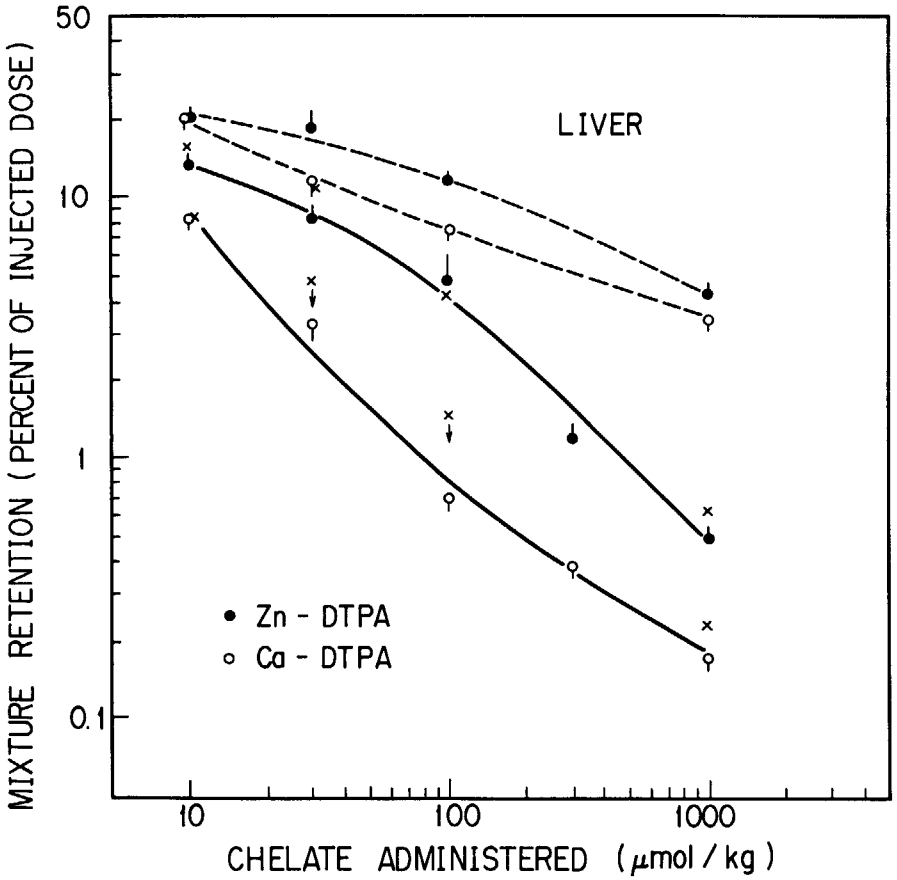

Fig. 14 The effect of the amount of DTPA administered on the retention of mixture of ^{242}Cm and ^{238}Pu in the liver of the rat. The mixture retention by control rats on days 7 and 8 was 31.9±0.6 and 30.5± 1.0, respectively (mean ± standard errors from 25 and 10 animals). See also the caption of **Fig. 13**.

Table 6 The effect of delayed and repeated administration of Ca- or ZnDTPA on the retention of mixture of ^{242}Cm and ^{238}Pu in the organs of the rat

Treatment	Number of rats	Percent of injected dose[a]		
		Skeleton	Liver	Kidneys
NaCl	6	27.6 ± 1.1	3.27 ± 0.37	0.28 ± 0.02
CaDTPA	7	17.8 ± 0.8	0.72 ± 0.08	0.15 ± 0.02
ZnDTPA	7	18.7 ± 0.4	0.73 ± 0.04	0.11 ± 0.01

a Mean values and standard errors. The rats were sacrificed 7 days after the last DTPA administration, namely, 46 days after the injection of mixture of ^{242}Cm and ^{238}Pu.

control values are 0.22 ± 0.04, 0.65 ± 0.04 and 0.54 ± 0.08 with CaDTPA, and 0.22 ± 0.03, 0.68 ± 0.03 and 0.39 ± 0.05 with ZnDTPA, respectively. In order to compare the effectiveness of Ca- and ZnDTPA, significance of difference of the contents of mixture in the organs after Ca- and ZnDTPA treatment was tested by t-test, and it was proved that the difference is insignificant ($p = 0.05$). These results show that the effectiveness of Ca- and ZnDTPA to remove the mixture of ^{242}Cm and ^{238}Pu from the rat organs is identical when the agents are multiply administered in delayed time.

4. Conclusion

(Metabolism)

(1) The ^{242}Cm injected intravenously to the rat as citrate disappeared from the circulation very rapidly and deposited mainly in the liver and skeleton. The amounts of deposition to these organs were about 60 and 20-25 percent of injected dose, respectively. Although the contents of ^{242}Cm deposited in the skeleton did not decrease during the observation period (16 days), that in the liver decreased with a half-time of 9.5 days. These data agreed fairly well with those obtained by other authors who intravenously injected curium to the rat as chloride or nitrate, and who intramuscularly injected curium chloride to the rat (absorbed fraction).

(2) The relationship between the disappearance from the plasma and the accumulation in the liver or skeleton of intravenously injected ^{242}Cm citrate was well described by a kinetic model assuming that the intravenously injected curium citrate distributes homogeneously throughout the whole ECF in the body shortly after the injection, and that a constant fraction of the rate of loss of curium from the ECF is taken up by the organ. From this result, the initial distribution space (IDS), or the actual site of transfer compartment used for dose calculation in the ICRP Publ. 30, of curium was identified as the ECF.

(3) The calculation showed that the difference between the radiation dose to bone surface or red bone marrow from short-lived curium isotopes evaluated under the current ICRP assumption, on one hand, and the same radiation dose, evaluated under the assumption that the actual site of transfer compartment is ECF, on the other, is not negligible.

(4) The ^{242}Cm and ^{238}Pu injected intravenously to the rat as mixture were metabolized in the body independently.

(Removal)

(1) The effectiveness of Ca- and ZnDTPA to remove the ^{242}Cm from the rat decreased rapidly as the time interval between ^{242}Cm injection and DTPA administration increased.

(2) When DTPA was administered early (within 1 day after ^{242}Cm injection), CaDTPA was superior to ZnDTPA in effectiveness of decreasing ^{242}Cm from the organs, but when the administration was delayed (after 1 day after ^{242}Cm injection), the effectiveness of both the chelates was virtually identical.

(3) The retention of ^{242}Cm in the organs decreased as the amount of DTPA administered increased. The slope of the dose-effectiveness curve in the early treatment was steeper than that in the delayed one.

(4) The results mentioned above show that, 1) the DTPA-treatment of a person who has incorporated curium into the body should be started as early as possible, 2) the first single prompt DTPA should be administered as Ca salt, and the following multiple delayed DTPA, as the less toxic Zn salt, 3) the dose of first CaDTPA should be as large as possible within the range not producing its side effect.

(5) The ^{242}Cm and ^{238}Pu injected intravenously to the rat as mixture were removed from the body with DTPA independently.

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Appendix

1. Estimation of *f* for the liver and skeleton

(1) f_{liver}

The content of ECF in the liver of the rat is 24.6% of the organ weight[45]. In the present experiment, when the dissection was made, 3-5 mℓ of the blood were drawn from the body and undetermined amount of blood was lost from the liver by washing with saline. Therefore, this loss of ECF from the liver must be corrected. According to Durbin et al.[63], the plasma content of the rat liver is 0.188 mℓ/g. If it is assumed that half the plasma of the liver was lost by dissection,

$$f_{liver} = \frac{(0.246 - 0.188 \times 0.5) \times 8.28}{190 \times 0.223} = 0.030$$

where 8.28 and 190 are the average weights (g) of the liver and the total body of the present rats, and 0.223 is a content of ECF in the total body of the present rats[44].

(2) $f_{skeleton}$

Data on the amount of ECF in the skeleton can not be found in the literature. However, the total water content of the fresh femur (bone + bone marrow) of the rat is 34.6%[64]. If the ratio of the amount of ECF to the amount of total water in the femur is assumed to be identical to that (18000/42000 = 0.43) in the total body of reference man[45], the content of ECF in the femur becomes 14.9%. The weight of the whole skeleton of the present rat was estimated to be 15.5 g by multiplying 190 g (the total body weight of the present rat) by the ratio of the weight of skeleton (20.4 g) to the total body weight (250 g) of S-D rats[63,65]. On these assumptions,

$$f_{skeleton} = \frac{15.5 \times 0.149}{190 \times 0.223} = 0.055 \ .$$

2. Estimation of *R(t)* for the liver and skeleton

(1) $R(t)_{liver}$

The determination of true $R(t)_{liver}$ is very difficult. In the present study, as in the case by Hollins and Storr, it was estimated from the descending part of the ^{242}Cm retention curve for the organ after intravenous injection. If the retention of a radionuclide in the cells of the organ is long enough as compared with that in the ECF, the value of $R(t)$ estimated in this way will be a reasonable one.

The liver content of curium from 0.5 to 16 days postinjection decreased with time single-exponentially with a half-time of 9.5 days, where the half-time was calculated by the least-squares method. The retention of a single instantaneous uptake of unit amount of curium in the cells of the liver was assumed as

$$R(t)_{liver} = e^{-(0.693/9.5)t}.$$

(2) $R(t)_{skeleton}$

The amount of curium once deposited in the skeleton did not decrease during the whole experimental period. Consequently, $R(t)_{skeleton}$ was assumed as 1.