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Durbin, Patricia W.

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METABOLISM AND BIOLOGICAL EFFECTS OF
THE TRANSPLUTONIUM ELEMENTS*

Patricia W. Durbin

November 11, 1972

Donner Laboratory and the Division of Biology and Medicine, Lawrence
Berkeley Laboratory, University of California, Berkeley, 94720

Chapter for

HANDBOOK OF EXPERIMENTAL PHARMACOLOGY

Volume on Uranium, Plutonium and Transplutonium Elements

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I. Introduction

The transplutonium elements (SEABORG et al., 1949 a, b) -- formed from plutonium by sequential neutron captures and beta-particle decays -- are among the most hazardous by-products of nuclear power generation (E.D. ARNOLD, 1970). In his preliminary reports of the first biological studies with americium and curium, HAMILTON (1947, 1948) pointed out the potential dangers of the actinide elements; "They share the radioactive and metabolic characteristics of radium -- alpha-particle emission, long physical half-lives, and selective deposition in and prolonged retention in the skeleton." When these experiments were begun in 1946 (SCOTT et al., 1948a, 1949), only a few milligrams of americium and curium existed. They were scientific curiosities, and the time when they might be serious biological problems seemed very remote.

A. Americium and curium in power reactor wastes

Scarcely 10 years later (1957) pilot-model nuclear power plants were generating electricity. Anticipating the problems that would arise in the management of reactor wastes, and based on the projections of nuclear power development at that time, E.D. ARNOLD (1957) calculated that the U.S. inventory of americium and curium in the year A.D. 2000 would be about 300 kg.*

Large, water-cooled, uranium-fueled, power reactors are now being designed with thermal power ratings up to 3120 MW (PIGFORD, 1971); and reactors fueled with mixtures of uranium and plutonium, the so-called fast-breeder reactors, are being designed or are under construction in the United States

* E.D. ARNOLD's (1957) estimate assumed construction in the United States alone of 1000 nuclear reactors fueled with natural uranium (slightly enriched with ^{235}U), each operating at a thermal power level of 700 MW.

and the Soviet Union (GILLETTE, 1971). SEABORG (1968) estimates that production of separated americium and curium isotopes in the United States alone will be about 300 kg/yr by A.D. 1980 -- more than 20 times E.D. ARNOLD's prediction made 11 years before. If nuclear power development proceeds according to present plans, total production of americium and curium isotopes in the next 25 years will be measurable in metric tons, and hundreds of megacuries of these elements will have to be processed for recycling or storage.

B. Production of berkelium, californium, and einsteinium

As long as accelerators were the sole source of the transplutonium elements of atomic number 97 and greater (see Chapter 16 of this volume), the small amounts in existence were not of general biological concern. However, the world's supply of these heavier elements has also risen in recent years, and will continue to soar, as high-flux isotope reactors (HFIR) become fully operative* (KELLER, JR., 1967; SEABORG, 1968). At the Oak Ridge National Laboratory, the HFIR and its adjacent chemical processing facility alone, have the capacity to make and purify annually, grams of californium, hundreds of milligrams of berkelium, and milligrams of einsteinium. Elements 97 and greater are hard to contain and handle. Weight for weight, they are many times more dangerous -- both as external and internal radiation sources -- than plutonium, americium, or curium (DENHAM, 1969). They have higher specific activities, higher rates of spontaneous fission, and a large number of

*In addition to the HFIR, at least three other reactors were producing or were planning to produce transplutonium elements as of 1966: plutonium production reactors at Savannah River, U.S.; the BR-2 reactor at Mol, Belgium; and the EL3 reactor at Saclay, France (KELLER, JR., 1967).

the disintegrations are accompanied by ejection of energetic photons (see Table 1, Chapter 17 of this volume).

C. Practical applications of transplutonium isotopes

Several of the transplutonium isotopes possess special radiation and radioactive decay characteristics that make them especially suitable as self-contained thermoelectric power units (KALLFELZ et al., 1970), neutron sources (BUSHONG et al., 1970; OLIVER, 1971), and long-lived sources of monoenergetic photons (CAMERON, 1970). See also SEABORG (1968) and Chapter 21 of this volume. Production in the near future of large amounts of transplutonium isotopes and the eventual widespread use of some of them in radiation and power sources create the potential for accidental contamination even outside of controlled areas.

II. Chemical and biological similarities of the actinides and lanthanides

Before the transuranium elements were synthesized, chemistry textbooks showed a simple filling of the $6d$ shell of electrons in the elements of atomic number 89 through 92. The very stable (III) state exhibited by elements 95 (americium) and 96 (curium), along with other chemical evidence, convinced SEABORG (1944, 1945, 1946) of the existence of an actinide series (with filling of the $5f$ subshell) analogous in valence electron configuration to the lanthanide series (in which 14 electrons are added to the $4f$ subshell).

A. Similarities due to a common (III) valence state

The f electrons do not participate in bond formation. Thus, the lanthanide elements and the actinide elements beginning with americium exhibit a principle (III) state.* The common (III) state confers a general uniformity

* MALY et al. (1968) found that the most stable state of element 102, nobelium, is (II).

upon the biological behavior of these two groups of elements. The general features of the metabolism of yttrium, the lightweight lanthanides, and americium and curium, namely, low absorption with deposition principally in the liver and skeleton, were established in tracer studies with rats (HAMILTON, 1947, 1948; SCOTT et al., 1948a, 1949). HAMILTON (1948) was immediately impressed "by the fact that actinium, americium, and curium behave in an almost indistinguishable manner from the lanthanide rare earths."

B. Differences related to atomic size

Filling of the f shells is accompanied by a slow contraction of atomic dimensions (GOLDSCHMIDT et al., 1925; ZACHARIASEN, 1954; TEMPLETON and DAUBEN, 1954; PETERSON, 1967) which leads, as the atomic number increases, to diminished hydrolysis of aqueous ions, greater solubility of compounds, and greater stability of complex ions (MARTELL and CALVIN, 1952; EYRING, 1964; SILLEN and MARTELL, 1964; see also Chapter 17 of this volume).

Although the individual distribution patterns of all the lanthanides in the rat are generally similar, they are not identical (DURBIN et al., 1956). There is a regular shift in the initial distribution pattern, which appears to be related to ionic size (DURBIN, 1962). Liver deposition is high and skeletal deposition low for the lightweight lanthanides of larger ionic radius (cerium through gadolinium); whereas, skeletal deposition is high and liver deposition is low for the heavier lanthanides of smaller ionic size (terbium through lutetium). The initial partitions of americium and curium between liver and skeleton are closer to those of the lanthanides of comparable ionic radius than to the distributions of the lanthanides with the same number of f electrons (DURBIN, 1962).

C. Biology of the actinides related to both chemistry and radiation

The movement of the actinide elements in biological systems, that is,

their absorption into, distribution within, and elimination from organisms, is determined by their chemistry; but their biological effects are caused by radiation damage rather than chemical interactions. All of the transplutonium isotopes are radioactive, and with a few rare exceptions their physical half-lives are shorter than that of ^{239}Pu (24,360 yr). Thus, they all have very high specific activities,* and the mass required to produce demonstrable biological effects is usually too small to be weighed. For this reason units of radioactivity, microcuries (μCi), and concentrations of radioactivity, microcuries per gram of tissue ($\mu\text{Ci/g}$), will be used throughout this chapter.

Nearly all of the isotopes of the transplutonium elements decay with the emission of alpha-particles or by spontaneous fission (see Table 2 of Chapter 17, this volume). The radiation doses to tissue are largely from these densely ionizing particles. The high levels of radiation damage inflicted by even small amounts of these elements make it difficult to study their metabolism uncomplicated by radiation effects.

III. Interactions of multicharged cations with life forms other than mammals

The bulk of information about the biology of the transplutonium elements deals with their behavior in a few laboratory mammals. For the time being, their transfer from the environment into food chains and their behavior in living creatures other than mammals must be inferred from what is known of the biology of chemically similar elements, specifically yttrium, the lanthanides, and plutonium.

* In this chapter "specific activity" is defined as radioactive intensity per unit weight of element (Ci/g), and is the inverse of the mass per curie term shown in Table 2 of Chapter 17 of this volume.

A. Data sources on plutonium and lanthanide biology

There is a substantial body of data on the biology of the lanthanides, both stable and radioactive; and since its discovery in the 1940's, ^{239}Pu has been under constant investigation, because of its importance as a nuclear energy source. (See Chapters 10 and 11 of this volume.)

STEIDLE (1935) summarized the early biological and pharmacological studies of the lanthanide elements. More recent investigations have been reviewed by KYKER (1962). These elements have no known function in living systems, and although they are abundant in nature, they appear to be excluded from most organisms. Indeed, yttrium and the lanthanides are present in organisms in such small amounts, that until the recent development of very sensitive analytical chemical methods (GOFMAN et al., 1961; KAMEDA, 1962) their presence went largely undetected.

Unfortunately, the classical pharmacological and toxicological studies of the lanthanides reviewed by STEIDLE (1935) and KYKER (1962) are not especially suitable for predicting the biological behavior of the actinides. The mean lethal dose at 30 days ($\text{LD}_{50/30}$) of several stable lanthanides in mammalia (COCHRAN et al., 1950) and amphibia (STEIDLE, 1935) is about 100 to 300 mg/kg (simple salts injected intraperitoneally). Solutions of 0.0015M CeCl_3 are lethal to protozoa (STEIDLE, 1935). These toxic effects appear to be due to at least two mechanisms: (a) changes in pH resulting from hydrolysis of lanthanide ions, and (b) reactions with proteins, such as chelation, conjugation, and coagulation.

On the other hand, as was pointed out above, the toxicity of actinide isotopes with high specific activity is due to radiation. The mass of actinide associated with an acutely lethal radiation dose is exceedingly small.

The $LD_{50/30}$ in the rat of ^{241}Am , the longest-lived readily-available actinide isotope, is 110 $\mu\text{Ci/kg}$ — only 32 $\mu\text{g/kg}$ (ZALIKIN et al., 1968). Thus the mass of ^{241}Am associated with a lethal radiation dose is 0.003 to 0.009 of the mass of the $LD_{50/30}$ of the stable lanthanides. The radiation dose rate in a solution of 0.0015M ^{241}Am is 240 rad/min — sufficient to deliver a lethal dose to small, suspended organisms in a few minutes. Therefore, the following sections on the uptake and distribution of lanthanide radioisotopes by various organisms were considered more appropriate to the actinide case.

Many radioactive isotopes of yttrium and of the lightweight lanthanides are created in nuclear fission, and they account for about one-half of the fission-product radioactivity (PLUTONIUM PROJECT, 1946). Thus, reactor wastes and nuclear test debris contain large quantities of high-specific-activity isotopes of several trivalent elements, which are easily detectable because of their radioactivity. International concern about the consequences of radioactive fallout from nuclear weapons tests engendered the many studies of the occurrence of fission products in a variety of organisms and environments. Much of this information has been collected in reviews and conference proceedings (U.S. CONGRESS, 1957, 1959; UNITED NATIONS, 1958; SCHULTZ and KLEMENT, 1961; HUNGATE, 1965; NELSON and EVANS, 1967; NATIONAL RESEARCH COUNCIL, 1971).

B. Microorganisms

Many microorganisms assimilate trivalent elements during growth. RICHARDS and TROUTMAN (1940) found that yeasts accumulated lanthanum. G. T. JOHNSON and KYKER (1960) studied the uptake of ^{144}Ce by pure cultures of yeasts, molds, and bacteria. Significant ^{144}Ce uptake was found in all cultures in which adequate growth was obtained, and those of two bacteria, one yeast, and five molds each accumulated more than 85% of the added ^{144}Ce during 4 to 10 days of growth.

C. Algae

Many algae concentrate multicharged cations, often achieving concentrations 2000 to 4000 times that in the suspending medium (RICE, 1961). Radioisotopes of lanthanum and cerium have been detected in freshwater algae collected from the Columbia River near discharge points of the Hanford reactors (DAVIS et al., 1958); and radioisotopes of yttrium, cerium, and plutonium from fallout have been found in marine algae collected in the Gulf of Mexico (SIMEK et al., 1967) and near the Rongelap, Eniwetok, and Bikini atolls (HELD, 1961; WELANDER, 1967).

At the pH of natural waters, multicharged cations tend to hydrolyze, to aggregate, and to be adsorbed onto particulates. Fallout radioactivities have been shown to be largely associated with particulates (GREENSDALE and BALLOU, 1954). Most of the ^{90}Y and ^{144}Ce associated with algae, appear to be inside cells (RICE, 1961; SIMEK et al., 1967), and ZLOBIN and MOKANER (1970) suggest that assimilation of plutonium (and presumably chemically similar elements also) by algae involves active transport of colloidal particles. RICE (1961) demonstrated that several algae accumulated ^{90}Y more efficiently in the colloidal form than in the ionic.

D. Seaweeds and lichens

Fallout ^{144}Ce has been identified as the principle gamma-emitting radio-nuclide not only in seaweeds harvested from such widely separated locations as the Black Sea (GLAZUNOV et al., 1963) and the Gulf of Mexico (SHELBY, 1963) but also in lichens harvested from granite outcrops in the high rainfall region of the Georgia, U.S. piedmont (PLUMMER, 1967). Only small amounts of the ^{144}Ce could be washed from the lichens, leading PLUMMER (1967) to conclude that most of the ^{144}Ce had been assimilated into the cells.

E. Plants

Uptake by plants of ^{241}Am , ^{242}Cm , ^{239}Pu , and radioisotopes of several lanthanides has been studied under a variety of growth conditions. Multi-charged cations are excluded from plants (MENZEL, 1965). When soluble ^{241}Am was uniformly mixed with well-fertilized soil, uptake in soybean stems and leaves was 0.003% (WALLACE, 1972). Bean plants grown in loam soil took up 0.07% of ^{242}Cm (W.A. THOMAS and JACOBS, 1969).

Accumulation by a species varies with the element in the order: yttrium > cerium, americium, curium > plutonium. The quantities taken up by bean plants grown in nutrient solutions or clay suspensions were: ^{91}Y , 0.104% and ^{144}Ce , 0.03% (JACOBSON and OVERSTREET, 1948); ^{242}Cm , 0.03% (W.A. THOMAS and JACOBS, 1969); ^{239}Pu (IV), 0.002% and ^{239}Pu (III), 0.00045% (JACOBSON and OVERSTREET, 1948).

Accumulation in plants varies not only with species but also in the different parts of the plant; the uptake of ^{144}Ce is in the order: roots > leaves > stems > fruit > seeds (JACOBSON and OVERSTREET, 1948).

Increased availability of ^{239}Pu for assimilation by plants with continually developing root structures has been demonstrated. ROMNEY et al. (1970) found progressively larger amounts of ^{239}Pu in successive croppings of Ladino clover or alfalfa grown in soil contaminated with fallout particles.

WALLACE (1972) demonstrated that some of the ^{241}Am deposited in shoots and leaves of bush beans was translocated to new growth after plants grown in labeled soil were transplanted into uncontaminated soil.

Plants grown in highly contaminated soils (0.2 $\mu\text{Ci/g}$ soil of either ^{90}Y or ^{144}Ce) assimilated sufficient amounts to produce direct radiation injury of roots and indirect injury of tops, presumably because of impairment of water and nutrient transport (JACOBSON and OVERSTREET, 1948).

Plant uptake of ^{239}Pu and ^{241}Am can be changed by treatment of the soil. Assimilation of ^{239}Pu by oat plants was slightly increased by addition of nitrate and phosphorus fertilizers (CUMMINGS and BANKERT, 1971). Addition to the soil of the chelating agent, diethylenetriaminepentaacetic acid (DTPA), increased ^{241}Am uptake by soybeans to 25 times control values (WALLACE, 1972), and increased ^{239}Pu uptake by alfalfa to four times control values (ROMNEY et al., 1970).

F. Aquatic invertebrates

As predicted by RICE (1961), lanthanide radioisotopes and ^{239}Pu have been detected most frequently in filter-feeding and bottom-feeding marine invertebrates. Six years after the last nuclear tests at Eniwetok and Bikini atolls, the combined concentrations of ^{144}Ce and ^{155}Eu in marine invertebrates were 6.2 to 6.7 pCi/g dry weight — about 20% of the concentrations in algae and phytoplankton, their chief sources of food (WELANDER, 1967). Four years after the fallout accident at Rongelap atoll, bottom-feeding holothurians and marine snails still contained detectable amounts of lanthanide radionuclides and ^{239}Pu (HELD, 1961). Several pelecypod species were collected in 1963-64 from the lower Trent and Neuse rivers of eastern North Carolina (WOLFE and SCHELSKE, 1967). Samples were taken over a 30-mile range with salinities varying from 0.1 to 15‰. In all species sampled from all locations, ^{144}Ce contributed more than half of the detectable gamma-ray activity.

Lanthanide radioisotopes are also assimilated into the tissues of aquatic invertebrates directly from water. GONG et al. (1956) incubated a species of clam in labeled sea water. Lanthanide radioisotopes continued to accumulate in soft tissues over a 6-day period attaining concentrations as much as 280 times that of the water. KHMELEVA (1962) demonstrated tissue uptake of

^{144}Ce and ^{91}Y from water by an amphipod (Gammarus lacustris O. Sars.). Uptake was depressed by addition of the chelating agent, ethylenediaminetetraacetic acid (EDTA), to the water.

ZESENKO (1966) measured the uptake of ^{144}Ce and ^{91}Y from sea water by a species of crab (Carcinus maenas) and a species of mollusc (Mytilus galloprovincialis). The tissue distribution data are summarized in Table 1. The large amounts of these lanthanides found in the gill, shell, and byssus of the mollusc are more likely the result of surface phenomena than metabolic activity.

G. Fish

Stable lanthanide elements have been detected in fish. Using neutron activation analysis, KAMEDA (1962) detected lanthanum in concentrations of 0.1 to 10 parts per million (ppm) in bones, scales, gills, and fins and in concentrations of 0.001 to 0.01 ppm in organs and muscle. Other lanthanides found (praseodymium, samarium, europium, dysprosium, and holmium) were located most frequently in bony structures.

Lanthanide isotopes have not been detected in fish taken from the Columbia river below the Hanford reactor outfall (DAVIS et al., 1958), nor were they detectable in fish caught at Eniwetok or Bikini atolls 4 to 6 years after cessation of nuclear testing (WELANDER, 1967), nor in fish caught at Rongelap atoll 4 years after the fallout accident (HELD, 1961). However, ^{239}Pu , which has a much longer radioactive half-life than any lanthanide fission product, was present in all fish taken at Bikini and Eniwetok atolls at levels of 1 to 7 pCi/g dry weight (WELANDER, 1967).

Cerium-144 has been measured in tissues of the nonmigratory thornback ray (Raja clavata) taken from the Irish Sea near the Windscale reactor waste disposal area (MAUCHLINE and TAYLOR, 1964). These rays live their entire

lives in the presence of a nearly constant concentration of fission products. They feed chiefly on small crustaceans, and, as noted in the preceeding section, these bottom-feeding, filter-feeding invertebrates can accumulate significant amounts of lanthanide isotopes from both diet and water. The ^{144}Ce concentration of the gastrointestinal contents in the rays was 11 pCi/g wet weight. Tissue concentrations ranged from 0.04 pCi/g in flesh to 0.14 pCi/g in liver. The concentration in skin was high, 2.2 pCi/g, but some of this may have been related to surface phenomena. If the average tissue concentration is taken to be 0.07 pCi/g and the gastrointestinal tract and contents constitute 5% of the body weight, gastrointestinal absorption can be estimated to be about 3% of ingested ^{144}Ce .

PROSSER et al. (1946) studied the uptake of fission products by non-feeding goldfish. Lanthanide isotopes were taken up by gill and oral membranes, transported by the blood, and accumulated in viscera and in new or regenerating bone. BOROUGHS et al. (1956) administered ^{91}Y orally to a small marine fish (Tilapia mossambica); about 2% of the dose was absorbed by the gastrointestinal tract. Two weeks later the viscera contained 43% of the absorbed dose; and muscle, skeleton, and gills and integument contained 29, 16, and 12% of the dose, respectively. Based on the 2-week observation period, the biological half-life of ^{91}Y in the whole body was about 30 days.

IVANOV (1966) studied the effect of several radioisotopes on the development of fish eggs. Isotopes of cerium, yttrium, and iron accumulated on the egg surfaces. Chromosome aberrations and developmental anomalies in the embryos were observed and were related to both the radiation dose and the youth of the embryos at the start of radiation.

H. Insects

Radioisotopes of cerium and lanthanum were present in insect larvae collected from the Columbia River downstream from the Hanford reactors (DAVIS et al., 1958), and VOLKOVA (1963) reported that dragonfly larvae "like other aquatic insect larvae" accumulated ^{144}Ce . However, neither report makes clear whether the isotopes were assimilated into larval tissues or were present in the digestive tracts.

The toxicity of ^{239}Pu has been demonstrated in adult wasps (Habrobracon juglandis). Virgin adult female wasps were fed ^{239}Pu in a single meal of a citric acid-sugar solution (ERDMAN, 1962). An oral dose of 0.11 to 0.14 μCi /wasp was lethal to all test hosts in 8 days. Lower doses induced temporary sterility (0.04 μCi /wasp) and reduced fecundity (0.02 μCi /wasp). Chromosome damage was observed in germ cells, and some ^{239}Pu was found in eggs at all three dose levels. These results are reported to be comparable to the results with x-irradiation or ingestion of beta-particle emitters.

I. Birds

DAVIS et al. (1958) were not able to detect lanthanide radioisotopes in ducks taken from the environs of the Columbia river near the Hanford reactors. Neither lanthanide radioisotopes nor ^{239}Pu were found in sea birds caught at Eniwetok or Bikini atolls (WELANDER, 1967). However, both ^{144}Ce and ^{239}Pu were present in significant amounts on bird skin and feathers, presumably because these birds "dust bathe" in the contaminated top soil. Cerium-144 was found in the tissues of ptarmigan (Lagopus lagopus) and squaw ducks (Clangula hyemalis) caught in Alaska in 1959, in amounts equal to those of ^{90}Sr (DAVIS et al., 1961).

MRAZ et al. (1964) conducted a laboratory investigation of the gastrointestinal absorption and tissue distribution of ^{91}Y , ^{140}La , ^{144}Ce , ^{142}Pr ,

^{147}Nd , and ^{147}Pm in mature White Leghorn pullets; these isotopes were given as chlorides either orally or by injection into a superficial pectoral muscle. Eggs were collected and the hens were killed 4 days later. Excreta were not analyzed. The isotope concentrations (percent administered dose per gram wet weight) reported for intramuscularly injected birds and the organ and tissue weights of White Leghorn hens published by MITCHELL et al. (1931) were used to calculate the isotope content of whole tissues, and the fraction of the body content in each tissue as shown in Table 2. Neglecting excretion, the absorption of each nuclide following intramuscular injection was calculated to be as follows: ^{142}Pr , 7%; ^{144}Ce , 10%; ^{147}Nd , ^{147}Pm , ^{91}Y , each 30%; and ^{140}La , 64%. More than 40% of the body content of all the lanthanide isotopes was calculated to be in the skeleton (including marrow), and 3.5 to 22% was estimated to be in the liver.

In the studies in which the isotope was administered orally, the concentrations were reported only for blood, liver, muscle, tibia shaft, and egg components. The concentrations in the remainder of the tissues, which contributed more than one-third of the body weight, were assumed to be the same as those in blood. Tissue isotope contents were calculated as above, and the range of lanthanide radioisotopes absorbed from the G. I. tract of the hen was estimated to be as follows: ^{144}Ce , ^{147}Pm , and ^{91}Y , 0.07 to 0.1%; and ^{140}La , ^{142}Pr , and ^{147}Nd , 0.3 to 0.6%. Their distribution in the hen's tissues was unusual; a surprisingly large percentage of the body content (56 to 70%) was estimated to be present in skeletal muscle. The skeleton contained from 20 to 37% of the body content, while the liver contained no more than 5% of the body content — in both cases less than when these same radioisotopes were administered intramuscularly.

IV. The metabolism and distribution of the transplutonium elements in mammals: Absorption

The research objectives and experimental conditions of the animal experiments with the transplutonium elements are summarized in Tables 3 and 4.

The results of some experiments performed in this Laboratory are reported in this Chapter for the first time. The experimental conditions are included in Table 3. These experiments have been included in the bibliography as well: studies of the metabolism and microscopic distribution of ^{241}Am in rats and cynomolgus monkeys (DURBIN et al., 1972c); studies of the distribution of $^{249-252}\text{Cf}$ in the rat (DURBIN et al., 1972d); studies of the weights and microscopic anatomy of the tissues and bones of the female rat from birth to senescence (DURBIN et al., 1972e).

A. Absorption from the gastrointestinal tract

Absorption following oral administration of the trivalent transplutonium elements has been studied only in rats. Single doses of slightly acid solutions of chlorides were administered by gavage. SCOTT et al. (1948a, 1949) reported the subsequent absorption of $^{241}\text{AmCl}_3$ to be <0.01% and of $^{242}\text{CmCl}_3$, <0.05%. Recalculation of their original data suggests that those values are low, and that absorption from oral administration of either $^{241}\text{AmCl}_3$ or $^{242}\text{CmCl}_3$ was probably between 0.05 and 0.1%. So, absorption of these elements by the rat after oral inoculation has been restudied: Based on analyses of selected tissues, ZALIKIN et al. (1968) estimated absorption of $^{241}\text{AmCl}_3$ to be 0.03%, and SEMENOV (1971b) estimated absorption of $^{244}\text{CmCl}_3$ to be 0.05%. After oral administration of $^{249}\text{BkCl}_3$ and $^{253}\text{EsCl}_3$ to rats, HUNGATE et al. (1972) found 0.009% of the ^{249}Bk and 0.036% of the ^{253}Es in bone and tissues. Correcting for urinary and endogenous fecal excretion, total absorption by rats, subsequent to oral administration of these elements, was about 0.1% of

^{249}Bk and 0.06% of ^{253}Es .

Studies have been made of the gastrointestinal absorption of $^{144}\text{Ce(III)}$ and $^{239}\text{Pu(IV)}$ in very young animals, and of the influence on absorption of the presence of citrate ion and multiple vs. single feedings. No comparable studies have been made with the transplutonium elements, so the effects of these factors on absorption of the trivalent actinides must be inferred from experience with chemically similar elements.

Absorption following a single oral dose of $^{144}\text{CeCl}_3$ in rats was originally reported to be 0.02% (SCOTT et al., 1947). GRIGORYAN (1966) fed to rats 120 consecutive daily doses, each 0.8 μCi of $^{144}\text{CeCl}_3$, and from analysis of tissues calculated the average overall absorption to be 0.1 to 0.15%. Administration of an easily measurable amount of ^{144}Ce and the long feeding period insured (a) accurate tissue analyses, (b) good mixing of the isotope with the gastrointestinal contents, and (c) compensation for the daily fluctuations of gastrointestinal tract function.

The absorption by 1.5-year-old sheep following oral dosage of $^{144}\text{CeCl}_3$ remained constant -- 0.03% of the daily dose throughout periods of daily feeding varying from 18 to 1140 days (BULDAKOV and BUROV, 1967). These same authors fed single doses of $^{144}\text{CeCl}_3$ to lambs about 25 and 180 days old and obtained absorption values of 0.15% and 0.07%, respectively.

The greater absorption of multicharged cations by the intestinal tract of the very young animal has also been demonstrated in rats and dogs. SIKOV and MAHLUM (1972a) found that 1-day-old rats absorbed nearly four times more orally administered $^{239}\text{Pu(IV)}$ citrate than did 20- to 35-day-old rats, and 3-day-old pups absorbed more than four times as much $^{239}\text{Pu(IV)}$ citrate as did adult dogs (BULDAKOV et al., 1969).

The absorption of oral doses of $^{239}\text{Pu(IV)}$ is enhanced if it is administered with an excess of sodium citrate. See the review by BULDAKOV et al. (1969). For example, the rat's body content of $^{239}\text{Pu(IV)}$, after various feeding regimens, ranged from 0.002 to 0.012% if $^{239}\text{Pu(IV)}$ was given in a nitrate solution of pH 1 to 2, but was 0.04 to 0.2% after feeding $^{239}\text{Pu(IV)}$ in a sodium citrate solution of pH 4 to 6.5.

The best available estimates of intestinal absorption of multicharged cations by the rat are as follows: $^{144}\text{Ce(III)}$, 0.1 to 0.15%; the trivalent actinides, 0.01 to 0.06%; and Pu(IV) , 0.003 to 0.012%. Intestinal absorption of actinide (III) chlorides is about five times as great as that of $^{239}\text{Pu(NO}_3)_4$ and one-tenth to one-half as much as the absorption of $^{144}\text{CeCl}_3$.

Based on experience with $^{144}\text{Ce(III)}$ and $^{239}\text{Pu(IV)}$ it could be anticipated that (a) the fraction of actinide (III) absorbed during a period of continuous ingestion would not be too different from the fraction absorbed from a single feeding; (b) absorption of an oral dose of actinide (III) elements by newborn or very young animals would be about four times as great as that absorbed by adults; and (c) intestinal absorption of actinide (III) elements would probably be increased 10- to 20-fold if they were fed in a sodium citrate solution.

B. Absorption from an intramuscular injection

The intramuscular injection route was used in the earliest studies of the biology of the lanthanides and actinides because these easily hydrolyzable elements could be introduced into the body in a way that avoided formation of colloidal aggregates in the circulation (SCOTT et al., 1947, 1948a, 1949). Intramuscular absorption per se was not studied purposefully, but the information is available as an experimental by-product. The circulation of tissue fluids in the leg muscles of the rat is not the same as that in

the fleshy parts of the human hand -- the most common site of accidental lacerations and puncture wounds -- however, the patterns of absorption of these elements, after intramuscular injection in animals, represents nearly all the information upon which to base judgments of the consequences of contaminated wounds.

The data available on the intramuscular absorption of simple salts of the trivalent actinides administered intramuscularly to rats are collected in Table 5. The intramuscular absorption of multicharged cations is complex and is related to the administered mass, the chemical form of the element, and the pH and volume of solution injected. In the case of long-lived alpha-particle emitters, there is the added complication of local tissue damage if a significant amount remains at the injection site for a long enough time.

Absorption of intramuscularly administered lanthanide elements in the rat is summarized in Fig. 1.* The dependence on the administered mass is apparent. When the amount injected was less than 0.01 μg , about 50% was absorbed in the first day or so; another 40% was absorbed with a half-time of about 25 days; and the remaining 10% left the injection site with a half-time of 100 to 200 days. As the amount of the injected mass was increased, the fraction absorbed in the first few days declined, and the amounts associated with the slower absorption rates increased. If 100 μg or more were injected, only 5 to 10% was absorbed

* The curves in Fig. 1 were drawn from a composite of many observations made in the course of metabolic studies of radioisotopes of yttrium and the 14 lanthanide elements administered as chlorides. These experiments were performed at the Crocker Laboratory, University of California, in the years 1943 to 1957 under the general direction of J. G. Hamilton, K. G. Scott, and P. W. Durbin. Some of the information was presented in Laboratory progress reports, but much is unpublished.

during the first few days, and very little was absorbed thereafter.

The mechanisms by which multicharged cations are absorbed from parenteral injection sites are not known exactly, but it is reasonable to suggest that those fractions rapidly absorbed (half-times: hours to a few days) represent passage of soluble isotope into the lymph. The slower migrating fractions are probably subject to a combination of mechanisms: the consolidation of hydrolysis products and their subsequent sequestration in tissue phagocytes. Absorption of ^{239}Pu from contaminated wounds is characterized by a component with a half-time of the order of years, which appears to be the result of the encapsulation of the unabsorbed material by a fibrous tissue reaction (LANGHAM et al., 1962; HAMMOND and PUTZIER, 1964).

The absorption of $^{241}\text{AmCl}_3$, $^{242}\text{CmCl}_3$, or $^{239}\text{PuCl}_3$, administered intramuscularly, (the solid points in Fig. 1) was comparable to absorption of lanthanides of the same specific activity. The $^{241}\text{AmCl}_3$ and $^{242}\text{CmCl}_3$ were each absorbed more easily than the $^{241}\text{Am}(\text{NO}_3)_3$ or $^{242}\text{Cm}(\text{NO}_3)_3$,* and variable amounts up to 200 μg of stable $\text{La}(\text{NO}_3)_3$ carrier† depressed the uptake of ^{242}Cm still further.

Absorption of intramuscularly injected lanthanides (DURBIN et al., 1956) and actinides is greatly accelerated if they are administered as citrate

*It is possible that the apparently better absorption of the chlorides, compared to the nitrates, was caused by introduction of the chlorides in a larger volume, 1 ml as compared to 0.1 ml of the nitrate solutions.

†The experiments described by LAFUMA et al. (1970) and NÉNOT et al. (1970) dealt with many of the same animals. The ^{242}Cm solutions used in those experiments contained some stable lanthanum (NÉNOT et al., 1972), and the mass of lanthanum given to each rat varied with the injected volume.

complexes. The amounts of trivalent actinides absorbed in the first 4 days after intramuscular injection of solutions containing 0.4 to 5% of sodium citrate were: in rats, 97% of ^{241}Am (DURBIN et al., 1967), 97.3% of ^{242}Cm (WILLIAMS et al., 1961), and 97.9% of $^{249-252}\text{Cf}$ (DURBIN et al., 1972d), in mice, 98% to 99% of ^{241}Am and ^{252}Cf (PARKER et al., 1962) and 96.5% of ^{253}Es (PARKER et al., 1972); and in monkeys, 98.4% of ^{241}Am (DURBIN et al., 1962).

Citrate complexes of the transplutonium elements are unstable in body fluids, and their behavior in the body is identical to that observed after intramuscular or oral administration of simple salts. The behavior of the stable complex with DTPA is different. Within 24 hours after intramuscular injection of $^{242}\text{CmDTPA}^{--}$, the ^{242}Cm was completely absorbed and was completely excreted in the urine (NENOT, 1971a).

LAFUMA et al. (1970) and NENOT et al. (1970, 1971a) investigated the influence of DTPA on the absorption of intramuscularly injected $^{241}\text{Am}(\text{NO}_3)_3$ or $^{242}\text{Cm}(\text{NO}_3)_3 + \text{La}(\text{NO}_3)_3$; their results are summarized in Table 6. Introduction of DTPA into the same muscle one minute after the injection of $^{242}\text{Cm} + \text{La}$ promoted nearly complete absorption and excretion of ^{242}Cm . If the interval between injections was either 30 minutes or as long as 24 hours, the ^{242}Cm absorption was 10 times as great as the control values (Table 5). About 40% of the administered dose remained at the injection site -- an indication of the speed with which trivalent cations are hydrolyzed in tissue fluids and are rendered less available for complexing. Repeated injections of DTPA increased the ^{242}Cm absorption to 74% of the dose in 20 days compared with 30% absorption by controls. The absorption of ^{241}Am increased by only an additional 10% of the injected dose (NENOT et al., 1971a).

when repeated systemic DTPA treatments were given intramuscularly in the opposite leg or by inhalation as an aerosol. (See Section XI. C. 7.)

Absorption of ^{241}Am from a puncture wound in an accident case was followed for 2 years by measurement of excreta and external monitoring of the contaminated hand (R. L. DOBSON, 1955; R. L. DOBSON, H. G. PARKER, M. C. WALES, and M. CHUPP, unpublished). A chemist was performing an experiment with a concentrated source of ^{241}Am in a closed gloved box. He struck the end of a thin glass pipette which pierced his glove, inflicting a small puncture wound between the thumb and forefinger. The pipette had not dipped into the ^{241}Am solution but had been used to bubble NH_3 gas over the solution and had become contaminated by splash. Therapy with EDTA (0.12 to 0.25 mM/kg/day of CaNa_2EDTA) was started 1.5 hr after the accident. The bulk of the ^{241}Am (20×10^5 dis/min) was removed surgically 2.5 hr after the accident. Two days later an additional 1×10^5 dis/min were removed surgically leaving 4.5×10^5 dis/min in the hand. The EDTA treatment was continued for 60 days.

The measurements of the ^{241}Am in the wounded hand are shown in Fig. 2. The ^{241}Am content of the body was measured 134 days after the accident and was estimated to be 0.8×10^5 dis/min (ROWLAND et al., 1956). At that time the hand still contained 2×10^5 dis/min. During the first 134 days approximately 4×10^5 dis/min were excreted in the urine.

The initial rate of ^{241}Am absorption was estimated from these data to be 80%/day (as shown in Table 7), and is of the same order of magnitude as the initial rate of ^{241}Am absorption from an intramuscular injection in the rat. The parameters of the two-component exponential curve drawn to the external measurements of the hand are given in Fig. 2. The half-time of the first component is 13 days. Absorption at this rate is assumed to have begun 2.5 days after the injection, when the wounded hand was first measured. Once scar

tissue formed, the absorption of ^{241}Am slowed markedly. The half-time of the long-lived component was 1870 days. At the time the body content was remeasured, 810 days after the accident, what had previously been judged to be a diffuse deposit of ^{241}Am in the hand had consolidated into a well-circumscribed knot of fibrous tissue (MILLER, 1957).

It seems unlikely that the EDTA treatments had influenced ^{241}Am absorption; EDTA was being given at a relatively low level, 0.12 mM/kg/day. A daily dose of EDTA 10 times as large, and given for 15 days, did not change the absorption of intramuscularly injected ^{242}Cm in rats (K. G. SCOTT, M. H. WILLIAMS, and H. I. JOHNSON, unpublished). A much larger quantity of a more efficient complexing agent, 50 mM/kg/day of DTPA, increased intramuscular absorption of ^{241}Am by only an additional 10% (NENOT et al., 1971a).

C. Absorption through the intact skin

The only trivalent actinide for which cutaneous absorption has been studied is ^{253}Es (HUNGATE et al., 1972). The $^{253}\text{Es}(\text{NO}_3)_3$ in 0.01N HNO_3 was applied to washed rat skin from which the hair had been previously clipped. The solution was removed after 30 min. Tissue analyses 7 days later indicated an absorption of 0.03%/cm² of the applied ^{253}Es ; 0.049%/cm² if a correction was applied for urinary excretion.

Some clues to the behavior of the less soluble, lighter weight actinides can be obtained from experiments with $^{144}\text{Ce}(\text{III})$. GRIGORYAN et al. (1966) applied a slightly acid solution of $^{144}\text{CeCl}_3$ to rat skin that had been shaved 4 days before. At the end of a 3-hr exposure period, the ^{144}Ce was washed off. Absorption was 0.07 to 0.15%, calculated from tissue analyses of animals killed 1 or 7 days after the ^{144}Ce application. The amount of ^{144}Ce absorbed was increased 2 to 3 times if the rat skin had just previously been exposed to

60 μ R-min of ultraviolet light. Apparently the effect of the UV treatment was to increase capillary circulation.

D. Absorption of inhaled transplutonium elements

Internal burdens of the transplutonium elements have been acquired most frequently as a result of accidental inhalation of particles or droplets (FOREMAN et al., 1958; CALDWELL, 1966; BRODSKY et al., 1966, 1969; MAY, 1968; JEANMAIRE and BALLADA, 1970; SANDERS, 1971; ROSEN et al., 1971). A general model of lung dynamics has been developed to predict for man the lung deposition and retention and the systemic absorption of radioactive aerosols of varying sizes and solubility properties (ICRP, TASK GROUP ON LUNG DYNAMICS, 1966). The quantities of inhaled airborne particles selectively deposited in the several regions of the respiratory tract depend largely upon the size and density of the particles. The quantities eliminated from the lungs, either by absorption into the body or by various clearance mechanisms, depend on the chemical properties of the particles, chiefly their solubility (HATCH and GROSS, 1964).

1. Deposition of particles

The toxicity of inhaled radionuclides is a function of the radiation doses delivered to the regions of the respiratory tract and to the organs in which the absorbed radionuclide is deposited. The radiation doses, in turn, are functions of the amounts of radionuclide initially deposited in each tissue and the time courses of their release.

The initial body burden (IBB) of an inhaled radionuclide is

$$IBB = (N-P) + (T-B) + (P) \quad \text{Eq. (1)}$$

where all terms are in units of radioactivity or are expressed as fractions of the amount inhaled. The ICRP Task Group (1966) divided the respiratory tract

into three regions: naso-pharynx (N-P), tracheobronchial tree (T-B), and pulmonary (P). The schematic model of the particle deposition sites and clearance processes in man, developed by the ICRP Task Group (1966), is shown in Fig. 3; for unit density particles with AMAD* of $1\mu\text{m}$, the IBB = 0.59, N-P = 0.20, T-B = 0.09, and P = 0.30 of the total amount inhaled. The IBB can be obtained experimentally from either (a) the relationship between air concentration ($\mu\text{Ci/liter}$) and the total volume breathed, (b) the immediate in vivo measurement of the whole-body radioactivity, or (c) the sum of the radioactivity in the body and in all the excreta accumulated to the time of the body measurement.

2. "Solubility" of compounds

The ICRP Task Group (1966) also considered the influence of the chemical properties of inhaled materials. Simple chemical compounds were classified according to available information on their solubility in water, dilute alkali, or in protein solutions:

Class D is comparable to the designation "soluble" of the lung model in current use (ICRP, 1959). These compounds exhibit clearance and absorption half-times of the order of 1 day or less. No compounds of the lanthanides or actinides are included in Class D; however, Class D would include lanthanide and actinide complexes such as those with citrate and the aminopolycarboxylic acids, EDTA and DTPA.

Class W compounds approximate the presently used classification of "insoluble" (ICRP, 1959) and are expected to exhibit clearance half-times ranging from a few weeks to a few months. Lanthanide and actinide halides, nitrates, carbonates, phosphates, and presumably also sulfates and sulfides are considered Class W compounds.

The biological half-times ($T_{1/2}$'s) shown in Fig. 3 are those for Class W compounds.

*AMAD, activity mean aerodynamic diameter.

Class Y contains those compounds that are nearly insoluble in biological fluids. They are tenaciously retained in the lung, and are poorly absorbed into the body. They manifest clearance half-times of the order of months to years. Lanthanide and actinide hydroxides, oxides, fluorides, and carbides comprise the bulk of simple chemical compounds of Class Y.

3. Clearance of particles from the lung

The cilia of the nasopharynx and tracheobronchial tree (to the level of the terminal bronchioles) continuously move a layer of mucus toward the esophagus. The early phase of rapid clearance of particles from the upper respiratory tract is usually considered to be the result of the muco-ciliary transport process. Most of the particulate material initially deposited in the N-P and T-B regions is cleared to the G. I. tract within an hour; 50% of soluble aerosols (Class D), 90% of poorly soluble aerosols (Class W), and 99% of insoluble aerosols (Class Y) so deposited are cleared with biological half-times of 4 to 10 min (ICRP, 1966).

4. Evaluation of initial lung deposition in dogs

The immediate purpose of inhalation studies of radioactive materials is to ascertain the relationships between local radiation doses and observed toxicity, and the ultimate goal is prediction of the chronic toxicity of a given level of inhaled radioactivity. Therefore, the material initially deposited in the upper respiratory tract, and which is cleared rapidly, is usually not considered to contribute significantly to the total radiation dose to the lungs or other organs. There is an exception in the case of short-lived radionuclides that deliver most of their radiation dose to the upper respiratory tract structures and to the gastrointestinal tract during the early clearance phase.

It is also customary to eliminate from long-term consideration that fraction of the initial pulmonary deposit that is cleared by migratory phagocytes

and subsequently entrained in the muco-ciliary transport process during the first few days after exposure (pathway f in Fig. 3, $t_f = 1$ day). Long-term results are then discussed in terms of the initial lung burden (ILB) which is defined as

$$ILB = (P - f) = (P - 0.4P) = 0.6P \quad \text{Eq. (2)}$$

where P is the initial pulmonary deposit, f is the fraction of that deposit cleared with a 1-day half-time. All terms are expressed in radioactivity units or as percent of the amount inhaled.

In their studies with dogs, R. G. THOMAS et al. (1972) and MCCLELLAN et al. (1972) define ILB as in Eq. 2 except that t_f is taken to be 7 or 8 days after exposure. These workers determine ILB in two ways: (a) from an immediate whole-body measurement less the first 7 days' feces, or (b) from the sum of the radioactivity of all the tissues and excreta at sacrifice less the first 7 days' feces.

5. Deposition of inhaled actinides in the dog lung

The ICRP Task Group report (ICRP, 1966) was completed in mid-1965. At that time there was only one brief report of whole-body retention of ^{241}Am citrate administered intratracheally to rats (FOREMAN, 1962). In some very new studies beagles have been exposed by inhalation to precisely-known quantities of well-characterized particles of $^{241}\text{AmO}_2$ (R. G. THOMAS et al., 1972), $^{244}\text{CmCl}_3$, and $^{244}\text{CmO}_{1.73}$ (MCCLELLAN et al., 1972). Some of the experimental details and some of the results of these studies are shown in Tables 4 and 8 respectively.

The measured values of the IBB and ILB for the various particle sizes are compared in Table 8 to those predicted by the ICRP model for man (ICRP, 1966). The agreement is excellent for the 1.6- μm -AMAD particles of $^{244}\text{CmCl}_3$ and the 0.5- μm -AMAD particles of $^{244}\text{CmO}_{1.73}$, but nearly twice as much of the

^{241}Am radioactivity from the 0.9- μm -AMAD particles of $^{241}\text{AmO}_2$ was deposited in the dog lung as was predicted by the human deposition model.

6. Body absorption of actinides deposited in the dog lung

It was necessary to recalculate the data as originally reported by R.G. THOMAS et al. (1972) and MCCLELLAN et al (1972) in order to estimate the amount of the actinide compounds deposited in dog lung that was subsequently absorbed into the body.

R.G. THOMAS et al (1972) expressed the important results of their inhalation studies of $^{241}\text{AmO}_2$ as μCi of ^{241}Am ; these included the total amount inhaled, IBB, ILB, and total urinary and fecal excretion. Tissue contents of ^{241}Am were presented as a percent of the sacrifice body burden (SacBB). The percent of the ILB was calculated from the relationship

$$\text{ILB}(\%) = [\text{SacBB}(\%)] [\text{SacBB}(\mu\text{Ci})/\text{ILB}(\mu\text{Ci})] \quad \text{Eq. (3)}$$

MCCLELLAN et al. (1972) expressed the major results of their inhalation studies with $^{244}\text{CmCl}_3$ and $^{244}\text{CmO}_{1.73}$ as μCi of ^{244}Cm . The results included the total amount inhaled, IBB, and ILB. Urinary excretion was presented as the percent ILB per day, and tissue- ^{244}Cm content was reported as percent ILB per gram wet tissue. The tissue results were converted to percent ILB in whole tissues and organs using the beagle tissue weights given by CUDDIHY et al. (1970) and HOBBS et al. (1970) of that same Laboratory. The recalculated data agreed with preliminary results reported by GALLEGOS et al. (1970).

The lung-clearance model (ICRP, 1966) designates actinide halides and nitrates as class W compounds, and predicts that Class W compounds will be eliminated from the lung with an average half-time of 90 days by a combination of absorption into the body (pathways e and h, Fig. 3) and clearance to the gastrointestinal tract (pathway g). The model predicts that the ultimate disposition of

the ILB of class W compounds will be as follows: 33% of the ILB (6% of the inhaled dose) will be absorbed into the body while 67% of the ILB (12% of the inhaled dose) will be cleared by phagocytic and ciliary action to the gastrointestinal tract. Actinide oxides are designated Class Y compounds, for which the predicted average lung elimination half-time is 360 days -- only one-fourth as fast for Class W compounds -- although the ultimate distribution of the ILB between absorption into the body and gastrointestinal tract clearance is presumed to be the same as for Class W compounds.

Elimination of $^{244}\text{CmCl}_3$ (a class W compound) from the dog lung (Fig. 4) is the complex resultant of several processes, but most of these processes seem to involve solubilization and absorption into the body rather than clearance via the gastrointestinal tract. The curve of elimination from the lung for $^{244}\text{CmCl}_3$ can be described approximately by 4 exponential terms: (1) 20% of ILB, $T_{1/2} = 4$ hr; (2) 60% of ILB, $T_{1/2} = 2.5$ days; (3) 12% of ILB, $T_{1/2} = 21$ days; (4) 9% of ILB, $T_{1/2} \geq 200$ days. The rates at which ^{244}Cm was simultaneously being deposited in skeleton and liver and eliminated in urine (half-times of 4 to 9 hr and 2 to 3 days) corresponded roughly to rates of the two rapid phases of elimination from the lung.

Elimination of $^{244}\text{CmO}_{1.73}$ (a class Y compound) from the lung was only a little slower than that of $^{244}\text{CmCl}_3$ and also could be approximated by 4 exponential terms: (1) 14% of ILB, $T_{1/2} = 1$ hr; (2) 31% of ILB, $T_{1/2} = 0.9$ days; (3) 37% of ILB, $T_{1/2} = 5.4$ days; (4) 18% of ILB, $T_{1/2} \geq 80$ days. Uptake in skeleton and liver and excretion in urine were all characterized by half-times of 0.6 day and 3 to 4 days -- again close to the early rates of elimination from lung.

Absorption from the lung of the moderately soluble $^{244}\text{CmCl}_3$ was almost the same as the water-insoluble compounds, $^{241}\text{AmO}_2$ and $^{244}\text{CmO}_{1.73}$, at the time

when the lung burden had been reduced to 10% of the ILB (LB_{10}).^{*} As shown in Table 9 the absorption of all three actinide compounds (85% of the ILB at LB_{10}) was much greater than expected [33% of the ILB is predicted by the lung model (ICRP, 1966)]. By definition, 10% of the ILB remained in the lungs, and less than 5 to 8% of ILB was probably eliminated from the lungs by a clearance mechanism coupled to gastrointestinal tract excretion (the lung model predicts 67% of ILB elimination by such clearance mechanisms). The brief report by BULDAKOV et al. (1972) of their studies of the inhalation of $^{241}\text{Am}(\text{NO}_3)_3$ aerosols by mongrel dogs did not provide enough details to be included in Table 9. However, they reported that elimination of ^{241}Am from the lungs was 96% complete by 414 days after exposure at which time skeleton and liver combined contained 82% "of the initial deposit."

7. Inhalation and intratracheal instillation studies in rats

NENOT et al. (1971 a,b,c) exposed rats by inhalation to a mist containing $^{241}\text{Am}(\text{NO}_3)_3$. The mean diameter of the particles was stated to be less than 5 μm , but the diameters were not measured. The deposition parameters were calculated for this aerosol (shown in Table 8) using the ICRP lung model (ICRP, 1966) and an average particle diameter of 2.5- μm AMAD, but the biological behavior was more like that of a particle of 1.6- μm AMAD.

^{*}Most studies of inhalation or intratracheal instillation do not extend over a long enough interval to achieve complete lung clearance, but most such studies, especially of relatively soluble compounds, are carried out long enough to achieve 90% lung clearance. For purposes of comparing the results of studies of varying duration in which varying degrees of lung clearance were achieved, an artificial common time has been adopted, designated LB_{10} , the time after exposure at which the lung burden has been reduced to 10% of the ILB.

NENOT et al. (1971a,b,c) defined ILB as

$$ILB = IBB - \sum_{t=0}^{t=3} Fe. \quad \text{Eq. (4)}$$

where Fe is fecal excretion, and t is days after exposure. The IBB was determined by whole-body counting immediately after cessation of exposure. Tissue content and excretion of the inhaled $^{241}\text{Am}(\text{NO}_3)_3$ aerosol were reported as percent of the administered dose (NENOT et al., 1971c), which is assumed to be equal to the IBB. Fecal excretion data were available only for the first day postexposure. For the present calculations, the ILB was assumed to be equal to the IBB less the ^{241}Am excreted in the feces during the first day (day-1 feces also included the ^{241}Am in the contents of the gastrointestinal tract which would have been discharged on day 2). The data calculated in this way compared favorably to other results expressed by these authors as a percent of the ILB (NENOT et al., 1971a,b).

Experiments in which solutions or suspensions are instilled directly into the lungs are useful in the determination of the solubilities of various compounds in the lung. Lung retention and tissue uptake of chlorides and nitrates of ^{241}Am (ZALIKIN et al., 1968; TSEVELEVA and YEROKHIN, 1969) and ^{253}Es (HUNGATE et al., 1972) have been studied after instillation of slightly acid solutions in the lungs of rats. The data from these investigations and from the inhalation studies mentioned above have been recalculated* in terms of the percent ILB. Some of the results of a study in which $^{241}\text{AmCl}_3$ was administered to rats by intratracheal instillation (ZALIKIN et al., 1968) appear in Fig. 5.

* The details of these calculations are given in Appendix A.

8. Absorption of actinides from the lungs of rats after inhalation or instillation

Assessment of absorption of actinide compounds from rat lung is complicated. Of the americium or curium isotopes absorbed by the rat, a large percentage (45 to 65%) is deposited in the liver and is almost quantitatively excreted in the feces within 30 days (SCOTT et al., 1948a, 1949; DURBIN et al., 1967). A large fraction of $^{253}\text{EsCl}_3$ about 40% of that in the blood, is promptly excreted by kidney (HUNGATE et al., 1972). If only the tissue content is measured, and urinary and fecal excretion of absorbed nuclide are neglected, total absorption will be seriously underestimated. Urinary excretion of $^{253}\text{EsCl}_3$ can be estimated, if one assumes that the rat kidney excretes the same fraction of $^{253}\text{EsCl}_3$ after it is absorbed, whether from the lung or from parenteral injection,

$$\text{Ab}(\%) = \Sigma \text{ tissues } (\%) + 0.4\text{Ab.} \quad \text{Eq. (5)}$$

A more complicated method was required to describe the simultaneous deposition in, and elimination of actinide nuclides from the liver, and to evaluate the fraction of the total quantity of nuclide that was absorbed from the lung and that had subsequently passed through the rat liver. A description of the mathematics and of the calculations are given in Appendix B.

Table 9 shows the time required to clear 90% of the ILB (LB_{10}); the fractions of ILB in the tissues and excreta, and the total absorption into the body at $t = \text{LB}_{10}$; and an estimate of the fraction of ILB cleared by phagocytosis coupled to gastrointestinal tract excretion. The mean LB_{10} was 30 days in rats for ^{241}Am instilled as a solution or inhaled as droplets of nitrates or chlorides. Reduction of the lung burden in 30 days to 10% of its initial value corresponds to an effective or average elimination half-time (T_{eff}) of 10 days. For

elimination of $^{253}\text{EsCl}_3$ $T_{\text{eff}} = 6$ days. The elimination of transplutonium elements inhaled by dogs as dry particles was somewhat slower; $T_{\text{eff}} = 15$ days for $^{244}\text{CmCl}_3$ and $T_{\text{eff}} = 20$ days for $^{244}\text{CmO}_{1.73}$. In every experiment, elimination of trivalent actinides from the animal lung was more efficient than was predicted by the lung model for Class W or Class Y compounds in man (ICRP, 1966). In addition, the lung clearance model, based largely on experience with compounds of plutonium, predicts that two-thirds of the ILB of these relatively insoluble materials will be eliminated by clearance processes and one-third by absorption. The experiments do not agree with the model. Absorption into the body accounted for 75 to 85% of the americium compounds and 90% of the $^{253}\text{EsCl}_3$ initially present in the lung. Less than 15% (5 to 15%) could be presumed to have been cleared and excreted in the feces.

9. ^{241}Am in the human lung

In reporting accidental inhalations of ^{241}Am compounds, several authors have commented on the disappearance of ^{241}Am from the lung and its subsequent reappearance in the body (MAY, 1968; RUNDO et al., 1970; ROSEN et al., 1971). In all cases, either the contamination levels were very low or chelation therapy was started as soon as possible, so these results are difficult to evaluate. It appears, however, that ^{241}Am compounds inhaled as dry dusts left the human lung more rapidly than did dusts of plutonium compounds, but perhaps not as rapidly as was measured in the animal studies discussed above. In vivo measurements of small amounts of ^{241}Am were imprecise, but it seems clear that a large fraction of the ^{241}Am leaving the human lung was absorbed into the body.

The ^{241}Am contaminant of modern plutonium* has been used to estimate, by

* ^{241}Am is the daughter of 13-year ^{241}Pu which is produced from ^{239}Pu by successive neutron captures. The amount of ^{241}Am present in a ^{239}Pu sample depends on the neutron flux of the reactor, the length of bombardment, and the elapsed time since the isotopes were separated.

in vivo measurement, ^{239}Pu lung burdens in dogs (MORROW et al., 1967; BAIR, 1970) and in man (LAGERQUIST et al., 1967). The body absorption and lung clearance results shown in Table 9 were obtained in experiments using total masses of transplutonium compounds of 10^{-6} to 10^{-9} g. If ^{241}Am is present as a minor contaminant of an insoluble matrix, the behavior of ^{241}Am in the lung seems to be the same as that of the matrix. Neither BAIR (1970) nor MORROW et al. (1967) were able to detect dissociation of ^{241}Am from inhaled $^{239}\text{PuO}_2$ or $^{239}\text{PuF}_4$, but absorption of ^{241}Am in excess of ^{239}Pu was detected if the inhaled matrix was the more soluble $^{239}\text{Pu}(\text{NO}_3)_4$.

V. Circulatory transport

Many multicharged cations are transported in mammalian plasma in association with proteins. About one-half of serum calcium is associated with protein, mainly albumin (MCLEAN and HASTINGS, 1935). Almost all of plasma iron is bound to the β_1 -globulin, transferrin (KATZ, 1970). More than 90% of plasma copper is bound to the α_2 -globulin, ceruloplasmin (ADELSTEIN and VALLEE, 1962). Plasma zinc is associated with several proteins in varying amounts and with variable stabilities, but most of the plasma zinc is rather firmly bound to globulins (VALLEE, 1962).

A. Circulatory clearance

In vivo and in vitro studies with rat, dog, horse, and human plasma have demonstrated conclusively that in normal or iron-deficient plasma, Pu(IV) is bound firmly and almost quantitatively to transferrin, and that Pu(IV) and Fe(III) occupy the same binding sites (POPPLEWELL and BOOCKOCK, 1967; STOVER et al., 1968; TURNER and TAYLOR, 1968a,b; STEVENS et al., 1968a). The slow disappearance from the blood of intravenously injected, soluble Pu(IV) (PAINTER et al., 1946; LANGHAM et al., 1951; STOVER et al., 1959) and its equally slow deposition in tissues (SCHUBERT et al., 1950; D. M. TAYLOR, 1962) are consequences of the

stability of the Pu-transferrin complex in the circulation.

In contrast, clearance of the trivalent actinides from the blood is prompt, and tissue uptake is likewise prompt. As shown in Fig. 6, intravenously injected ^{241}Am or ^{244}Cm is 90% cleared from the blood in 0.25 to 1 hr and 99% complete in 2.5 to 10 hr in rats, beagles, lactating Suffolk ewes, and cynomolgus monkeys. Circulatory clearance of ^{249}Cf and ^{252}Cf in beagles proceeds somewhat more slowly (Fig. 7).

The time course of the circulatory clearance of the trivalent actinides is similar to that of radioisotopes of calcium, strontium and several lanthanides in the beagle (Fig. 7), the rat (Fig. 8), and the lactating ewe (Fig. 9).^{*} Although the circulatory clearance

* Data regarding blood clearance were reported from the following papers as percent of injected dose in plasma volume or blood volume, and values read from tables or figures could be used without further manipulation: ^{241}Am and ^{244}Cm in rat (D.M. TAYLOR, 1962; TURNER and TAYLOR, 1968b); ^{144}Ce , ^{152}Eu , and ^{160}Tb in rat (DURBIN et al., 1955); ^{45}Ca in rat (COPP et al., 1951); ^{241}Am and ^{249}Cf in the beagle (STEVENS and BRUENGER, 1972). In beagles, data for ^{89}Sr (SWIFT and PROSSER, 1947) and ^{47}Ca (COLLINS et al., 1962) were reported as percent dose per milliliter of blood or of plasma, respectively. Values for volumes of total plasma or total blood of the beagle given by STOVER et al. (1959) and J. H. DOUGHERTY and SEYMOUR (1957) were used to convert these data to percent of nuclide circulating. Data for all of the nuclides in the blood of sheep (MCCLELLAN et al., 1962 a,b, 1963) were converted from percent dose per ml of plasma, or of plasma X body weight using a plasma volume of 3.75% of the body weight for the sheep (V. G. HORSTMANN and L. K. BUSTAD, unpublished) and a body weight of 56 kg for the adult ewe (GRIGORYAN, 1966).

rates of the trivalent actinides are faster than that of Pu(IV), which exists in plasma as a stable transferrin complex, they are much slower than the clearance rate of colloidal material (E.L. DOBSON et al 1949; TURNER and TAYLOR, 1968b). After intravenous injection of slightly acid solutions of chlorides or nitrates of americium or curium in rats, dogs, or monkeys, neither the gross nor the microscopic deposition patterns resembled those of colloidal material (D.M. TAYLOR, 1962; WILLIAMS et al., 1961; ZALIKIN et al., 1968; BELYAEV, 1969; LLOYD et al., 1970; RUDNITSKAYA and MOSKALEV, 1970; K. G. SCOTT, J. G. HAMILTON, and M. H. WILLIAMS, unpublished). Usually the injection solutions of these high-specific-activity nuclides are so dilute (less than 1 $\mu\text{g/ml}$), and circulatory mixing is so rapid that intravascular aggregation of primary hydrolysis products is not likely to occur.

B. Protein binding

Prompt blood clearance without intravascular formation of colloidal aggregates suggests that the trivalent actinides exist in plasma as complexes or loose associations with either inorganic plasma constituents or plasma proteins or both. The interaction of these elements with serum proteins has been studied using the techniques developed to elucidate the protein binding of Pu(IV).

Gross separation of a protein-bound nuclide from low molecular weight, largely inorganic compounds (gel filtration with Sephadex G 25 or G 50) indicates that at least 60% of americium, curium, or californium is associated with protein after incubation in vitro with human plasma (POPPLEWELL and BOOCOCK, 1967; BRUENGER et al., 1969a; STEVENS and BRUENGER, 1972). Interpretation of the results for americium and curium is complicated, because they react strongly with the gel.

Separation of the plasma proteins by size and weight (gel filtration with Sephadex G 200 or G 100-G 200 combined) indicates that americium, curium, and

californium elute from the gel primarily with the protein peak that contains albumin, transferrin and α -globulins (molecular weight about 70,000). A smaller amount eluted with the protein peak containing lipoproteins and macroglobulins (molecular weight more than 200,000) (POPPELWELL and BOOCKOCK, 1967; BRUENGER et al., 1969a, 1971; STEVENS and BRUENGER, 1972).

Resolution of the albumin-transferrin fraction (anion-exchange chromatography with Sephadex DEAE A-50 cellulose) showed that the radioactivity peaks of americium, curium, and californium fall either between, and slightly overlapping, the small transferrin and the larger albumin peaks (POPPELWELL and BOOCKOCK, 1967), or are associated to some extent with both albumin and transferrin peaks (BRUENGER et al., 1969a; STEVENS and BRUENGER, 1972). Association of americium with transferrin was more pronounced if competition with Fe(III) was reduced by the use of iron-deficient plasma (BRUENGER et al., 1969a). The behavior of californium was more like that of Pu(IV); that is, more of the ^{249}Cf radioactivity was more closely associated with the transferrin peak. But unlike Pu(IV) the ^{249}Cf and transferrin peaks did not coincide (STEVENS and BRUENGER, 1972).

Two explanations have been offered: First, BOOCKOCK and POPPELWELL (1967) suggested that the actinides(III) form complexes with transferrin, but that the unstable complexes do not survive the separation processes intact. Second, BRUENGER et al., (1969a) and STEVENS and BRUENGER (1972) suggested that the complexing protein may not be transferrin, but an as-yet-unidentified plasma constituent of about the same size as transferrin and with a slightly greater effective charge.

The status of americium and curium has been studied in the plasma of living animals (TURNER and TAYLOR, 1968b; BRUENGER et al., 1969a). An estimate of the extent of protein binding of intravenously injected ^{241}Am and ^{244}Cm

in rats and ^{241}Am in dogs is shown in Table 10. One minute after injection, protein binding of the actinides(III) ranged from 13 to 58% of the circulating nuclide compared with 72.5% of Pu(IV) protein-bound. After 1 hr, 85 to 95% of americium or curium still circulating was, like Pu(IV), associated with proteins. As expected, the protein-bound fraction of the actinides(III) and Pu(IV) left the blood more slowly than the fraction which was not associated with protein. During the first hour after injection, protein-bound and unbound ^{241}Am left the circulation at rates of 1.6 and 6.7%/min, respectively; protein-bound and unbound ^{244}Cm left the circulation at rates of 3 and 10%/min, respectively. Clearance of both protein-bound and unbound Pu(IV) was much slower--0.22 and 1.5%/min, respectively.

VI. Deposition kinetics

Tissue deposition kinetics of the transplutonium elements have not been studied in detail, but the general features of an uptake model can be obtained by combining the available data with what is known about the accumulation of the lanthanides and Pu(IV).

A.. Kinetic experiments with ^{241}Am

DM. TAYLOR (1962) demonstrated that the uptake pattern of intravenously injected $^{241}\text{Am}(\text{NO}_3)_3$ in the ends and shaft of the femur of 7-week-old male rats was more like that of Ca(II) than that of Pu(IV). BELYAEV (1969) injected $^{241}\text{AmCl}_3$ intravenously in 160 to 180 g male rats* and measured the simultaneous disappearance from blood and uptake in liver and skeleton.

The Am(III) bone-uptake data from these two experiments are shown in Fig. 10 along with comparable data for Ca(II), Sr(II), Ce(III), Eu(III), and

* Growth curves of two albino strains and one hooded strain indicate that the rats used by BELYAEV (1969) were 6.5- to 7.5-weeks old.

Pu(IV). In each case the data have been recalculated as a percent of the maximum bone uptake, in order to permit direct comparisons of results originally reported in several different ways. As expected, because experimental animals of the same sex and age were used, the results of the two ^{241}Am studies were superimposable, and the data have been combined.

B. Recalculation of ^{241}Am kinetic data

In addition to information on uptake of Am(III) in bone and liver, the BELYAEV (1969) study provides an opportunity to estimate the movement of Am(III) in extracellular fluid (ECF). Values for ^{241}Am in blood, liver, and skeleton at times ranging from 3 min to 16 hr after intravenous injection, were read from the published curves. Liver and skeleton values were corrected for the ^{241}Am in their contained plasma as described by DURBIN et al. (1972a) assuming that skeleton and liver constitute 9 and 3% of the body weight, respectively. The corrected data were replotted linearly (not shown) to interpolate additional values intermediate between the widely spaced data points.

Assuming that injection and radioanalytical techniques were accurate, the ^{241}Am content of soft tissues plus extracellular fluid (ST + ECF) was estimated as

$$(\text{ST} + \text{ECF})(\%) = 100 - (\text{Li}_t + \text{Sk}_t + \text{Bl}_t + \text{Ex}_t), \quad \text{Eq. (6)}$$

where Li_t , Sk_t , Bl_t , and Ex_t are the percent of injected dose in liver, skeleton, blood, and accumulated excreta, respectively, at time t after injection.

In this experiment early excretion was not measured, so (ST + ECF) also includes the small amount of ^{241}Am excreted.

Accumulation of ^{241}Am in liver and skeleton was calculated according to the method described by COMAR (1955) in which A_t and A_{eq} represent tissue accumulation at time t and maximum tissue uptake, respectively:

$$\text{Accumulation} = A_t / A_{eq} \quad \text{Eq. (7)}$$

C. Clearance and accumulation equations

In BELYAEV's (1969) experiment, clearance of ^{241}Am from blood and (ST + ECF) and its accumulation in liver and skeleton can be described by the semilogarithmic curves in Fig. 11 and by the following equations (t is min):

$$\text{Blood}_t(\%) = 62e^{-0.33t} + 32e^{-0.024t} + 5e^{-0.0035t}; \quad \text{Eq. (8)}$$

Uptake in soft tissues and extracellular fluid, $t = 0$ to $t = 5$ min

$$(\text{ST} + \text{ECF})(\%) = 43(1 - e^{-0.46t}); \quad \text{Eq. (9)}$$

Clearance of soft tissues and extracellular fluid, $t > 5$ min

$$(\text{ST} + \text{ECF})(\%) = 23e^{-0.06t} + 14e^{-0.003t} + 9; \quad \text{Eq. (10)}$$

$$\begin{aligned} \text{Liver}_t(\%) &= 20(1 - e^{-0.14t}) + 19(1 - e^{-0.019t}) \\ &\quad + 22(1 - e^{-0.0033t}); \end{aligned} \quad \text{Eq. (11)}$$

$$\begin{aligned} \text{Skeleton}_t(\%) &= 8(1 - e^{-0.058t}) + 16(1 - e^{-0.0033t}) \\ &\quad + 6(1 - e^{-0.0034t}). \end{aligned} \quad \text{Eq. (12)}$$

The equations describing accumulation of Am(III) in liver and skeleton, Eq. 11 and 12 respectively, have rate terms in common with each other and also in common with the blood- and (ST + ECF)-clearance equations, Eqs. 8 and 10, respectively. The common rate terms in the Am(III) liver and bone accumulation equations indicate that Am(III) is being deposited in both tissues from a common pool. The common rate terms in the transport equations, blood and (ST + ECF), and the accumulation equations, liver and skeleton, suggest that the rate-limiting reactions are in the transport system rather than in the liver and skeleton. The rate of accumulation of the transplutonium elements in the major organs of deposition seems to depend on (a) the rates of transfer of protein-bound and unbound nuclide between blood and ECF, and (b) the rates of protein binding and release in blood and ECF.

D. Kinetic model for uptake of multicharged cations

A kinetic model embodying the above features has been proposed to describe

the transport and deposition of Pu(IV) in the rat (DURBIN et al., 1972a). The model, shown in Fig. 12, consists of four interconnected transport compartments, protein-bound and unbound, both in blood and in ECF; and four effectively nonreturning accumulation compartments, liver, skeleton, soft tissue, and excretion.

1. Movement in extracellular fluid

As shown in Table 11, within the first 5 min after intravenous injection of Ca(II), Ce(III), Eu(III), Am(III), and Pu(IV), nearly one-half of the injected nuclide leaves the circulation but cannot be accounted for by excretion or by uptake in liver or bone. Balance studies with ^{45}Ca (L. PALMER and E. PALMER, unpublished), ^{90}Sr (G. D. BARR and P. W. DURBIN, unpublished), and several lanthanides (DURBIN et al., 1955) demonstrated that the missing nuclide was present in soft tissues, though only transiently. Only 20 to 25% of the nuclide that was present in soft tissue at 5 min after injection remained for 24 hr, indicating that the nuclides were associated with ECF rather than with cellular components.

The amount of nuclide leaking into the ECF depends on the stability of protein binding. The more stable the nuclide-protein moiety, the more rapidly it forms--the more will remain in the circulation, and the less will pass into ECF or be immediately deposited in liver and bone. Pu(IV)-transferrin is an example of a stable, rapidly-forming, nuclide-protein complex. Leakage of Pu(IV) into the ECF has been calculated to range from 20 to 40% of the injected dose depending upon whether $\text{Pu}(\text{NO}_3)_4$ or Pu(IV) citrate, respectively, was injected (TURNER and TAYLOR, 1968b; DURBIN et al., 1972a). At the other extreme are Ca(II) and Ce(III), which are only loosely and transiently associated with serum proteins: 50 to 60% of the injected dose of these nuclides passes into the ECF in the first 5 min after intravenous injection.

The Pu-transferrin complex is so stable that the degree of protein binding was the same after injection of $\text{Pu}(\text{NO}_3)_4$ or Pu(IV) citrate (TURNER and TAYLOR, 1968b). In the case of the trivalent actinides, the serum protein complex (formed most likely with transferrin) or complexes are much less stable. In the rat there was less protein binding of ^{241}Am injected intravenously as a citrate complex, than of either ^{241}Am or ^{244}Cm injected as nitrates.

Clearance of Am(III) from the (ST + ECF) compartment is represented by at least two exponential terms and one constant term (Eq. 10). The rapidly disappearing component has a rate constant of 6%/min. The rate constant of the same term in the (ST + ECF)-clearance equations of Ca(II), Ce(III), and Eu(III) ranged from 2.5 to 3.2%/min (see references cited in Table 11). The slower component of Eq. 10 has a rate constant of 0.3%/min compared to a range of 0.12 to 0.22%/min for the other elements listed above.

Although the protein in the ECF is quite dilute, it includes about 50% of the human transferrin (KATZ, 1970); thus, protein binding is possible in the ECF as well as in the blood. The components of the (ST + ECF)-clearance equation may represent the separate return to the circulation of unbound and protein-bound Am(III), respectively. Multiple rates of ECF clearance may also be the result of the many different rates of ECF and lymph flow in the various tissues (WINCHELL et al., 1964). The real situation is probably a combination of free and protein-bound Am(III) returning from a variety of ECF sites at a variety of rates.

TSEVELEVA and YEROKHIN (1969) administered $^{241}\text{Am}(\text{NO}_3)_3$ intraperitoneally--effectively placing all of the ^{241}Am in the ECF-unbound compartment at $t = 0$.

The liver uptake data (shown also in Fig. 13) were recalculated* as described above, yielding an accumulation equation (t is in min),

$$\text{Liver}_t(\%) = 16(1 - e^{-0.0088t}) + 49(1 - e^{-0.0022t}). \quad \text{Eq. (13)}$$

The slower of the two rate constants in Eq. 13 (0.22%/min), obtained in an experiment in which all of the Am(III) was initially in the ECF, is very nearly the same as the slowest rate constant of the clearance equation of the (ST + ECF) compartment (0.3%/min, Eq. 10) determined in an experiment in which $^{241}\text{AmCl}_3$ was injected intravenously, placing 100% of Am(III) in the unbound compartment of plasma at $t = 0$ (BELYAEV, 1969). Thus, there is independent support for the view that this term is associated with return of the nuclide from the ECF to the circulation.

2. Deposition of Am(III) in bone and liver

The bone uptake of Am(III) (shown in Fig. 10) occupies a position closer to the rapid accumulation of the lanthanides and alkaline earths than to the slowly accumulating Pu(IV). The difference between bone uptake of Am(III) and the other (II) and (III) elements shown was greatest during the first few minutes after injection. Five min after injection Am(III) uptake in bone was only 19% of maximum uptake compared with 38 to 50% of maximum uptake calculated for the lanthanides and alkaline earths. After the first 30 min, except for Pu(IV), all of the bone uptake curves were quite close together. The lower, very early, bone uptake of Am(III) is probably the result of its greater, early protein binding compared with the other (II) and (III) elements studied.

Liver accumulation of Am(III) apparently is also influenced by the somewhat more stable, early, protein binding of this element compared with the lanthanides and alkaline earths. Five min after injection, the Am(III) in

* The bone data were not amenable to recalculation, because A_{eq} could not be determined with sufficient precision.

the liver was 24% of the maximum uptake (see Fig. 13), and Eu(III) and Ce(III) in liver were 42 and 50% , respectively, of the maximum uptake (DURBIN et al. , 1955).

VII. Distribution and retention of transplutonium elements in the skeleton

In all of the mammals studied thus far, the transplutonium elements are deposited primarily in liver and skeleton with lesser amounts initially present in kidney and spleen. The early distributions, 4 to 60 days after administration of soluble noncolloidal solutions of the transplutonium elements, are given in Tables 12 through 17: ^{241}Am , ^{242}Cm , ^{249}Bk , $^{249-252}\text{Cf}$, and ^{253}Es in adult rats—Table 12; ^{241}Am , ^{242}Cm , and ^{252}Cf in immature rats—Table 13; ^{243}Am , ^{252}Cf , and ^{253}Es in adult mice—Table 14; ^{241}Am and ^{252}Cf in adult Chinese hamsters—Table 15; ^{241}Am and ^{249}Cf or ^{252}Cf in adult beagles—Table 16; and ^{241}Am in adult cynomolgus monkeys and adult baboons—Table 17. All of the nuclide distribution data in Tables 12 through 17 are presented as either percent of injected dose (intravenous or intraperitoneal administration) or the equivalent, percent of absorbed dose (intramuscular administration). In the text the nuclide content of specific organs is given as percent of dose, and normalization to 100% absorption and 100% recovery is implied.

A. Gross deposition

1. Americium

The initial deposition of ^{241}Am or ^{243}Am in the adult mammalian skeleton ranges from a low of 19% of the dose in Chinese hamsters (MCKAY et al. , 1972) to a high of 58% in young rats (D. M. TAYLOR et al. , 1961, recalculated). In 4 of the 6 species studied, initial skeletal deposition of ^{241}Am was about 30% of the dose. The low initial deposition of ^{241}Am in the Chinese hamster skeleton has not yet been clarified. Eleven metabolic

studies of rats parenterally injected with ^{241}Am include measurement of the ^{241}Am content of the skeleton. Within a single experiment the standard deviations (S. D.) ranged from 9 to 18% of measured bone values. In the largest group studied, 20 young adult female rats that were killed 1 to 16 days after intramuscular injection of ^{241}Am citrate, deposition in the skeleton and teeth was $35.7 \pm 4.1\%$ (DURBIN et al. , 1967, 1972c). The S. D. was 11% of the measured mean for skeleton, and the range of ^{241}Am in the skeletons of individual rats was 28 to 45% of the dose.

Variability within a species is therefore, as great as or greater than the differences among species. In addition to individual variations among animals, other causes of the variability of results from the same species include the age of the animals and experimental and analytical techniques.

Three of the 11 ^{241}Am investigations in rats shown in Table 18 were balance studies; that is, all excreta were collected and all tissues were analyzed. Experimental and analytical techniques were refined until approximately 100% of the injected nuclide was recovered (SCOTT et al. , 1948a; LANGHAM and CARTER, 1951; DURBIN et al. , 1967 1972c). Reports of three other ^{241}Am studies with rats include enough information to allow material balances to be calculated (D. M. TAYLOR et al. , 1961; ZALIKIN et al. , 1968; BELYAEV, 1969). The results of NÉNOT et al. (1971b) are not included with the balance studies; although excreta were collected, experimental recoveries were not reported, some tissues were not analyzed, and details of the calculation of ^{241}Am in skeleton were not included.

In five studies with rats, four of which can be classified as balance studies, ^{241}Am was measured in the whole skeleton or in selected bones and the residual carcass (SCOTT et al. , 1948a; LANGHAM and CARTER, 1951; D. M. TAYLOR et al. , 1961; DURBIN et al. , 1967; HOLLINS and DURAKOVIC, 1972). In the other six studies, skeletal ^{241}Am was apparently

estimated as the product of a predetermined or assumed proportionality factor and the ^{241}Am content of one bone or a group of bones (ZALIKIN et al., 1968; BELYAEV, 1969; TSEVELEVA and YEROKHIN, 1969; NÉNOT et al., 1971b). * Unfortunately, none of these reports include the details of any calculations. For the purposes of this review, ^{241}Am measured in whole skeleton has been considered more reliable.

* Several experiments in this Laboratory yielded ^{241}Am measurements in whole skeleton and leg bones (K. G. SCOTT, unpublished; DURBIN et al., 1972c). In adult female rats 1 to 180 days after intramuscular injection of $^{241}\text{AmCl}_3$ or ^{241}Am citrate, the ^{241}Am in whole skeleton was 23.2 times one femur, 26.4 times one tibia, and 12.4 times femur-tibia-fibula. In young male rats (D. M. TAYLOR et al., 1961), ^{241}Am in whole skeleton was 21.3 times one femur, 26.2 times one tibia-fibula, and 12.1 times femur-tibia-fibula.

There are no systematic studies of the variations of ^{241}Am metabolism as a function of injection route, chemical form, or experimental animal age. The 11 studies of the rat (Table 18) can be grouped roughly by animal age as follows: adult (SCOTT et al., 1948a; DURBIN et al., 1967; ZALIKIN et al., 1968; HOLLINS and DURAKOVIC, 1972), immature (LANGHAM and CARTER, 1951; D. M. TAYLOR et al., 1961; BELYAEV, 1969), and age not reported—probably young or intermediate between young and adult (TSEVELEVA and YEROKHIN, 1969; NENOT et al., 1971b).

In the most complete studies, between 80 and 90% of parenterally administered ^{241}Am is initially partitioned between skeleton and liver (Table 18). For purposes of this discussion ^{241}Am in the gastrointestinal contents and passed feces was assumed to have originated in the liver, and was added to the measured liver value to estimate maximum tissue uptake. Within the age groupings above, it appears that initial skeletal deposition of ^{241}Am was greater (and deposition in liver smaller) (a) after administration of the ^{241}Am citrate complex, compared with nitrate or chloride; (b) when ^{241}Am was injected intramuscularly, compared with intravenous administration; (c) in rats with immature skeletons as compared with adults; (d) in those studies in which analytical techniques yielded close to 100% material recoveries, and (e) in those studies in which whole skeletal ^{241}Am was measured rather than estimated.

2. Curium

Skeletal deposition of ^{242}Cm in the rat is nearly the same as that of ^{241}Am . In both young and adult rats, 30.7 and 34.3%, respectively, of intramuscularly injected ^{242}Cm was initially deposited in the skeletons. (SCOTT et al., 1949; K. G. SCOTT, M. H. WILLIAMS, and H. I. JOHNSON, unpublished). Distribution of curium in a larger species (dogs) has been

studied only after inhalation (Table 9). Fifty to 64 days after beagles were exposed to an aerosol of $^{244}\text{CmCl}_3$ or $^{244}\text{CmO}_{1.73}$, their skeletons contained 38.5 and 33.8%, respectively, of the initial lung burden (MCCELLAN et al., 1972); about 85% of the ILB had been absorbed, and skeletal burdens represented slightly more than 40% of the absorbed dose. In comparable inhalation studies with $^{241}\text{AmO}_2$, the skeleton of one beagle killed 127 days after exposure contained 36.2% of the ILB, about 42% of the absorbed dose (R. G. THOMAS et al., 1972).

Nine studies of ^{242}Cm in rats are compiled in Table 19. All but two (NÉNOT et al., 1970) were complete balance studies in which ^{242}Cm was measured in the whole skeleton.* Like ^{241}Am in rats, 80 to 90% of parenterally administered ^{242}Cm is initially divided between liver and skeleton (Table 19). The initial partition of ^{242}Cm between these two tissues seems to be similarly influenced--but to a lesser degree--by the same factors that influence the initial distribution of ^{241}Am in this species (see Section VII. A. 1. above). In adult female rats early skeletal deposition of ^{242}Cm was the same after intramuscular injection of either $^{242}\text{CmCl}_3$ or ^{242}Cm citrate, but was slightly reduced if either compound were given intravenously. Early skeletal deposition seems to be greater in the younger rats, but the effect is not certain, because the age of the young rats is not known exactly.

3. Berkelium

There is only one study of the metabolic behavior of berkelium. HUNGATE et al. (1972) reported that at 4 hr and 21 days after intravenous injection of $^{249}\text{BkCl}_3$ in rats, the skeleton contained 30 and 38% of the

*In this Laboratory ^{242}Cm in the whole adult rat skeleton was 11.3 times the ^{242}Cm in one femur-tibia-fibula.

injected dose, respectively. The amount contained in the total skeleton was calculated using 20 times the measured value for one femur. The femur contents of ^{241}Am and $^{249-252}\text{Cf}$ in the rat were 0.043 and 0.045 of the total skeletal nuclide, respectively. Using the average femur content of these two closely related elements, the calculated values for ^{249}Bk in the rat skeleton are 34.4 and 43.5% at 4 hr and 21 days after injection, respectively. The recalculated values for ^{249}Bk in skeleton were used to prepare Table 12.

Although excreta were collected and analyzed, as were most tissues, the calculated recovery of the injected ^{249}Bk 21 days after injection was only 84.5%. A low recovery implies that the stated values of all tissues including skeleton, are low, unless all of the losses were incurred in collection of excreta. The soft tissues (excluding liver) still contained 11.5% of the dose 21 days after injection, and undoubtedly contained a larger fraction of the dose immediately after injection. During the same period, the skeleton probably accumulated additional ^{249}Bk released from soft tissues, thus the amount of ^{249}Bk in the skeleton 21 days after injection may overestimate the initial deposition in bone.

4. Californium

Biological studies have been conducted with ^{249}Cf , ^{252}Cf , or a mixture of californium isotopes designated herein as $^{249-252}\text{Cf}$ (the ^{250}Cf and ^{252}Cf isotopes contribute more than 75% of the weight of the original mixture). Even though isotopic designations have been retained for clarity, this usage does not imply any differences in the metabolic behavior of the different isotopes in the absence of radiation damage.

Initial skeletal deposition of californium (see Tables 12 through 17) ranged from 28% of ^{252}Cf in Chinese hamsters (MEWHINNEY et al., 1972) to 64.3% of $^{249-252}\text{Cf}$ in adult rats (DURBIN et al., 1972d). In all species

examined to date, initial skeletal deposition of californium has been greater than that of americium, curium, or berkelium. In the three most thoroughly studied species, the early bone depositions of both californium and americium declined in the order: rat > beagle > Chinese hamster. It is not known at the present time whether the larger amounts of californium and americium deposited in the skeletons of the rats (compared with other species) are caused by less efficient renal excretion or greater skeletal affinity or both.

In all of the studies to date, californium has been administered as a citrate complex, so there is no information on whether the nature of the compound influences distribution. Trends in chemical properties, especially the lesser tendency towards hydrolysis compared with americium and curium, suggest that the distribution pattern of californium will not be significantly changed by its introduction as a potentially hydrolyzable salt.

The data in Tables 12 and 13 indicate a somewhat lower initial bone deposition of ^{252}Cf in growing rats (56.3%) than of $^{249-252}\text{Cf}$ in adults (64.3%)--the reverse of expectation. However, the amount of $^{249-252}\text{Cf}$ in the hind-leg bones was 5.5% in the growing rats and 5.2% in the adults 4 days after injection. Some of the difference in total skeletal content may have resulted from the proportionality factor ($18.7 \times$ one femur) used by MEWHINNEY et al. (1972) to estimate total skeletal ^{252}Cf . In the adult rats $^{249-252}\text{Cf}$ was measured in all of the bones, and the entire skeleton contained 21.8 times the $^{249-252}\text{Cf}$ in one femur, 28.1 times that in one tibia, and 12.3 times that in the femur-tibia-fibula, (DURBIN et al., 1972d).

5. Einsteinium

Some preliminary studies have been made of ^{253}Es metabolism in rats and mice. In both species the initial skeletal deposition of ^{253}Es was slightly greater than or equal to that of $^{249-252}\text{Cf}$ (Tables 12 and 14). Seven days after

intravenous injection of $^{253}\text{Es}(\text{NO}_3)_3$ the rat skeleton contained 68.8% of the dose (V. H. SMITH, 1972b) compared to 64.3% of $^{249-252}\text{Cf}$ (DURBIN et al., 1972d). Four days after intramuscular injection of ^{253}Es citrate, skeletal deposition in the mouse was 46.5% compared to 43% of ^{252}Cf (PARKER et al., 1962, 1972).

When $^{253}\text{EsCl}_3$ was administered to rats, initial urinary excretion of ^{253}Es was higher and skeletal deposition lower than when $^{253}\text{Es}(\text{NO}_3)_3$ was injected. The ^{253}Es in the skeleton and in accumulated urine and feces was 31.3%, 41.3%, and 4.4%, respectively, 21 days after intravenous injection of $^{253}\text{EsCl}_3$ (HUNGATE et al., 1972). [Compare these results with the data shown in Table 12 for intravenously injected $^{253}\text{Es}(\text{NO}_3)_3$.] If the raw data from the $^{253}\text{EsCl}_3$ study are normalized to take account of the 4-fold greater urinary excretion of $^{253}\text{EsCl}_3$, the initial skeletal deposition becomes 50% of the normalized dose--closer to, but still less than the initial skeletal uptake of ^{253}Es administered as the nitrate.

The ^{253}Es content of several separate bones of the rat was measured 24 days after injection of $^{253}\text{Es}(\text{NO}_3)_3$, and the total ^{253}Es in the bony tissues was found to be 23.9 times the ^{253}Es content of one femur.

6. Trends in skeletal deposition of the actinides

As noted in Section II.B, a systematic study of the metabolism in rats of the 14 lanthanide elements (DURBIN et al., 1956) revealed several trends that could be related to the decrease in ionic radius that accompanies the filling of the 4f-shell of electrons--greater initial skeletal uptake, greater early renal excretion, and reduced initial liver uptake. The metabolic behavior of ^{241}Am and ^{242}Cm resembled that of lanthanides of comparable ionic size (DURBIN, 1962). Two more actinides, ^{249}Bk and ^{253}Es , have recently been investigated, and more reliable information is now available for ^{241}Am , ^{242}Cm , and $^{249-252}\text{Cf}$. It seems appropriate to reexamine the

dependence of the metabolic behavior of the trivalent actinides on their ionic radii.

Table 20 summarizes the initial partitions of the lanthanide and trivalent actinide elements among skeleton (including incisors), liver ($L_{\max}$), and residual soft tissues (S. T.) of the rat. The data have been recalculated to reduce the variability caused by (a) differences in material recovery, (b) less than complete absorption in intramuscular studies, and (c) greater renal excretion of the heavier members of both series. In 16 of 19 studies, tissue distribution data were available 4 days after injection, and results have been expressed as percent of the body burden at 4 days (BB).*

The behavior of lanthanides and actinides with the same ionic radii, in chemical reactions that depend on the ionic radius, is similar (COTTON and WILKINSON, 1966). On the basis of their chemistry and on the earlier observation of the behavior of ^{241}Am and ^{242}Cm , it was expected that the initial distributions of the heavier actinides would also resemble those of the lanthanides of the same ionic radii but with fewer f -electrons. It can be seen from Table 20 that the initial distribution pattern of ^{241}Am was, as expected, nearly the same as that of ^{147}Pm (same ionic radius, 0.98 Å and two less f -electrons). There is no ready explanation, except for the great stability of the $5f^7$ configuration of ^{242}Cm , to account for its unusual metabolic behavior which most closely resembled that of cerium and praseodymium (with larger

*
$$\text{BB} = \text{Sk} + L_{\max} + \text{S. T.} = 100 - \Sigma \text{U} \quad \text{Eq. (14)}$$

where BB is the body burden 4 days after injection corrected for material recovery and absorption; Sk and S. T. are the skeletal and residual soft tissue nuclide contents at day 4; ΣU is the amount of nuclide excreted in urine during the first 4 days after injection, and $L_{\max}$ is the maximum liver uptake calculated from Eq. 23 (Section VIII.A.1.)

ionic radii and 5 to 6 fewer f-electrons). The distributions of the three heavier actinides, ^{249}Bk , $^{249-252}\text{Cf}$, and ^{253}Es , most closely resembled lanthanides of slightly smaller ionic radii and one to two fewer f-electrons.

The trivalent lanthanides and actinides form stable complexes with many organic acids (Chapter 17, this volume). The formation constants of the complexes of the trivalent elements and the aminopolycarboxylic acids, EDTA, DCTA, and DTPA, have been measured (lanthanides, MACKEY et al., 1962; MOELLER and THOMPSON, 1962; MOELLER and HSEU, 1962; actinides, FUGER, 1958, 1961; BAYBARZ, 1965, 1966). The stabilities of the EDTA-actinide chelates are much greater, and those of the DCTA-actinide and DTPA-actinide chelates are somewhat greater than the chelates of the lanthanides of the same ionic radii. It appears that the initial uptake of the heavier actinides in bone fits the pattern of the stabilities of the actinide-organic acid chelates.

In the 10 years since it was suggested that the distributions in mammals of the lanthanides and actinides were dependent upon their ionic size, much information has accumulated on the mechanisms of transport of these elements in blood and of their binding in bone and liver.

The reactions between trivalent cations and bone surfaces probably do not control the overall distribution of these elements, although they may influence it. Bone surfaces accumulate many cations present in the circulation that can neither be utilized nor excreted. The mechanisms of accumulation in bone may include such reactions with bone mineral as adsorption, ion exchange, and ionic bond formation (NEUMAN and NEUMAN, 1958) and (or) the formation of complexes with proteins or other organic bone constituents (D.M. TAYLOR, 1972; Chapter 17, this volume).

The uptake of lanthanides and actinides by bone mineral appears to be independent of the ionic radius. D. M. TAYLOR et al. (1971) have shown

that the in vitro uptake on powdered bone ash of $^{241}\text{Am(III)}$ (ionic radius 0.98 Å) and of $^{239}\text{Pu(IV)}$ (ionic radius 0.90 Å) were nearly the same, $97\% \pm 1.6$ and $98.3\% \pm 0.7$, respectively. In vitro experiments by FOREMAN (1962) suggested that Pu(IV) accumulates on powdered bone or bone ash by adsorption, a relatively nonspecific reaction. On the other hand, reactions with organic bone constituents appear to be dependent on ionic radius. The complexes of the smaller Pu(IV) ion and any of the organic bone constituents tested thus far were much more stable (as determined by gel filtration) than the complexes with Am(III) or Cm(III) (D. M. TAYLOR, 1972).

The mechanisms by which the liver accumulates noncolloidal trivalent cations are not yet understood, but because they involve membrane transport, they are likely to be specific and dependent upon ionic size. It has been shown in the case of iron (FAWWAZ et al., 1966) and suggested in the case of Pu(IV) (DURBIN et al., 1972a) that liver accumulates only nuclide not bound to plasma protein. If that interpretation is correct, liver uptake would depend on the degree of plasma protein binding, which is in turn dependent upon ionic size. Further, the smaller the ionic radius of a lanthanide (and presumably of an actinide also) the greater is the tendency to hydrolyze; however, the hydrolysis products of the heavier lanthanides are soluble.* The liver does not accumulate most divalent cations, and the primary hydrolysis products of trivalent cations are of the form, M(OH)^{+2} . Thus, hydrolysis would also tend to reduce liver uptake of the smaller, heavier members of both series in a regular way that was also dependent upon ionic radius.

Binding to plasma proteins, which has been shown to be dependent upon ionic size (TURNER and TAYLOR, 1968b; BRUENGER et al., 1971;

*The greater solubility of primary hydrolysis products of the heavier lanthanides may account for their greater early renal excretion.

STEVENS and BRUENGER, 1972), is obviously important and may well be the determining factor, in the partition of the multivalent cations among bone, liver, soft tissues, and renal excretion. Both a high degree of plasma protein binding and formation of soluble, less highly-charged hydrolysis products would inhibit liver uptake and lead to greater deposition in bone as well as greater renal excretion.

B. Intraskkeletal distribution

The ^{241}Am , $^{249-252}\text{Cf}$, or ^{253}Es contents of separate bones of rats, the ^{241}Am or ^{249}Cf contents of selected bones of beagles, and the ^{241}Am contents of individual bones of cynomolgus monkeys and baboons are shown in Table 21. Data are presented as percent of the total skeletal nuclide. Also included is the percent of total skeletal ash in the various bones of rats, beagles, and cynomolgus monkeys.

Except for the larger ^{241}Am content of the skull and mandible of the monkey, the intraskkeletal distributions of ^{241}Am were nearly the same in the two primate species. The intraskkeletal distributions of ^{241}Am , $^{249-252}\text{Cf}$, and ^{253}Es were similar in the rats; ^{241}Am and ^{249}Cf distributions were similar in the beagles. In all four species the fraction of skeletal nuclide was about the same as the skeletal ash content of scapulae, clavicles, cervical vertebrae, ribs, humeri, femora, * pelvis, and patellae. The skeletal nuclide was greater than the ash fraction of the thoracic, lumbar, and caudal vertebrae and sternum. Skeletal nuclide content was less than the ash fraction of skull, mandible, distal long bones, * and paw bones.

C. Microscopic distribution

The local deposition of ^{241}Am on trabecular, endosteal, and periosteal surfaces and around cortical vascular channels in the long bones of

*The nuclide content of the rat tibiae was the same as the ash fraction.

mature and growing rats was demonstrated autoradiographically almost as soon as the nuclide was available for biological study (HAMILTON, 1947, 1948; SCOTT et al., 1948a; LANGHAM and CARTER, 1951; ASLING et al., 1952). The detailed autoradiographic studies of J. S. ARNOLD and JEE (1957) using ^{239}Pu and of HERRING et al. (1962) using ^{241}Am show conclusively that the ultimate site of deposition of these cations is the mineralized bone surface immediately beneath the cellular layer of trabeculae, endosteum, periosteum, or cortical vascular channels.

The early observations of ^{241}Am in rat bone have been confirmed and extended by others using improved bone sectioning techniques and special nuclear emulsions (D. M. TAYLOR et al., 1961; DURBIN et al., 1967; NÉNOT et al., 1972). The microscopic distribution of ^{241}Am has more recently been studied in the bones of other species: dog (HERRING et al., 1962; LLOYD et al., 1972a), mouse (HAMMARSTRÖM and NILSSON, 1970a,b), and cynomolgus monkey (DURBIN et al., 1972c). Curium-242 and $^{249-252}\text{Cf}$ have been studied only in the bones of rats. The microscopic distribution of these two actinides in the long bones and vertebrae of rats was indistinguishable from that of ^{241}Am (HAMILTON, 1947, 1948; SCOTT et al., 1949; NÉNOT et al., 1972; MEWHINNEY et al., 1971; DURBIN et al., 1972d).

1. Initial distribution of ^{241}Am and $^{249-252}\text{Cf}$ in rat long bones

Typical autoradiographs are shown of the initial deposition of ^{241}Am in the femur (Fig. 14a) and of $^{249-252}\text{Cf}^*$ in the tibia of the young adult rat (Fig. 15a). The animals were killed 4 days after the intramuscular injection of the nuclides as citrate complexes; absorption was nearly complete. As HAMILTON (1947, 1948) and SCOTT et al. (1948a, 1949) described for comparable preparations with ^{241}Am or ^{242}Cm , the nuclides shown in

*The ^{252}Cf isotope had largely decayed by the time the autoradiographs were prepared.

Figs. 14 a and 15 a were deposited most heavily about the trabeculae of the primary spongiosa and on epiphyseal and metaphyseal trabeculae. Less intense deposits were found on the endosteal and periosteal surfaces of the shaft and in spots throughout the cortex corresponding to the locations of blood vessels. The local bone depositions of ^{241}Am and ^{242}Cm were described by HAMILTON (1948) as indistinguishable from the depositions of the trivalent nuclides, ^{144}Ce , ^{147}Pm , and ^{227}Ac , but different from the depositions of the tetravalent nuclides, ^{95}Zr , ^{228}Th , and ^{239}Pu , in that the +4 nuclides were not deposited in significant amounts around cortical blood vessels.

The autoradiographs in Figs. 14 a and 15 a, prepared by more refined techniques, permit the demonstration of additional initially heavy concentrations of ^{241}Am or $^{249-252}\text{Cf}$ in the long bones of female rats 4 to 5 months old--on the surfaces of newly forming trabeculae beneath the articular cartilage and on the bony plate just above the proliferating cartilage of the epiphyseal plate. As in the early gross preparations, the bone spicules of the primary spongiosa are too small and too crowded to be resolved.

Using the method of alpha-track counting, D. M. TAYLOR et al. (1961) estimated local radiation dose rates at various locations in the femora of 7-week-old male rats. The average dose rates 1 to 8 days after intravenous injection of $3.3\mu\text{Ci/kg}$ of ^{241}Am citrate were as follows: in the epiphysis, ossification centers below the articular cartilage and above the epiphyseal cartilage, 102 to 108 rad/day; in the metaphysis, above and below the active band in the primary spongiosa, 30 to 65 rad/day; in the active band, 136 rad/day; beneath the periosteum, 101 rad/day; and in the diaphysis, endosteum, 20 rad/day; periosteum, 35 rad/day; and perivascularly, 36 rad/day.

2. Initial deposition of ^{241}Am in monkey bone

The distribution of ^{241}Am in several bones of cynomolgus monkeys is shown grossly in Figs. 16 and 17. In the autoradiographs prepared from the

bones of adult females (more than 6 years of age^{*}) killed 8 days after intravenous injection of $0.56 \mu\text{Ci/kg}$ of ^{241}Am citrate, bone surfaces--trabecular, endosteal, periosteal, and perivascular--were labeled almost uniformly. HERRING et al. (1962) showed that the microscopic distribution of ^{241}Am on the bone surfaces of growing dogs varied with the growth activity of those surfaces. In decreasing order ^{241}Am deposition was: resorbing surfaces $\geq$ inactive (resting) surfaces $>$ active (growing) surfaces. LLOYD et al. (1972a) measured alpha-track densities of endosteal and periosteal surfaces of bones of young adult beagles killed 21 days after injection of $2.8 \mu\text{Ci/kg}$ of ^{241}Am . The intensity of labeling of epiphyseal and metaphyseal trabeculae in the distal femur was 1.5 times that of periosteal surfaces, and in the vertebral body the trabecular label was twice as intense as that of the periosteal surfaces. At age 6 years or more one would not expect a significant fraction of the total bone surface of the monkeys either to be growing or resorbing at any given time. Although the overall impression of the ^{241}Am distribution in the adult monkey bones is that of uniform labeling, closer inspection revealed gradations in the intensity of the label, as predicted by the studies of HERRING et al. (1962) and LLOYD et al. (1972a).

Autoradiographs were also prepared from bone sections taken from an adolescent monkey (2.5 years of age) killed 8 days after intravenous injection

^{*}The ages of the monkeys were estimated from the dentition-age data of HURME and VAN WAGENEN (1961) and skeletal roentgenograms and the bone-age data of VAN WAGENEN and ASLING (1958).

of 0.56 $\mu\text{Ci/kg}$ of ^{241}Am citrate. (See Figs. 16 c,d and 17 a, c.) Distribution of ^{241}Am in the adolescent skeleton was less uniform than in the adult skeleton and resembled the distribution of ^{241}Am in bones of young adult beagles (LLOYD et al. 1972a). Especially heavy concentrations of ^{241}Am were present on ragged (presumably resorbing) surfaces of the humerus midshaft (Fig. 16 e), below the articular cartilage and in the primary spongiosa of the proximal humerus (Fig. 17 a), and on apparently resorbing surfaces of the spinous process of the lumbar vertebra (Fig. 17 c). Some lightly labeled surfaces on the trabeculae in the proximal humerus and vertebral body were also apparent.

Using thin sections of undecalcified rat long bone permanently affixed to nuclear track plates, LANGHAM and CARTER (1951) showed that the intense band of radioactivity just below the epiphyseal cartilage (see Figs. 14 a, 15 a, 17 a) was the result of ^{241}Am deposited on the many tiny newly calcified spicules of the primary spongiosa. Interdigitated with capillary tufts, these fine spicules of bone constitute a large, well-vascularized, readily available mineralized surface. A high power view of the calcifying cartilage of the proximal humeral epiphysis of an adolescent monkey is shown in Fig. 18 a.

JEE and ARNOLD (1960) demonstrated the accumulation of ^{228}Th and ^{239}Pu on the dentinal surfaces of the pulp cavity and the cemental surfaces of the roots of the teeth of young adult dogs. HAMMARSTRÖM and NILSSON (1970 a, b) used whole-body sections of adult mice and of suckling rats to demonstrate the presence of ^{241}Am in the pulp of the incisors and the developing molars (as well as on the dentinal surfaces) during the first few hours after injection. Presumably the presence of ^{241}Am in the dental pulp is temporary as is the presence of ^{241}Am in bone marrow (HAMMARSTRÖM and NILSSON, 1970 a). Deposition of ^{241}Am on the cemental surface of the premolar of an adult monkey is shown in Fig. 16 b. The section was not central, and two small dark spots at the level of the gum line are all that can be seen

of the pulp cavity.

3. The effect of bone remodeling on distribution

As a whole, the mammalian skeleton is not static. During the life span the skeleton undergoes a great deal of structural change (FROST, 1963). During growth, remodeling is extensive and rapid and is accompanied by a net increase in bone mass. In adult life, remodeling proceeds slowly and involves only a fraction of the skeleton at any one time; there is little net change in skeletal mass. In some bones of some mammals during the last one-half to one-third of the life-span, resorptive activity exceeds bone replacement leading to a net loss of skeletal mass.

Most of the information concerning the effect of skeletal remodeling on the distribution of the transplutonium elements in bone has been obtained from the study of ^{241}Am in rats. J. S. ARNOLD and JEE (1957) described the effects of growth and remodeling on the distribution pattern of ^{239}Pu in the bones of rats. In general, the long-term distribution and redistribution of the transplutonium elements is much like that of ^{239}Pu (D. M. TAYLOR et al., 1961; DURBIN et al., 1967). Surfaces labeled on the day of injection may be unchanged (Fig. 18 b); they may be partially or completely resorbed or they may be buried by new bone laid down on trabeculae (Figs. 14 b and 15 b), beneath endosteum or periosteum (Figs. 15 c and 18 a), or on the surfaces of vascular channels (Fig. 18 d).

Skeletal maturation in the rat is different from that of most mammals. The epiphyses of the long bones comprising the knee and elbow joints--those bones that have been studied most--do not undergo true union (SIMPSON et al., 1950). Although longitudinal growth ultimately ceases, and the epiphyseal cartilage becomes thin and inactive, degeneration of chondrocytes and formation of new primary spongiosa proceed slowly in both sexes well

into middle life (6 to 12 months beyond sexual maturity). In spite of the unusual persistence of un-united epiphyses in the rat, it is a useful animal in which to study bone growth and remodeling: It is a well-characterized species; its life span is only about 3 years—compressing growth, adulthood, and senility into a short span of time.

The most obvious effect of bone remodeling on ^{241}Am distribution in growing rats is the prompt resorption of the active band of ^{241}Am deposited in the primary spongiosa on day 1. In their studies of ^{241}Am distribution, D. M. TAYLOR et al. (1961) examined the femora of male rats injected at 7 weeks of age with $3.3 \mu\text{Ci/kg}$ of ^{241}Am citrate and killed at intervals up to 21 days later. * Twenty-one days after injection, the primary spongiosa elaborated on day 1 had been resorbed except for that portion that had been incorporated into the shaft. The ^{241}Am deposited beneath the articular cartilage had been covered by new bone. Some of the endosteal deposit in the upper metaphysis had been resorbed, and the periosteal deposit in the diaphysis had been buried by new bone.

Alpha-track counting yielded the following local dose rates 21 days after injection: in the epiphysis, the ossification center beneath the articular cartilage, 43 rad/day--about one-half the dose rate delivered to that structure 1 to 8 days after injection; in the bony plate above the epiphyseal cartilage, 157 rad/day--50% greater than the initial dose rate; in the metaphysis the radioactivity was gone from the primary spongiosa and this structure was no longer being irradiated; beneath the periosteum of the upper metaphysis, in

*The skeletons of male and female rats grow at about the same rate during the early weeks of life. Between the ages 49 and 70 days the femora of female Charles River rats gained 18% in length, 29% in wet weight, and 113% in ash weight.

the remnant of the day-1 spongiosa, 144 rad/day--about 40% more than the early dose rate; in the diaphysis—in the endosteum, periosteum, and perivascularly—21, 24, and 38 rad/day, respectively--about the same dose rates in these structures as were measured 1 to 8 days after the injection.

In more mature female rats (injected with 0.37 $\mu\text{Ci/kg}$ of ^{241}Am citrate at 110 days of age) longitudinal growth was proceeding slowly, and 95 days after injection some of the day-1 spongiosa was still present (Fig. 14b). Remnants of the day-1 spongiosa persisted through 180 days, but these were completely removed by 300 days after injection (DURBIN et al., 1967). The autoradiographs shown in Figs. 15 a,b were prepared from bones of female rats injected with 0.33 $\mu\text{Ci/kg}$ of $^{249-252}\text{Cf}$ citrate at 140 days of age. During the 91 days after injection there was little growth in length; most of the day-1 spongiosa was still present. In the studies of MEWHINNEY et al. (1971) in which 7.7 $\mu\text{Ci/kg}$ of ^{252}Cf were injected into 37-day-old male rats, longitudinal growth continued, but some of the day-1 spongiosa was still present—associated with a bony plate in the upper diaphysis suggesting that resorption had been disturbed by the high radiation dose (HELLER, 1948; DURBIN et al., 1958; FABRIKANT and SMITH, 1964).

A significant fraction of ^{241}Am (DURBIN et al., 1967) and ^{239}Pu (J. S. ARNOLD and JEE, 1957) released from bone destroyed by remodeling recirculates and is redeposited on bone surfaces; some of these surfaces were present at the time of injection, some were formed later. If recirculated ^{241}Am is deposited on preinjection surfaces, their autoradiographic image will be augmented. If recirculated ^{241}Am is deposited on surfaces formed after the injection, their autoradiographic image will be lighter and less distinct than the surfaces labeled on day 1. In Figs. 15 b,c, prepared from bones of rats killed 91 days after injection of $^{249-252}\text{Cf}$, californium can be seen

deposited on recently formed primary spongiosa, on the endosteal surface of the dorsal metaphysis of the tibia, and on some new vertebral trabeculae. If the new surfaces are in a region undergoing continuous accumulation of new bone, the bone laid down after injection will be diffusely labeled throughout (COPP et al., 1947; J. S. ARNOLD and JEE, 1957; JEE, 1972).

The long-term effects of slow continuous remodeling and redistribution on the distribution of ^{241}Am are seen in the autoradiographs in Fig. 15 c prepared from a rat killed 739 days after injection of ^{241}Am citrate at 110 days of age. Radiochemically, the femur of this rat contained two-thirds of the ^{241}Am radioactivity present in the femur of a rat killed at 4 days. There are fragmentary remnants of the day-1 spongiosa in the dark bands in the upper metaphyseal cortex and in isolated spots in the marrow cavity of the diaphysis. Outlines of the epiphyseal trabeculae are light and woolly, indicating deposition on trabeculae formed after the ^{241}Am injection. The outline of the entire cortex is thin, and the endosteal deposit is light, suggesting that the original endosteal deposit had been resorbed and that the ^{241}Am now present was redistributed ^{241}Am that had been laid down on previously unlabeled surfaces. As the outline of the inner and outer margins of the bone from which Fig. 15 c was made shows, most of the original endosteal deposit in the diaphysis had been resorbed, and the entire circumference of the day-1 periosteal deposit had been covered by a thick layer of new bone. In the epiphysis, the trabecular outlines are pale and indistinct, indicating deposition on structures formed after the injection. The ^{241}Am deposit which was laid down just beneath the articular cartilage had been removed. The only identifiable remnant of the bone as it existed the day of injection was the bony plate above the epiphyseal plate, and even here the marrow had penetrated in several places in an approach to epiphyseal union.

D. Retention of ^{241}Am and ^{242}Cm

1. Rat

The original studies with ^{241}Am and ^{242}Cm in rats indicated that, like ^{239}Pu and the lanthanides, the fraction of these transplutonium nuclides deposited in the skeleton would very likely remain there for a long time. HAMILTON (1947, 1948) and SCOTT et al. (1948a, 1949) could not detect any loss of ^{241}Am or ^{242}Cm from the rat skeleton over a period of 256 days after injection. However, both nuclides had been administered intramuscularly as chlorides, and 4 to 6% of the injected dose of each nuclide was absorbed between the 16th and 256th days. A small loss from bone could have been masked by replenishment from the injection site. More recent long-term studies in rats demonstrate that ^{241}Am is lost very slowly from the skeleton (DURBIN et al., 1967; 1972c).

D. M. TAYLOR et al. (1961) reported a biological half-time of 1600 days for ^{241}Am in the rat femur when ^{241}Am citrate was injected intravenously in 7-week-old male rats at a level of $3.3 \mu\text{Ci/kg}$. Femurs were obtained from 37 rats that died or were killed from 21 to 539 days after injection. DURBIN et al. (1969) analyzed ^{241}Am in several bones, the incisors, and the entire skeletons of 150 young adult female rats killed from 1 to 779 days after a single intramuscular injection of $0.33 \mu\text{Ci/kg}$ of ^{241}Am citrate. The complexed ^{241}Am was absorbed rapidly (97% in 24 hr), so the results were not perturbed by a persistent reservoir. The standard deviations of the mean values of the skeletons and the sampled bones were of the order of 10% at 1, 4, and 8 days after injection. In some cases the S. D. exceeded the amount of ^{241}Am apparently lost during the entire 779-day observation period. The scatter of the data was reduced by eliminating from calculations the data from 39 rats for which the measured or estimated material recovery deviated more than one S. D. from the mean recovery for all 150 rats.

The smoothed data for retention of ^{241}Am in the whole skeleton (incisors excluded) and for 20X femur are shown in Fig. 19, which also includes a curve prepared from the data of D. M. TAYLOR et al. (1961) for retention of ^{241}Am in the femora of young male rats. Retention curves* were fitted by the method of least squares as follows (t is days after injection:

$$\text{Femora, } F_t(\%) = 0.44e^{-0.013t} + 2.92e^{-0.0002t} \quad \text{Eq. (15)}$$

$$\text{Tibiae, } T_t(\%) = 0.30e^{-0.015t} + 2.45e^{-0.00026t} \quad \text{Eq. (16)}$$

$$\text{Vertebrae, }^{**}V_t(\%) = 0.32e^{-0.017t} + 1.48e^{-0.00027t} \quad \text{Eq. (17)}$$

$$\text{Ribs, }^{**}R_t(\%) = 0.10e^{-0.013t} + 0.32e^{+0.00015t} \quad \text{Eq. (18)}$$

$$\text{Mandibles, } M_t(\%) = 0.98e^{+0.00009t} \quad \text{Eq. (19)}$$

$$\text{Skeleton, } Sk_t(\%) = 2.0e^{-0.017t} + 33e^{-0.00015t} \quad \text{Eq. (20)}$$

There was a small but measurable early loss of ^{241}Am from long bones, vertebrae, ribs, and the whole edentate skeleton--half-times ranged from 40 to 50 days. However, the major losses occurred more slowly: half-times were 2500, 2700, and 3500 days in lumbar vertebrae, tibiae, and femora, respectively. The slopes of the ^{241}Am retention curves for ribs and mandibles were positive. Retention of ^{241}Am in the whole skeleton is the summation of the retentions in the separate bones, and the half-time of retention of ^{241}Am in the entire skeleton was 4600 days.

There is a two-fold difference between the biological half-times of ^{241}Am measured in the femora in the two experiments. DURBIN et al. (1967, 1972e) used rats in which the growth of the long bones was 90% complete. The ^{241}Am dose was low; there were no detectable hematological changes,

*The parameters of the retention equations, Eq. 15 through 20, are from DURBIN et al. (1967).

**Samples consisted of 3 lumbar vertebrae (L4, 5, 6) and 5 large ribs.

and, except for some transient morphological changes in liver and kidney, no detectable consequences of radiation in the tissues and bones. On the other hand, D. M. TAYLOR et al. (1961) used rapidly growing rats. They were injected at a level of $3.3 \mu\text{Ci/kg}$ of ^{241}Am , a dose which was shown subsequently by the same investigators to disturb the growth of the long bones--with osteoporosis in the ends and osteosclerosis in the shafts--and to induce bone tumors in 20% of the rats within 525 days of the injection (FABRIKANT and SMITH, 1964; BENSTED et al., 1965). Either greater resorption during growth, or bone loss consequent to radiation damage, could lead to more rapid elimination of ^{241}Am than was observed in the more mature rats given the smaller amount of ^{241}Am .

J. S. ARNOLD and JEE (1957, 1959) proposed that ^{239}Pu does not participate in exchange reactions, but was only lost from bone surfaces when they were physically destroyed by resorption. DURBIN et al. (1967) showed that ^{241}Am was lost from long bones and vertebrae of rats (bones that lose ash weight after middle life), but was not lost from the mandibles (bones that achieve constant ash weight late in life), and continued to accumulate in the ribs (bones that gain ash weight during the entire life span). These findings were interpreted as evidence that ^{241}Am , and presumably the other trans-plutonium elements, are lost from bone only in the course of remodeling.

The autoradiographs in Figs. 14 a,b,c and 15 a,b show that during the life span of the female rat the long bones undergo extensive remodeling, which appears to involve most of the initially labeled trabecular surfaces. Yet during the 779 days of the experiment, that portion of the initial ^{241}Am deposit that had been eliminated was only 26% in the femora and 35% in the lumbar vertebrae (DURBIN et al., 1967).

There is a persistent but declining level of ^{241}Am in all of the soft tissues and in the continually growing incisors of the rat long after the initial

deposits of ^{241}Am have been cleared from these sites. The autoradiographs in Figs. 14 b, c and 15 b also show that both ^{241}Am and $^{249-252}\text{Cf}$ continue to be deposited in bone. The source of the persistent low-level supply of these nuclides can only be the skeleton itself. Using the material balance of ^{241}Am in the skeleton, tissues, and excreta, DURBIN et al. (1967) calculated that at least 40% of ^{241}Am released from bone was redeposited in bone and that the measured biological half-time in bone, $T_{1/2 \text{ obs}}$, was related to the physiological half-time of the labeled surfaces, $T_{1/2 \text{ phys}}$, by the equation

$$T_{1/2 \text{ obs}} = T_{1/2 \text{ phys}} / (1 - fr), \quad \text{Eq. (21)}$$

where fr is the fraction of circulating nuclide that is redeposited. In general, redeposition has the least effect on the skeletal retention of the alkaline earths. The presence of the large excess of stable calcium dilutes the radionuclide, promotes excretion, and reduces reutilization. The loose protein binding also facilitates excretion. Redeposition has the greatest influence on retention of Pu(IV) . The strong protein binding promotes reutilization and impedes excretion. The trivalent lanthanides and actinides lie somewhere between these extremes.

2. Chinese hamster

MCKAY et al. (1972) calculated the skeletal content of ^{241}Am from analyses of bones taken 225 and 360 days after injection of $1 \mu\text{Ci/kg}$ of ^{241}Am citrate into Chinese hamsters. The half-time of ^{241}Am in the Chinese hamster skeleton, based on these two measurements, is at least 1450 days.

3. Monkey

In an ongoing long-term study of ^{241}Am metabolism in cynomolgus monkeys, 19 adult females have been injected with 0.44 to $0.87 \mu\text{Ci/kg}$ of ^{241}Am citrate (DURBIN et al., 1972c). Eighteen complete skeletons have been analyzed (taken from monkeys killed 1 to 973 days after injection). The

^{241}Am content of the skeleton of one living animal (#75) has been estimated from continuous excretion measurements (Fig. 20) and from the liver and soft tissue ^{241}Am -retention curves (Fig. 21). The skeleton of monkey #75 was estimated to contain 35% of the dose 1400 days after injection. Determination of the retention of ^{241}Am in the skeleton of this species is complicated by (a) individual variation in initial skeletal uptake and (b) by the continuous skeletal accumulation of ^{241}Am during the 300-day interval of soft-tissue and liver clearance (Fig. 20).

After 100 days the skeletal retention curve appears to consist of 2 components. The slope of the long-term component, defined by only 4 animals killed between 700 and 1400 days, is not different from zero. If it is assumed that the liver and soft tissues continue to lose ^{241}Am at the rates shown in Fig. 21, the sum of the liver and soft-tissue ^{241}Am can be calculated and then subtracted from the whole-body retention shown in Fig. 20. Using only the data from monkey #75, the half-time of skeletal retention of ^{241}Am in the monkey is estimated to be 12,600 days (34.5 years). If a straight line with this slope is fitted to the whole-body retention curve in Fig. 20, the slope of the first component can be obtained graphically. The retention equation for ^{241}Am in the monkey skeleton is estimated to be (t is days after injection)

$$\text{Sk}_t(\%) = 11e^{-1.6 \times 10^{-3}t} + 36e^{-5.5 \times 10^{-5}t} \quad \text{Eq. (22)}$$

4. Dog

Long-term experiments with ^{241}Am in beagles have been underway for several years (LLOYD et al., 1967a,b). As of March 1972, 101 beagles had each been given a single intravenous injection of ^{241}Am citrate at dose levels ranging from 0.002 to 4.5 $\mu\text{Ci/kg}$ (LLOYD et al., 1970, 1971, 1972c; T. F. DOUGHERTY, 1972). Unfortunately, retention of ^{241}Am in the dog skeleton cannot now be estimated from analysis of the bones of individual dogs. At

the 2.8 $\mu\text{Ci/kg}$ level, radiation damage in the liver was so severe that by 100 days after injection there was massive destruction of liver tissue followed by release of a large fraction of the ^{241}Am initially deposited in that organ. Loss of ^{241}Am from the liver was delayed, but became significant 1 year after injection of 0.9 $\mu\text{Ci/kg}$ and 2 years after injection of 0.3 $\mu\text{Ci/kg}$ (LLOYD et al., 1970, 1972 a, c, d). The ^{241}Am released from the liver was partly excreted and partly recirculated to other soft tissues and to the skeleton. The skeletons of the dogs in the 0.9 and 2.8 $\mu\text{Ci/kg}$ groups contained 5 and 19% more of the injected dose 850 and 480 days, respectively, after injection than they were estimated by in vivo measurement to have contained on the day after injection. Thus far most of the analyzed skeletons are those of high-dose dogs in which ^{241}Am was apparently accumulating in bone faster than it was being released.

Whole-body and partial-body in vivo measurement techniques were developed to study separately the retention of ^{241}Am in liver and nonliver tissues. These measurements have been reported through 850 days after injection (LLOYD et al., 1970). Americium-241 in nonliver tissues was found primarily, but not exclusively, in bone: $28.8\% / 33.8\% = 0.85$ of the nonliver burden was in bone 1 to 22 days after injection. It can be assumed that during the first 200 days after injection the decline in nonliver ^{241}Am in the lower-dose level dogs (two dogs each at 0.02, 0.1 and 0.3 $\mu\text{Ci/kg}$) was largely loss from the soft tissues. The decline in nonliver ^{241}Am during the interval 200 to 850 days could be assumed to represent loss from both bone and soft tissues, but mostly from bone. Release of ^{241}Am from the livers of the 0.3 $\mu\text{Ci/kg}$ dogs began at about 2 years. At that time the best estimate of ^{241}Am retention in the dog skeleton was the slope of that portion of the nonliver retention curve lying between 200 and 600 days; the half-time was about 18 years.

E. Retention of $^{249-252}\text{Cf}$ and ^{253}Es

Skeletal retention of the elements heavier than curium has not been measured directly in any species--the experiments with rats, in which bone content of $^{249-252}\text{Cf}$ was measured, were too short to characterize long-term retention (MEWHINNEY et al., 1971, 1972; DURBIN et al., 1972d). In rats and mice--animals that promptly eliminate multicharged cations from liver and soft tissues--whole-body retention of $^{249-252}\text{Cf}$ was nearly the same as skeletal retention at times longer than 30 days after injection. S. R. WRIGHT (unpublished) measured the whole-body retention of ^{252}Cf in adult mice up to 120 days after injection of 4 $\mu\text{Ci/kg}$ of ^{252}Cf citrate and estimated the half-time to be 900 days. MEWHINNEY et al. (1971, 1972) measured whole-body retention of ^{252}Cf up to 64 days after injection of 7.7 $\mu\text{Ci/kg}$ of ^{252}Cf citrate into 35-day-old rats and estimated the half-time to be 1000 days. Later, MEWHINNEY and HARRIS (1972, and unpublished) measured whole-body retention of ^{252}Cf up to 130 days after injection of 5 $\mu\text{Ci/kg}$ of ^{252}Cf citrate into adults of several species. Whole-body half-times of ^{252}Cf in rats and mice were 490 and 410 days, respectively.

Whole-body retention measurements of ^{252}Cf in Chinese hamsters, Syrian hamsters, and beagles included the large contribution of the ^{252}Cf retained in the liver as well as that in bone; measured half-times for these animals were 285, 580, and 630 days, respectively. Whole-body and partial-body measurements up to 400 days after injection indicated that the retention half-time of ^{249}Cf or ^{252}Cf in nonliver tissue (mostly bone) of the beagle is at least 11 years (LLOYD et al., 1972e).

Whole-body retention can also be calculated from the difference between 100% and the summed excreta as is shown for $^{249-252}\text{Cf}$ and ^{241}Am in Fig. 22 (DURBIN et al., 1972 c,d). Beginning 50 days after injection, when

most of the $^{249-252}\text{Cf}$ has been cleared from the liver and soft tissues of the rat and, like ^{241}Am , the $^{249-252}\text{Cf}$ deposited in the incisors during the first few days has been lost by functional attrition (DURBIN et al., 1967), the slopes of the ^{241}Am and $^{249-252}\text{Cf}$ whole-body retention curves were the same ($T_{1/2} = 730$ days). From these findings californium appears to be retained in the rodent skeleton at least as long as is ^{241}Am .

Retentions of ^{249}Bk and ^{253}Es have not been studied beyond 24 days after injection. For ^{241}Am , ^{242}Cm , and $^{249-252}\text{Cf}$ the half-times of whole-body retention in rats (equivalent to skeletal retention in rats at times longer than 30 days after injection) have been found to be similar as far as available measurements permit comparison. One may infer that the half-time of retention of ^{249}Bk in the rat skeleton would also be similar, inasmuch as ^{249}Bk occupies the position between ^{242}Cm and $^{249-252}\text{Cf}$. The physical half-life of ^{253}Es , the major einsteinium isotope, is only 20.5 days, and except for rapid loss from short-lived bony structures, this is also its effective half-time in bone.

VIII. Deposition and retention of transplutonium elements in liver

One of the distinguishing features of the metabolism of the lighter weight members of the lanthanide and actinide series is their large initial uptake by the mammalian liver (HAMILTON, 1947, 1948). In controlled experiments in rats it has been shown that, like their lanthanide homologues, the amounts of the individual trivalent actinides taken up by the liver were related directly to the ionic radius and inversely to the atomic number (DURBIN, 1962).

A. Gross deposition

1. Americium

Four to 22 days after parenteral administration, the liver uptake of ^{241}Am ranged from 29% of the injected dose in mice to 54% in cynomolgus

monkeys and Chinese hamsters (Tables 12 through 17). The time at which liver ^{241}Am reached a maximum value varied among the species; in rats and mice this was 6 to 24 hours after injection of ^{241}Am citrate (Fig. 13). Between days 1 and 4 after injection, about 10% of the injected dose was eliminated from the livers of these rodents and appeared in the feces, so that the maximum liver content, L_{max} , of ^{241}Am as calculated from Eq. 23 was about 40% of the dose for the mice and 50% for the rats.

$$L_{\text{max}}(\%) = L_t + (\text{G. I. contents})_t + \Sigma \text{Fe}_t; \quad \text{Eq. (23)}$$

where L_t and $(\text{G. I. contents})_t$ are the amounts of ^{241}Am in liver and G. I. contents, respectively, at time t ; and ΣFe_t is the cumulative fecal excretion to time t . The initial deposition of ^{241}Am in the Chinese hamster liver appeared to be complete by 24 hr and changed little in the succeeding 64 days. The soft tissues (apart from liver and kidneys) of the dogs and monkeys contained appreciable amounts of ^{241}Am for several days after injection. Americium-241 continued to accumulate in the livers of these animals apparently as the result of the return to the circulation of the ^{241}Am cleared from soft tissues. The ^{241}Am in dog liver increased from 48 to 54% between days 7 and 22 (ATHERTON et al. 1968; LLOYD et al., 1970; ATHERTON and LLOYD, 1972). Between days 1 and 8 the ^{241}Am content of the monkey livers rose from 40 to 54% (DURBIN et al., 1972c).

Within-group variability of the initial liver uptake of ^{241}Am was not large (Table 18). In an experiment in which a large group of female rats of the same age and body weight were each given a single injection of $0.37 \mu\text{Ci/kg}$ of ^{241}Am citrate, the S. D. was 10 to 15% of initial liver uptake. The mean liver ^{241}Am of 5 rats killed 1 day after injection was $50.1\% \pm 7.4\%$ (DURBIN et al., 1967); the liver ^{241}Am (L_{max}) of 30 rats killed 1 to 46 days after injection was calculated from Eq. 23 to be $49.4\% \pm 4.6\%$ (DURBIN et al., 1972c).

In the rat experiments, initial liver uptake of ^{241}Am also varied to some extent with the experimental conditions (Table 18). Those factors that influenced initial ^{241}Am deposition in skeleton and liver--the age of the rats, the chemical form of the ^{241}Am , and the route of administration--were discussed in Section VII.A.1. Inasmuch as the sum of the initial deposits of ^{241}Am in the rat liver and skeleton was nearly constant, those conditions that favored skeletal uptake of ^{241}Am --active bone growth, administration of ^{241}Am as the citrate complex, and administration by intramuscular injection, by inhalation, or by mouth--tended at the same time to divert ^{241}Am from the liver. Conversely, those experimental conditions that favored liver uptake of ^{241}Am --absence of active bone growth, and administration of readily hydrolyzable salts by intravenous or intraperitoneal injection--tended at the same time to suppress ^{241}Am deposition in bone. In addition to the above factors, ZALIKIN et al. (1969) reported that initial deposition of ^{241}Am in liver was greater (by 11% of the injected dose) and skeletal deposition less by nearly the same amount when a large quantity of $^{241}\text{AmCl}_3$, $200\text{ }\mu\text{Ci/kg}$, was administered intravenously.

2. Curium

To date, the metabolism of parenterally administered curium has been studied only in rats (Tables 12 and 19). In 7 experiments with rats L_{max} calculated from Eq. 23 was $56.7\% \pm 4.2\%$ — somewhat lower than L_{max} calculated for ^{241}Am ($63.6\% \pm 7.2\%$ also in 7 studies with adult rats). Curium-244 metabolism has been investigated in beagles exposed to aerosols of $^{244}\text{CmCl}_3$ or $^{244}\text{CmO}_{1.73}$ (MCCLELLAN et al., 1972). The ^{244}Cm was rapidly absorbed into the body from these aerosols. Eight days after exposure, 80% of the ILB of $^{244}\text{CmCl}_3$ and 70% of the IBL of $^{244}\text{CmO}_{1.73}$ had been absorbed. The livers of 10 dogs with an average ILB of $0.26\text{ }\mu\text{Ci/kg}$ of

$^{244}\text{CmCl}_3$ contained $28.8\% \pm 4.1\%$ of the ILB (31% of the absorbed dose) from 8 to 256 days after exposure. The livers of 6 dogs with an ILB of $0.14 \mu\text{Ci/kg}$ of $^{244}\text{CmO}_{1.73}$ contained $31.5\% \pm 4.1\%$ of the ILB (34% of the absorbed dose) during the interval 8 to 64 days after exposure. The deposition of ^{241}Am in the livers of 2 dogs with an average ILB of $3 \mu\text{Ci/kg}$ of ^{241}Am was 34% of the ILB (38% of the absorbed dose) 127 and 256 days after exposure to an $^{241}\text{AmO}_2$ aerosol (R. G. THOMAS et al., 1972).

The within-group variability of the initial ^{242}Cm liver uptake in separate rat experiments was less than was found for ^{241}Am ; S.D.'s ranged from 1 to 6% of observed mean values. As was noted above in Section VII. A. 2, the sum of the initial depositions of ^{242}Cm in liver and skeleton was nearly constant. Examination of Table 19 suggests that the factors that influenced the initial partition of ^{241}Am between liver and bone also influenced, but to a lesser degree, the initial partition of ^{242}Cm between liver and bone. The fraction of ^{242}Cm originally deposited in the livers of rats was only slightly influenced by the growth status of the animals, the chemical form of the ^{242}Cm , or the route of administration.

3. Berkelium

HUNGATE et al. (1972) reported that the accumulation of ^{249}Bk in the liver of the rat was 23% of the dose 4 hr after intravenous injection of $^{249}\text{BkCl}_3$. By day 21 the liver contained only 4% of the injected ^{249}Bk (Table 12).

A systematic study of the metabolism of the lanthanide elements in the rat demonstrated that a significant reduction in liver uptake occurred at gadolinium ($4f^7$; ionic radius, $0.94 \text{ \AA}$) midway through the 14-element series (DURBIN et al., 1956 ; DURBIN, 1962). The $5f$ shell of the actinide series is half filled at curium, but the ionic radius of curium is $0.98 \text{ \AA}$

(ZACHARIASEN, 1954). The sharp downward shift in liver deposition occurs in the actinide series at berkelium ($5f^8$; ionic radius, 0.954 Å, PETERSON, 1967). (See also Section VII. A. 6.)

4. Californium

Distribution of $^{249-252}\text{Cf}$ in the mouse, rat, Chinese hamster, and beagle is shown in Tables 12 through 16. The liver content of $^{249-252}\text{Cf}$ 4 to 21 days after parenteral administration of the citrate complex varied from 7.5% of the injected dose in mice to 27% of the dose in Chinese hamsters. L_{max} of $^{249-252}\text{Cf}$ calculated from Eq. 23 was 25% of injected $^{249-252}\text{Cf}$ in rats and 26% of ^{252}Cf in mice--very close to the 4-day liver content of ^{252}Cf in Chinese hamsters and ^{249}Cf in beagles.

The L_{max} of $^{249-252}\text{Cf}$ in the rat was about the same as the 4-hr liver uptake, which constituted 23% of the injected ^{249}Bk , as reported by HUNGATE et al. (1972). In all species studied, $^{249-252}\text{Cf}$ uptake in liver was significantly less than the liver uptakes of ^{241}Am or $^{242-244}\text{Cm}$.

There are not enough experiments with one species to examine the possible influence of experimental conditions on the initial deposition of $^{249-252}\text{Cf}$. It was noted above, in the discussions of the factors influencing the deposition patterns of newly injected ^{241}Am and ^{242}Cm , that the distribution of ^{242}Cm seemed to be less dependent on experimental conditions than was that of ^{241}Am . If that trend is real and continues, one would anticipate that the gross initial distribution of $^{249-252}\text{Cf}$ in a single species would be even less affected by the growth status of the animals or the chemical form or route of administration of the $^{249-252}\text{Cf}$.

5. Einsteinium

The initial liver uptake of ^{253}Es is low in both mouse and rat. Four days after intramuscular injection of ^{253}Es citrate, the mouse liver contained

3.3% of the injected dose; 1.4% was found in passed feces, and 12% was not recovered (PARKER et al., 1972; Table 14). If the unrecovered ^{253}Es had been in feces, $L_{\max}$ of ^{253}Es in the mouse would lie between 5 and 17%.

Four hours after intravenous injection, rat liver contained 18% of the ^{253}Es administered as $^{253}\text{EsCl}_3$ (HUNGATE et al., 1972) and 33.5% of the ^{253}Es administered as $^{253}\text{Es}(\text{NO}_3)_3$ (V. H. SMITH, 1972b). Neither report included measurements of ^{253}Es in plasma or in accumulated urine during the first 4 hr, so it was not possible to account for the unusually high urine output of $^{253}\text{EsCl}_3$ which tended to divert ^{253}Es from all tissues [during the first 24 hr after injection 12% of $^{253}\text{Es}(\text{NO}_3)_3$ and 36% of $^{253}\text{EsCl}_3$ were excreted in the urine, see Section XI. A. 1.] The $L_{\max}$ for ^{253}Es was calculated from Eq. 23 and the data of V. H. SMITH (1972b) for rats killed 1, 7, and 24 days after injection of $^{253}\text{Es}(\text{NO}_3)_3$ and was 26, 23.5, and 22.2%, respectively. The average of the three estimates of $L_{\max}$ for ^{253}Es was 23.4%, very close to the 25% calculated above for $^{249-252}\text{Cf}$.

B. Microscopic distribution

The microscopic localization of ^{241}Am or $^{249-252}\text{Cf}$ in the livers of several mammals has been studied autoradiographically. The distribution of these elements within hepatic cells has been examined by fractionation of homogenates of canine liver.

1. Initial distribution of ^{241}Am , ^{249}Bk , and $^{249-252}\text{Cf}$

Within hours after administration in soluble form ^{241}Am , ^{249}Bk , and $^{249-252}\text{Cf}$ are distributed almost uniformly throughout liver tissue, and are associated with hepatic cells (Fig. 23a). The experimental animals in which this was observed include the mouse, ^{241}Am (HAMMARSTRÖM and NILSSON, 1970a); rat, ^{241}Am (ZALIKIN et al., 1968; RUDNITSKAYA and MOSKALEV, 1970; DURBIN et al., 1972c), $^{249-252}\text{Cf}$ (DURBIN et al., 1972d); beagle,

^{241}Am (G. N. TAYLOR et al., 1969a), ^{249}Bk , and ^{249}Cf (G. N. TAYLOR et al., 1972); and monkey, ^{241}Am (DURBIN et al., 1972c). The initial distribution of the transplutonium elements in mammalian liver appeared to be independent of the dose, within the limits of the doses that have been studied.

Cell fractionation showed that within the first few days after their administration as citrate complexes, ^{241}Am and ^{249}Cf in the liver of the dog are primarily bound to soluble ferritin, the iron-storage protein of the liver, but within a few weeks they had been shifted to insoluble ferritin incorporated into or on the surface of cellular organelles (STOVER et al., 1970, 1972; STEVENS et al., 1974; BRUENGER et al., 1972).

There are some early minor variations in the microscopic distribution of ^{241}Am in the livers of rats and monkeys, and these seem to be related to local fluctuations of the hepatic circulation. The overexposed autoradiographs of monkey liver shown in Figs. 23 a and 24 a (monkeys killed 1 and 8 days after intramuscular injection of ^{241}Am citrate) reveal concentrations of ^{241}Am near central veins about twice the concentration in portal areas.

The earliest autoradiographs of rat liver (Fig. 25 a : rat killed 1 day after intramuscular injection of ^{241}Am citrate, show variable numbers of intense foci of alpha tracks associated with clusters of 10 to 20 liver cells. In these foci the ^{241}Am concentration was 5 to 20 times the general hepatic background. It was not possible in these preparations to distinguish among ^{241}Am tracks emanating from hepatic cells, sinusoids, or bile ducts; however, the foci of greater ^{241}Am concentration did not appear to involve uptake in Küpfer cells.

Four days after intramuscular injection of $^{249-252}\text{Cf}$ citrate the concentration of $^{249-252}\text{Cf}$ in rat liver was somewhat greater around central veins, but there were no foci of high concentration (DURBIN et al., 1972d).

In the liver of the beagle (as in all other beagle tissues examined) the connective tissue of the small arterioles was an important secondary site of deposition of ^{241}Am , ^{249}Bk , and ^{249}Cf (G. N. TAYLOR et al., 1969a, 1972).

2. Sequential changes in microscopic distribution

After initial deposition is complete, a number of changes occur in the microscopic distribution of ^{241}Am and $^{249-252}\text{Cf}$ in the livers of rats, dogs, and monkeys. These changes, which vary with both the species and the injected dose, are the result of (a) excretion of the element from the liver into the gastrointestinal tract and (b) redistribution within the liver and (or) elimination into the circulation following radiation death of hepatic cells.

a. Rat. Americium-241, $^{242-244}\text{Cm}$, ^{249}Bk , and $^{249-252}\text{Cf}$ were promptly and quantitatively excreted from the liver into the feces of rats and mice if the injected dose was less than $5\text{ }\mu\text{Ci/kg}$ (PARKER et al., 1962; ZALIKIN et al., 1968; HUNGATE et al., 1972; LINDENBAUM and ROSENTHAL, 1972; and Tables 12 through 14). If the injected dose was large, excretion of these nuclides from the livers of rats and mice was delayed, and a fraction of the liver nuclide content was released into the circulation as shown by continued accumulation in the skeleton (TSEVELEVA and YEROKHIN, 1969; and Tables 13 and 14).

The changes in the microscopic distribution of ^{241}Am in the rat liver can be summarized from the low-dose experiment: $0.37\text{ }\mu\text{Ci/kg}$ of ^{241}Am citrate (DURBIN et al. 1967, 1972c). Decline of the ^{241}Am radioactivity in liver sections was visually detectable as soon as 4 days after injection, and excretion of ^{241}Am from the rat liver was nearly complete by the 64th day. Thereafter, microautoradiographs showed a faint overall dusting of single alpha tracks and occasional reticuloendothelial cells from which several alpha tracks emerged. As early as 15 days after injection, and even at this

low dose level, radiation damage (followed by hepatic cell death) could be demonstrated in the foci of the greatest ^{241}Am concentration (Fig. 25 a). The total radiation doses in the low- and high-intensity regions were estimated to be 9 and 90 rads, respectively. By the 15th day all of the ^{241}Am that had been initially associated with the high-intensity foci had been excreted (Fig. 25 b, c), and all of the damaged cells were gone. Evidence of cell destruction persisted--brown pigment, presumably hemosiderin (not observed heretofore) was present in many reticuloendothelial cells, and some of these pigment-laden cells also emitted multiple alpha tracks. The only evidence of repaired cellular damage (compared to age controls) was a slight elevation of the number of polyploid and binucleated hepatic cells.

The initial distribution of $^{249-252}\text{Cf}$ in rat liver was more uniform than was that of ^{241}Am . Excretion of $^{249-252}\text{Cf}$ from rat liver was prompt and complete, and 96 days after injection only occasional single alpha tracks could be seen. There was no evidence of residual or repaired cell damage.

In the rat, although high doses of ^{241}Am were lost from the liver both by excretion into bile and by recirculation, the net rate of loss of ^{241}Am was slower than in low-dose studies (LANGHAM and CARTER, 1951; D. M. TAYLOR et al., 1961; TSEVELEVA and YEROKHIN, 1969).

RUDNITSKAYA and MOSKALEV (1970) calculated that $5\text{ }\mu\text{Ci/kg}$ of ^{241}Am delivered a total radiation dose of about 300 rads to the rat liver. Thus, at dose levels greater than $5\text{ }\mu\text{Ci/kg}$ of ^{241}Am , radiation damage in the liver was severe, and removal of cell debris containing ^{241}Am was inefficient. As long as 200 days after injection of large doses of ^{241}Am , RUDNITSKAYA and MOSKALEV (1970) found that rat liver contained significant numbers of clusters of alpha tracks, presumably emanating from reticuloendothelial cells. Deaths that occurred later than 200 days after injection in the high-level groups were attributed to liver insufficiency.

b. Monkey. The livers of monkeys and baboons lost ^{241}Am , but more slowly than did the livers of rats and mice given comparable doses (ROSEN et al., 1972; DURBIN et al., 1972c; and Table 17). The dose range used in primate studies, 0.20 to 0.87 $\mu\text{Ci/kg}$, was estimated to deliver total radiation doses ranging from 95 to 415 rads, respectively, to the liver. At the higher doses, loss of ^{241}Am from monkey liver was a combination of excretion into feces and elimination into the circulation.

The general distribution of ^{241}Am throughout the monkey liver, with slightly greater early concentrations near central veins (Fig. 24 a) persisted almost unchanged for 42 to 70 days. After that time the decline in ^{241}Am concentration could be seen in the autoradiographs (Fig. 24 b). Concentrations of alpha tracks emanating from clusters of hepatic cells were found in some but not all portal areas 42 to 70 days after injection--coincident with the period of maximum fecal excretion. These clusters of ^{241}Am -bearing cells had disappeared by 168 days.

Between 42 and 70 days, aggregations of alpha tracks emanating from reticuloendothelial cells (which also contained granules of brown pigment) could be found beneath the capsule, in portal connective tissue, and occasionally near central veins. The number of these multiply-labeled pigment-laden cells rose to a maximum between 112 and 168 days (Fig. 24 b) and declined thereafter. After 336 days the general hepatic background was low, and the number of aggregations of tracks associated with pigmented reticuloendothelial cells was small. The aggregates of ^{241}Am were most often located beneath the capsule or near central veins (Fig. 24 c).

Radiation damage was either mild or, to a large extent, repairable. Although the livers of the 3 monkeys killed between 336 and 938 days might be considered slightly atrophic, the changes were so minimal that they were not distinguishable from normal aging.

c. Dog. The dog liver excretes little, if any, ^{241}Am (LLOYD et al., 1970). At low doses (less than $0.1 \mu\text{Ci/kg}$) ^{241}Am is retained; at high doses it appeared to be redistributed within the liver coincident with its release into the circulation following the radiation death of hepatic cells (G. N. TAYLOR et al., 1967, 1969a). Late uptake of ^{241}Am in the spleens and lymph nodes of the high-dose ^{241}Am dogs suggested that at least part of the redistribution of a high dose of ^{241}Am within the dog liver--a general shift from hepatic sinusoids to portal connective tissue--takes place via recirculation of cell debris. Both redistribution of ^{241}Am within the dog liver and recirculation of ^{241}Am to bone and other tissues were more rapid and more dramatic, the larger the injected dose (LLOYD et al., 1970).

The time-dependent changes of the microscopic distribution of ^{241}Am in the canine liver have been studied only in high-dose animals ($2.8 \mu\text{Ci/kg}$ of ^{241}Am). Biopsy specimens of liver taken 150 days after injection showed a generally uniform hepatic distribution similar to that seen in specimens taken from 1 to 22 days after injection. At 150 days occasional aggregations of alpha tracks could be found emerging from hemosiderin-laden reticuloendothelial cells in hepatic sinusoids. By 250 days, 27% of the original liver burden (13% of the injected dose) had been lost, and more than one-half of the remaining ^{241}Am was associated with reticuloendothelial cells in hepatic sinusoids. By the 401st day 54% of the original liver burden (26% of the injected dose) had been eliminated, and most of the remaining ^{241}Am was associated with aggregations of alpha tracks (some quite large) emanating from pigmented reticuloendothelial cells. These cells (containing both hemosiderin and ^{241}Am) were located for the most part interstitially in portal areas, frequently near small interlobular veins (G. N. TAYLOR et al., 1967, 1969a). At that time, the amount of radiation absorbed was large:

5500 to 7600 rads; the degree of hepatic cell damage (and presumably of reticuloendothelial cells also) was great; there was no regeneration. The livers of the 400-day dogs were only one-half normal weight. There was also evidence of damage in connective tissue and vasculature. Liver failure was the primary cause of death (G. N. TAYLOR et al., 1969a; LLOYD et al., 1970). Liver function tests indicated significant liver injury 1 to 2 years after 0.9 $\mu\text{Ci/kg}$ of ^{241}Am , and as of March 1972, liver insufficiency was the cause or a major contributor to the cause of deaths of 2 of the 12 beagles in that dose level group (LLOYD et al., 1972a). Cellular degeneration, fatty changes, and fibrosis were noted in the livers of two beagles killed 512 and 1022 days after receiving an average ILB of 2.8 $\mu\text{Ci/kg}$ from exposure to an aerosol containing $^{241}\text{AmO}_2$ (R. G. THOMAS et al., 1972).

C. Retention

Low doses of all the actinide elements are excreted almost quantitatively from the livers of rats and mice (Tables 12-14). The livers of the cynomolgus monkey and baboon excrete the major fraction of a low-dose ^{241}Am burden. Simultaneously, the remainder--apparently released from damaged liver cells--is recirculated (ROSEN et al., 1972; DURBIN et al., 1972c). The livers of beagles and Chinese and Syrian hamsters did not excrete significant amounts of any actinide element studied (STOVER et al., 1959, 1971; LLOYD et al., 1970, 1972e; MCKAY et al., 1972; MEWHINNEY et al., 1972; MEWHINNEY and HARRIS, 1972; and Tables 15 and 16). Some of the actinide burden in the dog liver was released into the circulation subsequent to the death of labeled hepatic parenchymal and reticuloendothelial cells.

1. Rat and mouse

Rapid clearance of ^{241}Am (Fig. 26) and ^{242}Cm from the rat liver and the quantitative recovery of the cleared nuclide in feces were demonstrated in the first animal experiments with these elements (SCOTT et al., 1948a, 1949).

The rapid decline in whole-body retention of ^{241}Am and $^{249-252}\text{Cf}$ between days 1 and 45 (Fig. 22) represents largely excretion from the liver.

The ability of rat and mouse liver to clear the trivalent actinides was not measurably impaired if the nuclide was given in soluble form and if the injected dose was less than about $5\ \mu\text{Ci/kg}$. The amount of radiation absorbed was apparently low enough so that local cellular damage could be repaired or compensated. Larger doses induced more damage, and biliary secretion--presumed to be the process by which monomeric cations are excreted from the liver--became slower and less efficient, prolonging liver retention (LANGHAM and CARTER, 1951). Polymeric or hydrolyzed actinides are lost from the rat and mouse liver at least in part by some other mechanism which proceeds more slowly than biliary excretion of unaggregated forms (TSEVELEVA and YEROKHIN, 1969; LINDENBAUM and ROSENTHAL, 1972).

The half-times of retention of soluble actinides in rat liver calculated from low-dose experiments for ^{241}Am , ^{242}Cm , $^{249-252}\text{Cf}$, and ^{253}Es are compared with retention half-times of three light-weight lanthanides, ^{144}Ce , ^{147}Pm , and $^{152,154}\text{Eu}$ in Table 22. The liver retention half-times were calculated either directly from measurements of dissected livers or indirectly from cumulative fecal excretion. * Whenever possible, both methods of calculation were used. On the average, the hepatic clearance half-time of soluble forms of three of the lighter and larger actinides (ionic radius $\geq 0.94\ \text{\AA}$) was 8.2 days for the rat. This compares favorably to the clearance half-times of ^{144}Ce and ^{147}Pm (8.3 and 7.0 days, respectively) in the rat and

* Calculation of liver retention from cumulative fecal excretion assumes that (a) between days 1 and 45 (after correction for attrition of incisors) radioactivity in the feces represents biliary excretion into the intestine, and (b) no radioactivity is reabsorbed from the gastrointestinal tract into the body.

to 9 days for ^{241}Am citrate in the mouse (LINDENBAUM and ROSENTHAL, 1972). Liver clearances of ^{253}Es and the heavier, smaller lanthanides, $^{152,154}\text{Eu}$ and ^{160}Tb (ionic radii $\leq 0.95 \text{ \AA}$), were faster, ranging from 5.6 to 6.5 days.

2. Monkey

Early clearance of ^{241}Am from the monkey liver (Fig. 21) is complex. At the dose levels studied, 0.44 to 0.87 $\mu\text{Ci/kg}$, ^{241}Am appeared to be lost from the monkey liver by both biliary excretion and by recirculation following liver cell damage. Hepatic clearance of ^{241}Am in rat and mouse began immediately; maximum daily rates of liver loss and fecal excretion both occurred between days 1 and 4 postinjection. In the monkey, on the other hand, there was a delay of 4 to 8 weeks after injection (the delay time for 10 to 12 monkeys was 4.5 weeks) during which time only 5% of the injected dose of ^{241}Am was lost from the liver and only 3% of the dose had been excreted in feces. After the quiescent period, nearly all of the initial ^{241}Am liver burden was lost with a half-time of 70 days (calculated both from measurements of dissected livers and from cumulative fecal excretion of several individual monkeys).

It is not yet known how much of the variation in the ^{241}Am content of the monkey skeleton (Fig. 21) was the result of the initial partition of ^{241}Am between skeleton and liver and how much was the result of late uptake of ^{241}Am recirculated from the liver. If it is assumed that (a) the initial deposition of ^{241}Am in the monkey liver, L_{max} , is 52.5% of the injected dose, and (b) ΣFe_t , the cumulative fecal excretion, represents biliary loss from liver, then the fraction of L_{max} which was lost by recirculation can be estimated:

$$\text{Amount recirculated} = L_{\text{max}} - (L_t + \Sigma \text{Fe}_t). \quad \text{Eq. (24)}$$

Fecal excretion of ^{241}Am by 11 monkeys killed 63 to 973 days after injection

accounted for 43 to 100% of the average $L_{\max}$ (40.6 to 52.5% of the injected dose). The average fecal excretion was $0.77 L_{\max}$. Loss of ^{241}Am from the monkey liver in the dose range 0.44 to $0.87 \mu\text{Ci/kg}$, as a consequence of re-circulation of ^{241}Am from damaged cells, was about 23% of $L_{\max}$.

In two baboons that received $0.2 \mu\text{Ci/kg}$ of ^{241}Am citrate (one-fourth to one-half the dose received by the monkeys) the clearance half-time of ^{241}Am from the liver was determined to be 152 days, based on periodic biopsies and in vivo measurements up to 86 days after injection (ROSEN et al., 1972). There was no indication in these animals that ^{241}Am originally deposited in the liver was released into the circulation.

3. Dog

Biliary excretion of ^{241}Am from dog liver has not been demonstrated, but it may contribute to the small fraction of a low dose of ^{241}Am that is lost slowly. The sequential changes in the microscopic distribution of ^{241}Am in the livers of high-dose dogs (G. N. TAYLOR et al., 1969a) and the time course of the uptake in the skeletons and soft tissues of these same dogs (LLOYD et al., 1970) indicate that nearly all of the observed loss from liver is the result of release of ^{241}Am from damaged cells.

The amount of nuclide lost from the dog liver, and the rate of that loss, are both dependent on the radiation dose in liver tissue, that is, proportional to the administered dose. At an injection level of $2.8 \mu\text{Ci/kg}$ of ^{241}Am , the dog liver began to lose ^{241}Am about 50 days after injection. The rate of loss of ^{241}Am continued to accelerate until the dogs died 401 and 448 days after injection. At that time the liver contained only 27% of its initial ^{241}Am deposit. The average half-time of liver retention was estimated to be less than 240 days. After injection of $0.9 \mu\text{Ci/kg}$ of ^{241}Am , very little ^{241}Am was lost from the liver during the first 200 days; but subsequently ^{241}Am was

lost from the liver with a half-time of about 750 days.

The net loss of ^{241}Am from the livers of dogs given still lower doses (0.02 to 0.3 $\mu\text{Ci/kg}$) was small, but appeared to proceed at a constant rate during the 850-day observation period. The liver retention half-time was about 3500 days, which is equivalent to a rate of loss of 0.02% of the liver burden per day.

Retention of ^{249}Cf or ^{252}Cf in beagle liver has been measured by a combination of whole-body and partial-body counting (LLOYD et al., 1972b, e). The average ^{249}Cf content of the livers of 7 beagles was 27% 1 to 2 days after injection (3 beagles each injected with 2.8 $\mu\text{Ci/kg}$ of ^{249}Cf citrate and 4 beagles injected with 0.3 $\mu\text{Ci/kg}$). By the 14th day the average ^{249}Cf content of the livers of 6 of these beagles (one was killed before the 14th day) had declined to 17.8% -- a loss of 9.2%. Between days 2 and 14, 4.3% was excreted in the feces providing suggestive evidence for early biliary excretion of ^{249}Cf by the beagle. The fact that all of the ^{249}Cf lost from the liver could not be accounted for by fecal excretion suggests further that some of the initial ^{249}Cf liver deposit was loosely bound and could be released into the circulation. Radiation damage of liver cells would not seem to be involved in such rapid release even at the high, 2.8 $\mu\text{Ci/kg}$ dose level. The declining concentrations of ^{249}Cf in contained blood and ECF were probably minor contributors to the reduction of total ^{249}Cf in liver, because by the end of day-1 the total blood volume contained only 1% of the injected dose.

Measurements of 4 beagles each injected with 0.3 $\mu\text{Ci/kg}$ of ^{249}Cf and 4 beagles injected with 0.3 $\mu\text{Ci/kg}$ of ^{252}Cf have continued for 400 days. The liver retentions of the two californium isotopes were identical. The half-time of retention of ^{249}Cf or ^{252}Cf in the beagle liver was estimated to be 3.3 years, which is only about one-third of the retention half-time of 9.6 years

determined for low doses of ^{241}Am in this species.

4. Chinese hamster

Unlike the rat and mouse, the liver of the Chinese hamster retains both ^{241}Am and ^{252}Cf , and the liver of the Syrian hamster retains ^{252}Cf (MCKAY et al., 1972; MEWHINNEY et al., 1972; MEWHINNEY and HARRIS, 1972). At a dose level of $1\ \mu\text{Ci/kg}$ of ^{241}Am , measurement of Chinese hamster livers dissected 225 and 360 days after injection indicated a retention half-time of about 3400 days (MCKAY et al., 1972).

Retention of ^{252}Cf in the Chinese and Syrian hamster livers has been measured only at a dose level of $5\ \mu\text{Ci/kg}$ --five times the dose used in the ^{241}Am studies. Measurements of livers from Chinese hamsters killed 1 to 64 days after injection indicated a retention half-time greater than 125 days (MEWHINNEY et al., 1972). During the 64-day postinjection interval, 8% of the dose (30% of the initial liver burden of ^{252}Cf) was lost from the liver, while the ^{252}Cf content of the carcass (mainly skeleton) increased by 5% of the injected dose. Simultaneous loss from liver and uptake in the skeleton suggested that the mechanism of liver loss of ^{252}Cf in the Chinese hamster was release from radiation-damaged cells.

D. Long-term content of ^{241}Am in rat and monkey liver

The initial clearance of low doses of ^{241}Am from the livers of rats, mice, and monkeys is rapid and efficient, but it is never complete. As can be seen from Figs. 21 and 25 a small amount of ^{241}Am is present in rat liver as long as 2 years after injection and in the monkey liver for as long as 3 years.

Sequential autoradiographs of rat livers (See Section VIII. B. 2.) indicated that significant numbers of reticuloendothelial cells, which contained aggregations of ^{241}Am tracks associated with hemosiderin, were still present 70 days after injection but were rarely seen after 300 days. The 50-day component of the ^{241}Am retention curve probably represents, at least in part,

the elimination of these ^{241}Am -labeled reticuloendothelial cells.

According to the general model of long-term metabolism of ^{241}Am proposed by DURBIN et al. (1967) and shown in Fig. 27 the longest-term components of the liver retention curve (half-times 500 days and 1200 days in monkey and rat livers, respectively) represent feedback to the circulation of ^{241}Am released from the skeleton in the course of normal bone remodeling.

Only two components could be extracted from the retention curve of ^{241}Am in the monkey liver (half-times of 70 and 500 days): The short-term component is presumed to represent a combination of several clearance mechanisms--biliary excretion, release to the circulation from damaged cells, and loss from labeled reticuloendothelial cells--which appear to proceed at rates that cannot be differentiated. The longer-term component is assumed to represent largely feedback from other soft tissues and bone.

IX. Deposition and retention of transplutonium elements in kidney

A. Initial deposition

The kidney is an important early deposition site of the transplutonium elements in mammals. In most species studied, more than one-half of the 60-day urinary excretion of these elements is passed in the first 24 hr when the plasma nuclide concentration is high. The kidneys of animals killed 1 day after injection still contain significant amounts of the nuclides. During the first few days after injection, the concentrations of transplutonium elements in the kidneys of all of the mammals studied (except the Chinese hamster) are nearly the same as the concentrations in bone, but only about one-fifth those in the liver.

One day after injection of chlorides or citrates of ^{241}Am , ^{242}Cm , $^{249-252}\text{Cf}$, or ^{253}Es the kidneys of rats and mice contained 1.5 to 4.5% of the injected dose (SCOTT et al., 1948a, 1949; ZALIKIN et al., 1968; BELYAEV, 1969; DURBIN et al., 1967, 1972c; WILLIAMS et al., 1961; PARKER et al.

1962, 1972; V. H. SMITH, 1972b). The kidneys of dogs and monkeys contained 0.5 to 1.5% of ^{241}Am or ^{249}Cf 1 day after injection (ATHERTON et al., 1968; ATHERTON and LLOYD, 1972; DURBIN et al., 1972c). The kidneys of Chinese hamsters contained 11 to 12% of the dose 1 day after intraperitoneal injection of ^{241}Am or ^{252}Cf citrate (MCKAY et al., 1972; MEWHINNEY et al., 1972). During the first week after injection the concentrations of ^{241}Am or ^{252}Cf in Chinese hamster kidney were nearly the same as those in the liver.

B. Microscopic distribution

1. Rat

By autoradiographic analysis, most of the initial deposit of a low dose of soluble ^{241}Am is found as single tracks in the cortex in association with the convoluted tubules (Fig. 28a). The rat kidney does not retain ^{241}Am . At postinjection times greater than 16 days, long autoradiographic exposures are required to demonstrate the presence of ^{241}Am (Fig. 28b).

Some point sources of multiple alpha tracks emanating from reticulo-endothelial cells could be seen in the connective tissue of the cortex of most kidney sections from 8 to 32 days after injection. The number of these labeled cells gradually declined, but they did not disappear. At postinjection times greater than 1 year most kidney sections still contained a few small foci of alpha tracks associated with brown pigment granules in reticuloendothelial cells.

At all times after injection, most rat kidney sections contained variable numbers of concretions, which stained light blue to deep purple with hematoxylin-eosin. These were usually located in the outer zone of the medulla or near the cortico-medullary junction (Fig. 28a). At short postinjection times, when the rats were young and relatively free from chronic renal disease, these concretions (presumably renal stones) were small and their

^{241}Am label was intense. With the passage of time, the small intensely labeled stones were either dissolved or passed, because at postinjection times longer than 1 year, renal stones were only lightly labeled on their surfaces (Fig. 23 d), even though they tended to be larger. The stones found in the kidneys of the older rats apparently were formed long after the injection and acquired their label at a time when the ^{241}Am concentration in the blood was low.

At the dose level used in this study ($0.37 \mu\text{Ci/kg}$ of ^{241}Am) early kidney damage could not be clearly demonstrated. Later in the study, any early damage that might have been present was repaired or obscured by the gradual onset of chronic pyelonephritis, which is endemic in the Charles River rat (DURBIN et al., 1972e).

In the high-dose studies of RUDNITSKAYA and MOSKALEV (1970) ^{241}Am was still detectable in the renal cortex, associated with both glomeruli and tubules, as long as 200 days after injection. After 30 days, clusters of ^{241}Am tracks could also be found in the medulla. The injection levels, 2.5 to $25 \mu\text{Ci/kg}$ of ^{241}Am , were calculated to deliver average radiation doses to the kidney of 17 to 170 rads, respectively. Early tissue damage included destruction of glomerular capillary tufts and focal destruction of tubules. The tissue damage was accompanied by accumulations of large clusters of alpha tracks in the intertubular connective tissue. Cysts in the cortico-medullary zone and sclerotic foci were common findings in the kidneys of the 200-day survivors.

Rat kidney containing $^{249-252}\text{Cf}$ was available only from two groups of rats killed 4 and 91 days after intramuscular injection of $^{249-252}\text{Cf}$ citrate (DURBIN et al., 1972d). The microscopic distribution of $^{249-252}\text{Cf}$ in rat kidney was indistinguishable from that of ^{241}Am at the same postinjection intervals.

2. Monkey

In the monkey kidney, ^{241}Am was initially deposited for the most part in the tubules, although not all segments of the tubules appeared to be involved. Neither the proximal convoluted tubules (identifiable by their brush borders) nor the collecting tubules in the medulla contained significant numbers of alpha tracks. The ^{241}Am was most prominent in the straight tubules, presumably the limbs of the loops of Henle, in the medullary rays (Fig. 29a).

Some tubules in most, but not all, of the monkey kidneys contained granules of brown pigment. Shortly after injection, the ^{241}Am associated with the renal tubules seemed unrelated to the presence of pigment. However, after 112 days, pigment-containing cells of the renal tubules and of the tubular interstitial tissue were the dominant sites of ^{241}Am deposition (Fig. 23 b).

Although the number of alpha tracks associated with the renal tubules and the interstitial tissue declined with time (Fig. 29b), such sites still contained ^{241}Am 938 days after injection (demonstrable by very long autoradiographic exposures).

More ^{241}Am was associated with the glomeruli of monkey kidney than was found in the rat kidney. During the first few days after injection, a light dusting of single tracks could be detected over most glomeruli. From 8 to 42 days some glomeruli contained point sources of multiple alpha tracks, "small stars" (Fig. 23 c). Smaller stars of tracks could occasionally be found in the capsular membrane. The number of glomerular stars declined, but they did not disappear. By 112 days single tracks over the glomeruli were more concentrated than the tracks over adjacent areas of tubules. Mid-sagittal sections of whole kidneys taken from monkeys killed 1 to 2 years after injection usually contained 1 to 5 small stars.

Shortly after injection, the greatest concentration of ^{241}Am in the monkey kidney was in the intertubular connective tissue in the renal papillae

(Fig. 29a). As in other kidney structures, the amount of ^{241}Am at this site decreased (Fig. 29b) but was still detectable 938 days after injection.

The kidneys of some monkeys contained concretions which were usually located in the connective tissue between the distal collecting tubules in the renal papillae. When renal stones were present, they were heavily labeled (Fig. 29b).

As G. N. TAYLOR et al., (1969a, 1972) had noted in the dog kidney, ^{241}Am was selectively localized in the media of arterioles in the monkey kidneys. Compared with the ^{241}Am concentrations in other kidney structures, the vascular deposit was not especially prominent at first. The impression was that of a persistent vascular labeling, even though there was some decline with time. Thus, at long postinjection times, ^{241}Am was more concentrated in the walls of arterioles than elsewhere in the kidneys (except for special sites such as pigment-containing tubules and renal stones).

The monkeys in these studies were of variable age (6 or more years old at the time of injection), and postinjection times ranged from 1 day to 3 years. The animals were caught in the wild, and their health histories were unknown. Histologically, their kidneys ranged from apparently good health to combinations of mild interstitial fibrosis, occasional glomerular fibrosis, occasional tubular plugging, and small numbers of renal stones--changes that could be related to age or disease history as well as to radiation damage.

3. Dog

Some of the features of the early deposition of ^{241}Am , ^{249}Bk , and ^{249}Cf in the kidney of the dog resembled those described above for the monkey (G. N. TAYLOR et al., 1969a, 1972; LLOYD et al., 1970). Single alpha tracks were prominent in the straight portions of renal tubules, especially in medullary

rays, and large aggregations of alpha tracks were associated with concretions and connective tissue in the renal papillae. The concentrations of these nuclides in the media of arterioles was greater than was found in the monkey kidney. The most important difference between the distributions of these nuclides in the kidneys of dogs and monkeys was the concentrated, and apparently permanent deposition in the basement membranes of the tuft and capsule of the glomeruli in the dog kidney. The level of ^{241}Am deposition in the dog glomeruli was sustained (or possibly even augmented) during 401 to 448 days after injection of $2.8 \mu\text{Ci/kg}$ of ^{241}Am citrate, and led to average radiation doses in kidney tissue of 800 to 850 rads. At death, the 2 dogs in this dose group exhibited renal hypertension; other dogs in lower dose groups showed varying levels of proteinuria. One dog injected at a level of $0.9 \mu\text{Ci/kg}$ of ^{241}Am died of renal failure 1533 days after injection (LLOYD et al., 1972a). Microscopically, there were great reductions in the size of the glomerular tufts and in the number of glomeruli. Local necrosis was observed in the cells adjacent to the "hot spots" of ^{241}Am on renal stones in the papillae, but the contribution of these radiation-induced lesions to reduced kidney function has not been evaluated, nor has it been possible to evaluate the contribution of irradiation of arteriole walls to the overall impairment of kidney function. Generalized glomerulosclerosis with fibrous replacement was found in the kidneys of 2 beagles killed 512 and 1022 days after exposure to an average ILB of $2.8 \mu\text{Ci/kg}$ from an aerosol containing $^{241}\text{AmO}_2$ (R. G. THOMAS et al., 1972).

C. Retention

1. Rat

As shown in Fig. 30, 3 exponential terms (half-times 8, 25, and 1870 days) were needed to describe ^{241}Am retention in rat kidneys.* The autoradiographs (Fig. 28 a,b) demonstrate the rapid disappearance of ^{241}Am initially associated with tubules in the renal cortex. Clearance of ^{241}Am from renal tubules is likely to be the major mechanism underlying the 8-day component of the ^{241}Am kidney retention curve.

During the interval 8 to 32 days postinjection, some of the ^{241}Am present on day 1 was cleared and some was apparently shifted from renal tubules to connective tissue and to pigment-laden reticuloendothelial cells. Clearance of ^{241}Am from connective tissue and the turnover of labeled reticuloendothelial cells probably contributed to the 25-day component of ^{241}Am retention.

*Variable numbers of stones in the kidneys of rats of all ages perturbed the kidney retention data. In all age groups kidneys with large numbers of stones contained more ^{241}Am than kidneys with fewer stones. In some age groups, mean ^{241}Am in the kidney was less than the S. D. Gross x-ray autoradiographs of kidney sections of the 150 rats in the low-dose study (DURBIN et al., 1967, 1972c) were examined for the presence of radioactive "hot spots" in the medulla, which were judged to be the images of ^{241}Am -labeled kidney stones. Rats were excluded from calculation of the mean kidney ^{241}Am if their autoradiographs showed more than twice the average number of "hot spots" determined for the age group.

According to the general metabolic model proposed by DURBIN et al. (1967) for the long-term behavior of multicharged cations, the 1870-day component of the kidney retention curve should represent feedback to the circulation of ^{241}Am released in the course of skeletal remodeling.

The available information on the retention in the rat kidney of ^{241}Am at various injection levels is collected in Fig. 31. Kidney retention curves determined in low-dose (DURBIN et al., 1972c) and moderate-dose (ZALIKIN et al., 1968) studies agreed reasonably well. The retention curve of ^{241}Am in the kidneys of the rats in the early experiments of SCOTT et al. (1948a) was parallel to those obtained in the later investigations, but at all all postinjection times the amount of ^{241}Am in the kidneys was almost twice that found in the recent studies. The heavy kidney deposition in the early study does not seem to be an artifact of experimental technique (intramuscular absorption was 90% complete by 4 days), nor does it seem to be related to the chemical form administered ($^{241}\text{AmCl}_3$ in a recent study gave the same results as ^{241}Am citrate). The heavy kidney deposition in the early ^{241}Am and ^{242}Cm studies (SCOTT et al., 1948a, 1949) may have been caused by the presence of early pyelonephritis and renal stones. *

*Modern methods of controlling endemic diseases in rodent colonies--caesarean-derivation, sterilization of food, bedding, and cages, and rigorous hygiene in colony rooms--were not introduced until the late 1950's. In the absence of such measures, renal infections were probably common even in young rats in most colonies.

The kidneys of the young rats in the high-dose studies of LANGHAM and CARTER (1951) initially lost ^{241}Am at about the same rate as the older rats that received the lower ^{241}Am doses. However, after the 16th day, the kidneys (like the bone and some other soft tissues) were accumulating the ^{241}Am released into the circulation from the damaged liver.

Retention of ^{242}Cm , ^{252}Cf , and ^{253}Es in the rat kidney is shown in Fig. 32. The retention of ^{242}Cm determined by SCOTT et al. (1949) was like that of ^{241}Am measured in a similar experiment by the same workers (SCOTT et al., 1948a).

Kidney retention of ^{252}Cf (administered intraperitoneally as a citrate, MEWHINNEY et al., 1972) by young male rats was very much like that of ^{241}Am (administered as a citrate intramuscularly) in adult females.

Intratracheally administered $^{253}\text{EsCl}_3$ (data corrected for the amount remaining in the lung), behaved somewhat differently in the rat kidney (HUNGATE et al., 1972; BALLOU and MORROW, 1972). The amount of ^{253}Es initially deposited in the kidney was 2 to 4 times greater than that of the other three actinides, and the initial rate of clearance of ^{253}Es from the kidney was 3 times faster than that of ^{241}Am or ^{252}Cf (^{253}Es half-time, 1.5 days; ^{241}Am and ^{252}Cf half-time, 4 to 5 days).

2. Monkey

As shown in Fig. 30, the retention in the monkey kidney of a low dose of ^{241}Am can be adequately described by two exponential terms with half-times of 15 and 430 days. During the first few days after injection, ^{241}Am concentrations in monkey kidney were associated, in ascending order, with (a) media of arterioles, (b) loops of Henle, (c) connective tissue in the renal papillae, and (d) renal stones. Retention of ^{241}Am was greater and more

prolonged in the kidneys that contained large numbers of renal stones. * All of the above listed soft-tissue deposits of ^{241}Am diminished, although not necessarily at the same rate, and all apparently contributed to the average initial renal clearance half-time of 15 days.

The data were not sufficient and the amount of ^{241}Am involved was too small to distinguish a separate component for the clearance (between 30 and 112 days) of ^{241}Am from the "stars" associated with the glomeruli and pigment-containing tubules.

DURBIN et al. (1972b) reported a half-time of 470 days for the longest-observed components of the renal and gastrointestinal excretion curves of these monkeys (measured between 500 and 1400 days postinjection). The longest half-times observed for ^{241}Am in monkey liver and residual soft tissues were 440 days and 880 days, respectively. At the low dose level used in these studies it seems reasonable to assume that the long-term component of the kidney retention curve represented an equilibrium with ^{241}Am that was being fed back into the circulation from other soft tissues and from bone.

3. Dog

The retention of ^{241}Am in the dog kidney has been studied only at high dose levels and is complicated by radiation injury sustained both from the initial ^{241}Am deposit in kidney and from the later accumulation of ^{241}Am

*The kidneys of the 3 monkeys killed at 81, 224, and 280 days contained many intensely labeled stones. The amount of ^{241}Am in these kidneys was unduly high, and the data from these animals were not included in the fitting of the slower component of the kidney retention curve. Histologic sections of the kidneys of the 4 other long-term monkeys did not contain any stones.

released from the radiation-damaged liver. Late accumulation of ^{241}Am in the kidney was also observed in rats that received a high dose of $30\text{ }\mu\text{Ci/kg}$ (LANGHAM and CARTER, 1951).

Shortly after injection, ^{241}Am appeared to leave the dog kidney. Reported values for the ^{241}Am in the kidneys of individual dogs were as follows: 1 day, 1.3% ; 7 days, 0.475% ; 8 days, 0.453% ; and 22 days, 0.362% (ATHERTON et al., 1968; ATHERTON and LLOYD, 1972). The kidneys of other dogs given $2.8\text{ }\mu\text{Ci/kg}$ of ^{241}Am contained 1.28% at 401 days and 1.13% at 448 days --nearly equal to the 1-day ^{241}Am content. Between 50 and 400 days after injection of $2.8\text{ }\mu\text{Ci/kg}$ of ^{241}Am , 30% of the dose was released from the liver, of which two-thirds (20%) was redistributed to soft tissues and bone, and one-third (10%) was presumed to have been excreted.

By 401 to 448 days, the kidneys of these dogs had sustained substantial irreparable radiation damage (LLOYD et al., 1969a, 1970). The radiation dose from the initial ^{241}Am deposit only, is calculated to be 25 rads at 30 days and, if no other processes intervene, 55 rads at infinite time. * It would appear that more than 90% of the damaging radiation dose (estimated above to be 800 to 880 rads) was delivered by the ^{241}Am taken up later in the course of its release from the liver. The late delivery of the radiation dose in the kidneys would help to account for the slow development of the renal lesions (R. G. THOMAS et al., 1972).

4. Mouse

The vasculature of the kidney was clearly outlined in whole-body autoradiographs of mice killed 5 min after intravenous injection of $^{241}\text{Am}(\text{NO}_3)_3$ (HAMMARSTRÖM and NILSSON, 1970a). The kidney exhibited a moderate

* Radiation dose was calculated using the following retention function,

$$\text{Dog } K_t(\%) = 0.92e^{-0.27t} + 0.53e^{-0.017t}.$$

amount of radioactivity throughout the 60-day study, and small foci of high concentration were seen in the cortex in some animals. There was no special accumulation of ^{241}Am in the renal pelvis, but the radioactivity over the ureter and urethra persisted up to 60 days. Measurements of dissected tissues indicate that a large fraction of the 1-day deposit of ^{241}Am in the mouse kidney was cleared with a half-time of about 4.5 days (WRIGHT, 1972).

5. Chinese hamster

The retention patterns of ^{241}Am and ^{252}Cf were the same in the Chinese hamster kidney (MCKAY et al., 1972; MEWHINNEY et al., 1972). Ten to 11% of the injected dose of both nuclides was cleared from the hamster kidneys with a half-time of about 5 days. The remaining 1% of each nuclide was not significantly diminished during the 64-day experiments. Radiation damage in the hamster kidneys has not been investigated, but the calculated average dose in kidney* of Chinese hamsters given $5\mu\text{Ci/kg}$ of either ^{241}Am or ^{252}Cf is calculated to be about 180 rads in 30 days. A radiation dose of this magnitude was shown to produce substantial tissue damage in the rat kidney (RUDNITSKAYA and MOSKALEV, 1970).

X. Deposition and retention of transplutonium elements
in soft tissues other than liver and kidney

The description of the behavior of the transplutonium nuclides in soft tissues other than liver and kidney is far from complete. Table 23 summarizes the nuclide concentrations in soft tissues sampled a few days after injection of ^{241}Am or ^{249}Cf in the beagle (ATHERTON et al., 1968; LLOYD et al., 1970, 1972d, e; ATHERTON and LLOYD, 1972) and of ^{241}Am in the baboon (ROSEN et al., 1972). Soft tissues, especially the small organs and glands, have been analyzed only occasionally in rodent studies. However, in rats, the spleen, lung, muscle, and pelt have been analyzed in several studies of ^{241}Am , ^{242}Cm , ^{249}Bk , $^{249-252}\text{Cf}$, and ^{253}Es . These data are collected in Table 24. *

The total amount of trivalent actinide in the soft tissues other than liver and kidney 1 to 2 days after injection ranged from 1.5 to 20% depending on the element, the species, and to some extent on the experimental conditions. The initial soft tissue burden was usually, but not always, greater in studies in which (a) the injected compound was easily hydrolyzed, (b) the route of injection was intravenous or intraperitoneal rather than intramuscular or intratracheal, (c) the injected dose was of the order of $25\mu\text{Ci/kg}$ or more, (d) the experimental subject was a large animal rather than a rodent. In similar experiments with dogs, rats, mice, and Chinese hamsters, the initial deposition of ^{241}Am in soft tissues has been found to be less than that of $^{249-252}\text{Cf}$.

From Tables 12 through 17 it is clear that the presence of trivalent actinides is temporary in most soft tissues. The bulk of the initial soft tissue content of ^{241}Am in rats (Fig. 33) and in monkeys (Fig. 21) is either excreted or redistributed to more permanent sites within a few days after

*Nuclide concentrations in the tissues of rats, mice, and Chinese hamsters may be obtained from the tissue nuclide contents in Tables 12 through 15, and 24, and the average tissue weights in Appendix C.

administration. Thereafter, the nuclide content of the soft tissue is low and proportional to feedback from bone.

A. Spleen

Americium-241, ^{242}Cm , ^{249}Bk , $^{249-252}\text{Cf}$, and ^{253}Es have been measured in the spleen in a variety of rat studies (Table 24). In similar experiments the amounts of the various nuclides in rat spleen were the same. If the administered dose was small, and the injected compound was not readily hydrolyzed, the amount of ^{241}Am or $^{249-252}\text{Cf}$ in spleens of several species (Tables 16, 17, 24) was 0.1 to 0.2% at 1 to 4 days postinjection. If the nuclide had been given intravenously or intraperitoneally in easily hydrolyzable form, the initial deposition in rat spleen was as much as 0.9%. In low-dose studies with rats, monkeys, and beagles, retention of trivalent actinides in spleen was characterized by either no change with time or a slow loss. In the high-dose rat study (LANGHAM and CARTER, 1951) the spleen lost ^{241}Am during the first 32 days, but accumulated ^{241}Am thereafter. In the dogs given $2.8 \mu\text{Ci/kg}$ (LLOYD et al., 1970) ^{241}Am was lost from the spleen during the first 21 days, but by 401 to 448 days after injection, the spleen contained three times as much ^{241}Am as on day 1.

Americium-241 was initially distributed as a uniform dusting of single alpha tracks throughout the red pulp of the spleens of mice (HAMMARSTRÖM and NILSSON, 1970a) and rats (RUDNITSKAYA and MOSKALEV, 1970; DURBIN et al., 1972d). One day after injection the ^{241}Am in monkey spleen was associated for the most part with the connective tissue of the capsule and trabeculae and with the media of the small arterioles. By 8 days this selective localization had largely disappeared. Subsequently, ^{241}Am distribution in the monkey spleen appeared to be nearly uniform over both red pulp and connective tissue, but very little was present in white pulp (DURBIN et al., 1972c).

In the high-dose rat studies of RUDNITSKAYA and MOSKALEV (1970) by 100 days after injection and in the beagle studies of G. N. TAYLOR et al. , (1969a) by 401 to 448 days after injection, aggregates of ^{241}Am were found in splenic red pulp associated with hemosiderin-laden macrophages. There were fibrous changes in both red and white pulp in the rat spleens 200 days after injection. Pathological descriptions of the dog spleens have not been published; however, 401 to 448 days after injection of $2.8 \mu\text{Ci/kg}$ of ^{241}Am the spleens were only one-fourth normal size (LLOYD et al. , 1970). Foci of extramedullary hematopoiesis were noted in the spleens of the 4 beagles killed 127 to 1022 days after inhalation of an ILB of $2.8 \mu\text{Ci/kg}$ of $^{241}\text{AmO}_2$ (R. G. THOMAS et al. , 1972).

B. Lymphatic tissue

Initial concentrations of ^{241}Am in lymph nodes of primates were 6.5 and 10%/kg in baboon and monkey, respectively, nearly the same as the ^{241}Am concentrations in spleen (DURBIN et al. , 1972c; and Table 23). The initial ^{241}Am concentration in the lymph nodes of dogs was 8.5% /kg, about 6 times that of spleen. The ^{241}Am or ^{253}Es concentrations in rat lymph nodes 1 to 7 days after injection were 77 and 100% /kg, respectively, much greater than in the larger animals (DURBIN et al. , 1972c; V. H. SMITH, 1972b).

Concentrations of ^{241}Am in the lymph nodes of the primates did not change for as long as 81 to 86 days after injection. In rat, ^{241}Am concentrations in the lymph nodes declined to 19% /kg by 256 days postinjection. At dose levels of 0.09 to $0.3 \mu\text{Ci/kg}$, the average ^{241}Am concentration in the lymph nodes of the beagles decreased; by 1510 to 1917 days after injection it was one-fourth of the initial value. In the beagles injected at the $2.8 \mu\text{Ci/kg}$ level, the ^{241}Am concentration in the lymph nodes declined during the first 22 days. Thereafter, either ^{241}Am was accumulated in the lymph nodes or the lymph nodes were reduced in size, because by 401 to 448 days after

injection the ^{241}Am concentration was twice as great as it had been 1 day after injection (LLOYD et al., 1970, 1972d).

RUDNITSKAYA and MOSKALEV (1970) reported an initially diffuse distribution of ^{241}Am in rat lymph nodes, but by 100 days after injection there was a tendency for most of the ^{241}Am present to be located in sinuses. Destruction of germinal centers was seen 200 days after injection of large doses of ^{241}Am in rats. At the late postinjection interval ^{241}Am in the lymph nodes of dogs was principally aggregated in macrophages in association with hemosiderin, though aggregates were fewer here in number than in the spleen (G. N. TAYLOR et al., 1969a).

C. Lung

With a single exception (TSEVELEVA and YEROKHIN, 1969), the initial lung deposition of ^{241}Am , ^{242}Cm , or ^{253}Es in rats ranged from 0.13 to 0.31% (Table 24). The average lung concentration was 100% /kg, about one-half that in rat spleen and five times that in skeletal muscle. The early concentration of ^{241}Am in dog lung was not as great as the concentration in kidney or trachea, but was higher than that in most soft tissues: for example, about 15 times the concentration in skeletal muscle. The ^{241}Am concentration in baboon and monkey lung was about 20% /kg, 1 to 32 days after injection: nearly the same as in trachea and 20 times that of muscle.

One day after intravenous injection of $^{241}\text{AmCl}_3$, rat lung contained single alpha tracks associated with alveolar epithelium and perivascular and peribronchiolar tissue (RUDNITSKAYA and MOSKALEV, 1970). Shortly after injection ^{241}Am could be found associated with the tracheal cartilages of mice (HAMMARSTRÖM and NILSSON, 1970a); 401 to 448 days after injection, autoradiographs of dog lung showed ^{241}Am localized in cartilaginous structures and occasionally associated with macrophages in alveolar epithelium (G. N. TAYLOR et al., 1969a). In the dog lung most of the ^{249}Cf present 7 to

21 days after injection was in or adjacent to the perichondrium of cartilaginous plates and to a lesser degree in the lamina propria of bronchioles. An occasional spot of intense radioactivity was found in the submucosa of bronchioles (G. N. TAYLOR et al., 1972).

D. Muscle and pelt

Skin and skeletal muscle constitute more than one half of the body weight of the mammals that have been used in transplutonium studies. The actinide concentrations in these tissues were not great at 1 to 7 days after injection, ranging from 0.3%/kg in dog muscle to 16%/kg in rat muscle, and from 0.8%/kg in dog pelt to 63%/kg in rat pelt. Although the concentrations in these two tissues are low, their bulk is large, and most of the transplutonium nuclide content of the residual soft tissues is contributed by the pelt and skeletal muscle. Therefore, retention of the transplutonium elements in muscle and pelt dominates the retention in residual soft tissue which is shown for rat and monkey in Figs. 21 and 33.

HAMMARSTRÖM and NILSSON's (1970a) whole-body autoradiographs of ^{241}Am in mice showed a significant but very transient uptake of ^{241}Am in the follicles of the vibrissa (whiskers): ^{241}Am was not demonstrable by this technique 24 hr postinjection. Seven to 21 days after injection of ^{249}Cf , a high concentration was found in the glassy membrane of primary hair follicles of the dog pelt. A low-level diffuse distribution of tracks was seen over the rest of the tissue (G. N. TAYLOR et al., 1972).

E. Heart

The transplutonium elements were more concentrated in heart than in skeletal muscle in all of the species in which the radioactivity of the heart was measured separately. One to 7 days after injection, ^{241}Am , ^{242}Cm , or ^{253}Es concentrations in rat heart were 120%/kg, nearly seven times as much as in skeletal muscle (SCOTT et al., 1948a, 1949; LANGHAM and CARTER, 1951;

V. H. SMITH, 1972b). The amounts of these nuclides in rat heart declined so that 256 days after injection the concentrations were 18%/kg, only twice that of muscle.

The concentration of ^{241}Am in dog heart 1 to 21 days after injection (0.8%/kg) was much lower than in rat heart, but it was greater than that of dog skeletal muscle (LLOYD et al., 1970, 1972d). In the beagles given 2.8 $\mu\text{Ci/kg}$, concentrations of ^{241}Am in heart were the same 401 to 448 days after injection as they were after only 1 to 22 days. However, the apparently prolonged retention of a high dose of ^{241}Am in heart, and presumably in several other tissues also, was more likely the net result of an early decline in ^{241}Am content followed by a late period of accumulation.

Americium-241 concentrations in baboon heart were higher than those in dog heart: 4 and 2%/kg at 32 and 86 days after injection, respectively (ROSEN et al., 1972; and Table 23). During that interval the concentrations of ^{241}Am in both baboon heart and muscle declined with a half-time of about 50 days.

Autoradiographs of rat heart 3 days after injection of ^{241}Am showed single alpha tracks 'projecting onto cardiac muscle fibers' (RUDNITSKAYA and MOSKALEV, 1970). One to 3 weeks after injection, ^{249}Cf was selectively localized in the connective tissue of the coronary artery as well as in that of the small arterioles, and some large aggregations of ^{249}Cf were found in the circumflex branch of the coronary artery (G. N. TAYLOR et al., 1972). Californium-249 was also concentrated in the connective tissue of the endocardium of the mitral valve. The transplutonium elements deposited in these locations in connective tissue of the heart and its blood vessels appear to remain there for some time. The pattern of distribution of ^{241}Am in dog heart 401 to 448 days after injection was almost identical to that of ^{249}Cf at 7 to 22 days after injection. Superimposed on a low-level diffuse background of alpha tracks, ^{241}Am was selectively localized in the media of arterioles and the coronary artery and in the subendocardium of the mitral valve (G. N. TAYLOR, 1969a).

R. G. THOMAS et al. (1972) observed fibrous intimal thickening of many medium-size to large branches of the coronary arteries in the heart of the dog that died 1022 days after inhalation of an ILB of $2.7 \mu\text{Ci/kg}$ of $^{241}\text{AmO}_2$. The hearts of the 200-day survivors of the high-dose study of $^{241}\text{AmCl}_3$ in rats showed sclerotic changes in both muscle and blood vessels (RUDNITSKAYA and MOSKALEV, 1970).

F. Aorta and other arteries

The media of all small arterioles, principally those with one or two muscle layers, was the most common deposition site of ^{249}Cf in the soft tissues of the dog 7 to 21 days after injection (G. N. TAYLOR et al., 1972). Deposition of ^{249}Cf was remarkably high in the media of at least two large arteries, the aorta and coronary artery. In dog liver, kidney, spleen, heart, lung, and prostate (other tissues were not reported), a high ^{241}Am deposition in the small arterioles was demonstrable autoradiographically 401 to 448 days after injection (G. N. TAYLOR, 1969a). The concentrations of ^{241}Am in the dog aorta, determined radiochemically, were higher than those of most other soft tissues at all post-injection times and all dose levels (LLOYD et al., 1972d).

The aorta and carotid artery were major sites of ^{241}Am concentration in the baboon: 15 and 12%/kg, respectively, 32 days after injection (ROSEN et al., 1972; and Table 23). These concentrations were about the same as those of lungs and trachea, and as much as one-half the concentration in bone. The ^{241}Am concentrations in these arterial structures were maintained at least until 86 days after injection. Autoradiographs indicate that small arterioles in monkey liver, kidney, and spleen were significant deposition sites of ^{241}Am 1 to 112 days after injection (DURBIN et al., 1972c).

G. Thyroid gland

The concentrations of ^{241}Am , ^{244}Cm , and ^{249}Cf in the thyroid gland of the beagle (shown in Table 25) exceeded those in any other tissue except liver and bone (LLOYD et al., 1970, 1972d; ATHERTON and LLOYD, 1972;

MCCLELLAN et al., 1972; R.G. THOMAS et al., 1972). The initial thyroid deposit was not large, usually less than 0.1% of the dose. However, the thyroid gland of the beagle weighs only about 1 g, and the net result was that 1 to 2 days after injection the concentrations of these nuclides in dog thyroid were of the order of 100%/kg.

Autoradiographic studies show that most of the ^{241}Am or ^{249}Cf in the dog thyroid was located in the connective tissue surrounding the follicles (G. N. TAYLOR et al., 1969b, 1972; LLOYD et al., 1970). The connective tissue in which the nuclides were bound was argyrophilic and gave a positive periodic acid-Schiff (PAS) reaction. Differential centrifugation of tissue homogenates confirmed the stability of the binding of ^{241}Am to the connective tissue of the dog thyroid gland (STEVENS et al., 1968b, 1969b; STOVER et al., 1972).

It appears from Table 25 that the transplutonium nuclide content of the dog thyroid declines during at least the first 8 months after injection. The high concentrations of ^{241}Am at 401 and 448 days in thyroids of dogs receiving $2.8 \mu\text{Ci/kg}$ and at 633 and 1533 days in those receiving $0.91 \mu\text{Ci/kg}$ may be partly the result of radiation-induced loss of thyroid tissue (thyroid glands were one-third to one-half normal weight LLOYD et al., 1970, 1972a), and partly the result of accumulation of late-circulating ^{241}Am released from the liver.

Autoradiographs of the 401- and 448-day dog thyroids showed some foci of intense ^{241}Am concentration that were not seen in the thyroids of the ^{241}Am - or ^{249}Cf -injected dogs killed 1 to 22 days after injection. Most of these aggregates of ^{241}Am appeared to coincide with foci of greater amounts of argyrophilic PAS-positive connective tissue. The small size of the thyroid glands of these two dogs (injection level, $2.8 \mu\text{Ci/kg}$ of ^{241}Am) suggest loss of glandular tissue with subsequent condensation of the remaining connective tissue framework. However, as of 448 days after injection, no definite thyroid lesions had been observed, nor had these beagles shown any clinical symptoms of reduced thyroid function (G. N. TAYLOR et al.,

1969b). The thyroid glands of two beagles killed 512 and 1022 days after exposure to an $^{241}\text{AmO}_2$ aerosol (average ILB, $2.7 \mu\text{Ci/kg}$) were atrophic; there was substantial fibrous replacement of the center of the gland, and only a few hyperplastic follicles persisted at the periphery (R. G. THOMAS et al., 1972). In a dog that died 1533 days after injection of $0.9 \mu\text{Ci/kg}$ of ^{241}Am , the epithelial component of the thyroid gland was markedly reduced and no well-defined follicles remained (LLOYD et al., 1972a).

ZALIKIN et al. (1968) detected significant amounts of ^{241}Am in the thyroid glands of rats, but the tissue concentrations were uncertain. SEIDEL and VOLF (1972) confirmed that observation and demonstrated the presence of high concentrations of both ^{241}Am and ^{242}Cm in the rat thyroid. At 6 and 13 days after intravenous injection, the thyroid contained 0.021 ± 0.002 and $0.028 \pm 0.006\%$ respectively, of the dose of ^{241}Am citrate, and 0.024 ± 0.004 and $0.022 \pm 0.002\%$ respectively, of the dose of ^{242}Cm citrate. The average weight of the rats was 190 g, and the thyroid weight estimated from Appendix C was 17 mg. Thus, the average concentration of ^{241}Am or ^{242}Cm , 6 to 13 days after injection was of the order of $1400\%/\text{kg}$, nearly 10 times that found in beagle thyroids shortly after injection of either ^{241}Am or ^{249}Cf .

Autoradiographs of the thyroids of rats given $12.5 \mu\text{Ci/kg}$ of $^{241}\text{AmCl}_3$ and killed 3 days later were reported to show alpha tracks "projected onto the colloid," but whether these emanated from endothelial cells, connective tissue, or blood vessels is not clear. At this high dose level some epithelial cell hyperplasia and edema of the connective tissue stroma were noted 200 days after injection (RUDNITSKAYA and MOSKALEV, 1970).

At a much lower dose of ^{241}Am ($0.037 \mu\text{Ci/kg}$) no effects of radiation could be detected in the thyroid glands of rats through 790 days after injection. The weights of the glands were the same as those of age controls, and the microscopic structures of the thyroids from injected rats and controls

were indistinguishable (DURBIN et al., 1972c, e).

Whole-body autoradiographs of ^{241}Am in mice revealed only low concentrations in thyroid at all postinjection times (HAMMARSTRÖM and NILSSON, 1970a). MCKAY et al. (1972) were not able to detect ^{241}Am in the thyroid glands of Chinese hamsters killed 32 days after injection.

ROSEN et al. (1972) reported only small concentrations of ^{241}Am in baboon thyroid, similar to those in other endocrine glands. The thyroid glands of monkeys were not analyzed for ^{241}Am content. However, the thyroid glands of the monkeys killed 2 to 3 years after injection of 0.44 to 0.87 $\mu\text{Ci/kg}$ of ^{241}Am were of normal weight and showed no microscopic signs of reduced follicular size or increased amounts of fibrous or fatty tissue (DURBIN et al., 1972c).

H. Adrenal gland

The concentrations of ^{241}Am and ^{249}Cf in the adrenal glands of baboons and beagles were small, 3 to 6% /kg, 8 to 32 days after injection (Table 23) declining to 1% /kg by 1917 days after injection.

In the adrenal glands of the rat, the concentrations of ^{241}Am , ^{242}Cm , or ^{253}Es measured 6 to 8 days after injection have been reported to range from 90 to 180% /kg (ZALIKIN et al., 1968; V. H. SMITH, 1972b; SEIDEL and VOLF, 1972). Whole-body autoradiographs of adult mice showed concentrations of ^{241}Am in the adrenal cortices equivalent to those detected in liver and spleen (HAMMARSTRÖM and NILSSON, 1970a). Somewhat contradictory results were obtained by RUDNITSKAYA and MOSKALEV (1970) who detected more alpha tracks in the medulla than in the cortex of the rat adrenal gland 200 days after injection of 2.5 $\mu\text{Ci/kg}$ of ^{241}Am .

I. Testes and prostate gland

The initial concentrations of ^{241}Am or ^{249}Cf in the testes of the beagles were low, about the same as those in pelt and heart and only two to three times the concentration in skeletal muscle (LLOYD et al., 1970, 1972d, e;

ATHERTON and LLOYD, 1972; and Table 23). In the prostate gland the concentrations were two to four times those in testes. The concentrations of ^{241}Am in beagle testes and prostate declined to about one-half their initial values by 1917 days after injection.

The testes of 47-day old rats given $30\text{ }\mu\text{Ci/kg}$ of $^{241}\text{AmCl}_3$ contained 0.08 and 0.04% of the dose 4 and 16 days after injection, respectively (LANGHAM and CARTER, 1951). Based on the weight of the testes of the adult rat (Appendix C) these amounts of ^{241}Am correspond to concentrations of 28 and 14% /kg, respectively—appreciably greater than those measured in the beagle.

Whole-body autoradiographs revealed a low, but increasing concentration of ^{241}Am in the interstitial tissue of mouse testes (HAMMARSTRÖM and NILSSON, 1970a). Americium-241 appeared to be present in parenchymal as well as stromal elements of rat testes (RUDNITSKAYA and MOSKALEV, 1970). In the dog prostate gland the ^{241}Am was associated with glandular epithelium and to a lesser degree with the media of small arterioles (G. N. TAYLOR et al., 1969a).

Testicular atrophy was observed 9 months after injection of $20\text{ }\mu\text{Ci/kg}$ of ^{241}Am in adult rats (OVCHARENKO, 1972). The pituitaries of some male rats showed castration changes 200 days after injection of a high dose of ^{241}Am (RUDNITSKAYA and MOSKALEV, 1970). HAMMARSTRÖM and NILSSON (1970a) also observed testicular atrophy in long-term studies of ^{241}Am in rodents.

J. Ovary, uterus, and mammary gland

In the baboons and beagles, ^{241}Am and ^{249}Cf were initially present in ovaries at concentrations of 3 to 5% /kg, five to ten times those in skeletal muscle (Table 23). Concentrations of ^{241}Am , ^{242}Cm , or ^{253}Es in rat ovaries, 6 to 8 days after injection, have been reported to range from 60 to 230% /kg -- two to ten times those in skeletal muscle (ZALIKIN et al., 1968;

V. H. SMITH, 1972b; SEIDEL and VOLF, 1972).

In whole-body autoradiographs of pregnant mice, HAMMARSTRÖM and NILSSON (1970a) noted high ^{241}Am concentrations in some ovarian follicles, a moderate concentration in ovarian interstitial tissue, and low concentrations in corpora lutea. In the nonpregnant dog ovary, 7 days after injection, ^{249}Cf was detected extracellularly in the deeply-staining zona pellucida of some of the more mature primary oocytes (Graafian follicles) (G. N. TAYLOR et al., 1972).

Histological changes in rat ovaries 200 days after injection of high doses of ^{241}Am included the presence of some follicles without oocytes and some focal stromal leuteinization (RUDNITSKAYA and MOSKALEV, 1970). Similar changes also occur in the normally aging female rat (DURBIN et al., 1972e).

Americium-241 has been measured in the uterus of the nonpregnant baboon, and the concentration was about the same as in the pelt (ROSEN et al., 1972; and Table 23). Whole-body autoradiographs of pregnant mice (19th day of gestation) showed detectable concentrations of ^{241}Am in fetal membranes (but not in placentae) and significant concentrations in mammary tissue (HAMMARSTRÖM and NILSSON, 1970a). Mammary glands of nonpregnant, nonlactating baboons concentrated ^{241}Am to about the same degree as adrenal gland and pancreas and about four times more than skeletal muscle (Table 24).

MCCLELLAN et al. (1962b) studied the passage of intravenously injected ^{241}Am or ^{244}Cm into the milk of the lactating ewe. Concentrations of these nuclides in milk were 2.3 to 3.2 times their concentrations in plasma. In the same experiment the ratio of the concentration of ^{45}Ca in milk to its concentration in plasma was 35. A milk:plasma concentration ratio greater than one suggests that there was a tendency towards active secretion of the trivalent actinides by the mammary gland of the sheep.

XI. Excretion of the transplutonium elements

Early rates of excretion of ^{241}Am , ^{242}Cm , ^{249}Bk , $^{249-252}\text{Cf}$, and ^{253}Es in the urine and feces of the rat are shown in Figs. 34 and 35, respectively. Long-term excretion rates of ^{241}Am , ^{242}Cm , and $^{249-252}\text{Cf}$ appear in Fig. 36 for urine and Fig. 37 for feces. The original data used to prepare Figs. 34 through 37 are collected in Table 26 as accumulated excretion in urine and feces to facilitate independent reanalysis by the interested reader.

The early rates of excretion of ^{241}Am in the urine and feces and the concentration of ^{241}Am in the plasma of an individual cynomolgus monkey and a baboon are shown in Figs. 38 and 39, respectively. Long-term rates of excretion of ^{241}Am by an individual monkey are given in Fig. 40. The original data (compiled as the average accumulated excretion of several animals) are presented in Tables 27 and 28.

The excretion of ^{241}Am or ^{249}Cf by the beagle during the first 3 weeks after injection is compared to ^{241}Am excretion by the monkey and baboon in Table 27.

Excretion of ^{241}Am , ^{252}Cf , and ^{253}Es by the mouse was reported only as accumulated totals 4 and 14 days after injection; these data appear in Table 14. Published reports of the metabolism of ^{241}Am or ^{252}Cf in the Chinese hamster did not include measurements of excreta.

A. Renal excretion

Transplutonium nuclides in the urine are derived entirely from the plasma. Urine is essentially an ultrafiltrate of plasma, and the amount of nuclide excreted in urine is proportional to the fraction of circulating nuclide that can be filtered by the kidney. The mechanisms by which the kidney excretes multivalent cations have not yet been investigated, and the discussion that follows -- based on calculated renal clearances, autoradiographic studies of localization in kidney, and on renal physiology -- is largely the opinion of the reviewer.

1. Renal clearance

The excretory function of the mammalian kidney is accomplished by a combination of glomerular filtration and secretion by the proximal convoluted tubules. Proteins with molecular weights greater than 68,000 and polysaccharides with molecular weights greater than 55,000 are not filtered by the normally functioning kidney. Many compounds and electrolytes that are filtered from the plasma through the glomerulus are not actively secreted by the tubules. However, there are no materials known to be excreted by the tubules that are not also filtered through the glomerulus of the mammalian kidney.

The kidney also functions as a homeostatic regulator, and many essential materials are reabsorbed from the glomerular filtrate also by the proximal tubules. Some passive reabsorption of water and electrolytes takes place in the loops of Henle and the distal convoluted tubules (H. W. SMITH, 1951; BERLINER, 1961).

Renal excretion can be described quantitatively in terms of the renal clearance (C_x), the volume of plasma from which substance (x) is removed per unit time, as follows:

$$C_x (\text{ml/min}) = \frac{U_x (\%/\text{ml}) \times V_u (\text{ml/min})}{P_x (\%/\text{ml})}, \quad \text{Eq. (25)}$$

where V_u is the rate of urine flow, and U_x and P_x are the concentrations in urine and plasma, respectively. In this discussion concentrations are expressed as percent dose per ml. If the measured quantity is total daily urine output ($\%/\text{day}$), and the average plasma concentration during the 24-hr interval is ($\overline{P}_x$), Eq. 25 becomes,

$$C_x (\text{ml/min}) = \frac{\overline{U}_x (\%/\text{day})}{1440 (\text{min/day}) \times \overline{P}_x (\%/\text{ml})}, \quad \text{Eq. (26)}$$

and V_u and U_x need not be evaluated.

The carbohydrate inulin, and in some species the normal metabolite, creatinine, are filtered by the glomerulus but are not secreted by the tubules. The rate of inulin (or creatinine) clearance is equal to the glomerular filtration rate (GFR). The GFR is given for several species in Appendix D. For materials that are actively secreted by the tubules, the renal clearance is

$$C_x (\% / \text{ml}) = \text{GFR}(\text{ml}/\text{min}) + \frac{T_x (\% / \text{min})}{P_x (\% / \text{ml})} \quad \text{Eq. (27)}$$

where T_x is the rate of tubular secretion. Clearance of materials secreted by the renal tubules exceeds the GFR. Tubular reabsorption can also be calculated from Eq. 27 except that T_x is negative in sign, and C_x is less than the GFR. Determination of the true renal clearance of materials that circulate bound to proteins, Ca(II) for example, must take account of the extent to which they can be filtered through the glomerulus.

Renal clearances (calculated using Eq. 26) for ^{241}Am in the rat, beagle, and monkey; for ^{249}Cf in the beagle; and for ^{239}Pu in the rat, beagle, and man are shown in Table 29; the average plasma concentrations and daily urinary excretion rates are shown in Table 29, and the appropriate values of GFR and total plasma volume (ΣV_p) are shown in Appendix D.

Renal clearances of total circulating ^{241}Am and ^{249}Cf ranged from 4.3 plasma volumes per day in the beagle to 7.3 plasma volumes per day in the rat. Clearances of ^{239}Pu were only one-fiftieth as great, ranging from 0.05 to 0.16 plasma volumes per day in human beings and rats, respectively. These clearances of total circulating nuclide did not include any correction for the large fractions of these nuclides that circulate bound to plasma proteins (see Section V.B.). Depending on the method of separation, measurements of plasma protein binding of multivalent cations lie between 85 and 100% (LEWIN, 1954; DURBIN et al., 1955; STEVENS et al., 1968a; BRUENGER et al., 1969a, 1971; TURNER and TAYLOR, 1968b). Gel filtration studies indicate that the fraction of nuclide not associated with plasma protein (or

not remaining associated during separation) could be recovered with a mixture of low-molecular-weight compounds which are presumed to be filterable. Reliable values of protein binding are not yet available for the various nuclides in different species; the Law of Mass Action predicts a higher degree of protein binding in larger species with larger plasma volumes and a larger total number of potential binding sites. *

Such low clearances ($< 10\%$) of total circulating nuclide make it seem quite unlikely that tubular secretion is involved in the renal excretion of multivalent cations. However, low renal clearance can be the net result of filtration combined with efficient reabsorption as well as the result of inhibited filtration. Mathematical demonstration of $T_x < 0$ in Eq. 27 is not sufficient proof of the existence of a renal tubular reabsorption mechanism for a given substance, because the value calculated for T_x is extremely sensitive to the value chosen for the filterability of the substance through the glomerulus. Independent evidence, preferably demonstration of the substance present at a much higher concentration in glomerular filtrate than in passed urine, is required to establish whether a substance is actively reabsorbed.

Nearly all of the protein-bound ^{239}Pu and probably a significant fraction of protein-bound ^{241}Am and ^{249}Cf are associated with transferrin, the iron-transport protein. One ought then to examine what is known about the renal

*The small plasma volumes of the mouse and Chinese hamster have limited total potential binding capacities, which may partially explain the high excretion of ^{241}Am and ^{252}Cf by these animals in the urine passed during the first 24 hr after injection (PARKER et al., 1962, 1972; WRIGHT, 1972; MEWHINNEY and HARRIS, 1972).

excretion of iron. Only small amounts of iron are normally excreted in the urine (0.1 to 0.2 mg/day by adult human beings); renal clearance of circulating iron is about 3% (MOORE and DUBACH, 1962; BOTHWELL and FINCH, 1962). Body iron is sustained by regulation of absorption and efficient binding to plasma protein. There is no evidence of the existence of a renal reabsorption pathway for iron. In fact, iron injected in excess of the transferrin binding capacity is filtered into the urine.

Renal reabsorption systems are quite specific. Except for iron, multivalent cations are foreign to the mammalian kidney. In order to be reabsorbed, they would have to participate in an existing transport system. Such a transport system apparently does not exist for iron, the essential mineral most similar chemically to the lanthanide and actinide elements. The possibility that multivalent cations could penetrate the renal reabsorption system of Ca(II) seems unlikely.

On the other hand, there is evidence that the transplutonium elements are not actively reabsorbed. The renal clearance of the actinide elements is greatest during the first few hours after injection when protein binding is not as complete as it becomes later on (Table 10). The renal clearance of the actinide elements by the rat with its small plasma volume and limited binding capacity is greater than the renal clearances of these elements by larger animals with their more efficient binding potential. Both secretion and reabsorption occur in the proximal convoluted tubules. If either mechanism were involved in the renal excretion of ^{241}Am , one would expect to find some radioactivity localized in that particular structure. However, autoradiographs of dog and monkey kidney* showed ^{241}Am or ^{249}Cf to be

*Autoradiographs of rat kidney showed ^{241}Am associated to some extent with convoluted tubules in the renal cortex, but the preparations were not good enough to distinguish between proximal and distal tubules nor among tracks emanating from tubule cells, tubular lumens, or interstitial tissue (DURBIN et al., 1972c).

most concentrated in the medullary rays where they appeared to be associated with the straight portions of the loops of Henle (G. N. TAYLOR et al., 1969a, 1972; DURBIN et al., 1972c; Figs. 23a, 29a, b). The concentrations of ^{241}Am or ^{249}Cf in the cells of the Henle loops and of neighboring interstitial tissue may be a consequence of the drastic changes that occur in the composition of the urine as it passes through the tubules. First, after passage through the proximal tubules the water content of the glomerular filtrate has been reduced by 80% and most of the major anionic complexing species -- including bicarbonate, amino acids, and citrate -- have been almost completely reabsorbed. Thus, there may be local enhancement of hydrolysis of multivalent cations leading to adsorption on cell surfaces. The tendency towards hydrolysis may be counteracted to some extent by the lower pH of urine as it passes into the descending loop. Second, there is a tendency for all remaining electrolytes to diffuse back into the circulation from the more concentrated fluid in the tubules, thus some passive reabsorption is possible.

Without evidence that multivalent cations are secreted or reabsorbed by the renal tubules, one may infer that their presence in urine is due to filtration alone, and that the amount filtered is an approximation of their in vivo binding to large molecules. The filtered fraction of circulating nuclide was estimated from the ratio of renal clearance and the GFR as shown in Table 28. The filtered fractions of circulating ^{241}Am or ^{249}Cf were

3.2 to 4.5% in rat, beagle, and monkey. * Renal filtration of ^{239}Pu was much lower -- 0.06 to 0.08% in rat, beagle, and man -- as might be expected from the greater stability of the $^{239}\text{Pu(IV)}$ -transferrin complex.

2. Rates of renal excretion

The general features of renal excretion of multicharged cations can be inferred from the kinetic models of deposition (Fig. 12) and long-term metabolism (Fig. 27). As discussed above, the multivalent nuclide in urine has been derived exclusively from the blood. Thus, the rate of renal excretion depends on the net rate at which nuclide is entering and leaving blood. During deposition (immediately after an injection or an accidental exposure) the rate of change of the blood level is the resultant of all the rates at which the nuclide is being cycled through ECF and being taken up by bone and liver. Later, renal excretion rates will reflect the rates at which the nuclide is returning to the circulation from soft tissue and short-lived bone

* One to 4 days after injection, the transplutonium nuclide content of the kidneys of rats was 13 to 42% of the nuclide in urine and kidney combined; in beagles and monkeys, kidney represented 6.7 to 8.1% of the combined total. After the first few hours little nuclide would have been present in the kidney's contained blood. Soluble (complexed) nuclide in formed urine would probably have been removed during fixation and processing of kidney sections, and would not have registered on autoradiographs. It appears from the autoradiographs that nuclide in the kidney at these early post-injection times is largely associated with straight tubules, interstitial tissue, and structures in interstitial tissue. If there is either adsorption of filtered nuclide on tubule cell surfaces or passive diffusion, some of the nuclide combined with these kidney structures was derived from glomerular filtrate. Thus, some of the nuclide in kidney may have been filtered but not passed in urine leading to underestimation of the renal clearance.

structures. Still later, after the nuclide has been cleared from soft tissues (see the discussion of long-term retention in Sections VIII, IX, and X), the renal excretion rate will depend on the rate of release from bone.

All of the features of the long-term model in Fig. 27 have not been tested in one species; it was constructed from observations in different animals. The experimental findings pertinent to the renal excretion aspects of the model include the following: (a) The initial distributions of ^{241}Am or ^{242}Cm in the rat were nearly the same, and the urine curves of these two elements were superimposable (Figs. 34 and 36); (b) In the rat, at times longer than 20 days after injection, the urine curves of ^{241}Am or $^{249-252}\text{Cf}$ had the same slope suggesting a common source of plasma nuclide (Figs. 34 and 36); (c) In the monkeys, from 20 to 500 days after injection of ^{241}Am , during which time some of the initial liver burden was being released into the circulation, the curves of liver retention and renal excretion had the same slope, indicating that the liver was the source of the urinary nuclide (Figs. 21 and 40); (d) At long times after injection, when nearly all of the ^{241}Am remaining in the body of the rat was in the skeleton, the slopes of the retention curves in liver, kidney, residual soft tissues, and combined urine and feces were all much alike. The skeleton was the only available source of nuclide entering the central plasma compartment from which the peripheral compartments were being replenished.

3. The quantity of transplutonium nuclide excreted in urine

The amount of transplutonium nuclide excreted in urine depends on how much of the circulating nuclide can be filtered by the kidney (as discussed above). After deposition is complete, the amount of nuclide in the circulation depends, in turn, on the amounts released from the returning compartments. Mathematical analysis of models of tracer behavior assumes that the rate of change of the amount of tracer in a depleting compartment (dq_2/dt) is a first-order reaction and proportional to the amount present in the compartment (q_2),

$$dq_2/dt = -q_2k_{12} \quad \text{Eq. (28)}$$

where k_{12} is the rate of loss of tracer from the peripheral compartment (2) to the plasma compartment (1). Thus, the amount of nuclide returned to the plasma depends, in its turn, on the initial partition of the nuclide between compartments which can return nuclide to the circulation (bone and soft tissues other than liver) and those compartments which are partly or wholly nonreturning (the incisors of rodents and the liver of several species).

After injection of transplutonium nuclides at doses low enough to avoid significant radiation damage in the liver, the initial liver deposit in rat and mouse (and apparently also in monkey and baboon) was eliminated directly into the gastrointestinal tract and did not contribute to renal excretion. The initial transplutonium deposit in the liver of the beagle and Chinese hamster was almost completely retained (see Section VIII.C.). The rate of release of ^{241}Am from the beagle liver approached that of release from bone (LLOYD et al., 1970, 1972c). It is not known whether any portion of the ^{241}Am or ^{252}Cf deposited in the liver of the Chinese hamster was either recirculated or excreted (A. L. BROOKS, private communication). If the injected dose is large enough to cause liver damage, the liver becomes a partly-returning compartment. Some of the initial nuclide deposit is released into the circulation, and during that time elevated urine levels have been observed in studies with monkeys (DURBIN et al., 1972b,c; Fig. 38) and rats (LANGHAM and CARTER, 1951).

The initial partition of ^{241}Am or ^{242}Cm in most species was 30 to 35% of the dose in hard tissues and 50 to 60% in liver; that of $^{249-252}\text{Cf}$ or ^{253}Es was the reverse; 60 to 65% of the dose in hard tissues and 25 to 30% in liver (Tables 12 through 19). In rats the initial deposit of $^{249-252}\text{Cf}$ or ^{253}Es in soft tissues was nearly twice as great as that of ^{241}Am or ^{242}Cm leading to higher early nuclide levels in urine. Compared

with the lighter weight actinides, the greater amount of $^{249-252}\text{Cf}$ in the rat skeleton, resulted in higher long-term levels in the urine* (Figs. 34 and 36). In the beagle, the larger initial deposits of ^{249}Cf (compared with ^{241}Am) in soft tissues other than liver (and probably also in short-lived bone structures) are presumed to be the sources of the greater amounts of ^{249}Cf excreted in the urine (Table 27).

B. Gastrointestinal excretion

The long-term metabolic model shown in Fig. 27 includes several routes by which transplutonium elements might enter the gastrointestinal tract to be excreted in feces. The following mechanisms appear possible in all mammals: (a) excretion from liver into bile, (b) elimination in digestive secretions other than bile, and (c) functional shedding of intestinal epithelium containing nuclide complexed with transferrin. In rodents there is an additional source of fecal nuclide -- the swallowing of labeled mineral in the course of functional attrition of the constantly growing incisors.

1. Biliary excretion

Early in the study of the biology of the transplutonium elements, SCOTT et al. (1948a) observed that the initial deposit of ^{241}Am in the liver of the rat

* During the first 50 days after injection in rats, the level of $^{249-252}\text{Cf}$ in urine was two to three times that of ^{241}Am , in accord with the deposition of $^{249-252}\text{Cf}$ in bone and soft tissues other than liver, which was two times higher. However, at postinjection times longer than 50 days, the urine level of $^{249-252}\text{Cf}$ was at least five times that of ^{241}Am . The possibilities that $^{249-252}\text{Cf}$ was released more readily from bone, or was redeposited in bone to a lesser degree than ^{241}Am or ^{239}Pu , or that $^{249-252}\text{Cf}$ was recirculated in a more readily filterable form are important for purposes of establishing radiation protection criteria and deserve investigation.

could be recovered entirely in the feces, and they suggested that the ^{241}Am excreted by the gastrointestinal tract had been eliminated from the liver in the bile. The quantitative excretion of the initial liver burden in feces has been observed for many other multivalent cations administered in soluble form to rats and mice (DURBIN et al., 1956, 1960; SCHUBERT et al., 1961; WRIGHT, 1972). The view that the multivalent nuclide present in feces had been derived by biliary excretion from the liver, was reinforced by the measurement of common slopes in the curves of liver retention and fecal excretion of ^{241}Am , ^{242}Cm , and $^{249-252}\text{Cf}$ during the first 30 days after injection in rats, and of ^{241}Am during the first 200 days after injection in cynomolgus monkeys (Section VIII.C, Table 22, and Figs. 21, 26, 34, and 40).

Bile appears to be by far the most important route of entry of multi-charged cations into the gastrointestinal tracts of rats, mice, and monkeys. The possible role of biliary secretion in the excretion of ^{241}Am or ^{249}Cf from the liver of the beagle was discussed in Section VIII.C.

Americium-241 in the monkey: At autopsy bile was collected (1 to 4 ml from the gall bladder) from two monkeys killed 8 days after injection of ^{241}Am citrate, and from two monkeys killed 21 and 42 days after injection. At 8 days, when fecal excretion was low (average for 16 monkeys, 0.09%/day), the ^{241}Am concentration in bile was 0.0035 to 0.008%/ml--the same as, or up to twice as great as, the concentration in skeletal muscle. Between days 21 and 42, when fecal excretion had risen to 0.17%/day (average for 14 monkeys), the ^{241}Am concentration in bile was 0.013 to 0.017%/ml--four to five times the concentration in muscle (DURBIN et al., 1972c). If the amount of gall-bladder bile produced daily by the monkey is similar to the amount estimated

to be elaborated by man* (HAWK et al., 1947), fecal excretion of ^{241}Am by the monkey can be accounted for almost completely by biliary secretion.

Plutonium-239 in the rat: BALLOU and HESS (1972) administered $^{239}\text{Pu(IV)}$ citrate intravenously to rats, perfused the intestine, and collected bile by cannulation of the bile duct. During the first 5 hr after injection, about one-half of the ^{239}Pu recovered from the intestinal contents was derived from bile.

Cerium-144 in the rat: Rats were injected with ^{144}Ce citrate and 1 hr later their bile ducts were ligated. At autopsy, 3 days later, the ^{144}Ce content of the liver was lower while the ^{144}Ce in the skeleton, soft tissues, and accumulated urine was greater than in sham operated controls, suggesting that bile was being regurgitated into the circulation. In another experiment bile was collected continuously through an indwelling catheter in the bile duct for 24 or 48 hr beginning on the 4th day after injection of ^{144}Ce . Bile volumes averaged 14 ml/day (75 ml/kg per day). The average concentration of ^{144}Ce in the bile of 10 rats was $0.022 \pm 0.008\%$ /ml (M. H. WILLIAMS, N. JEUNG, and P. W. DURBIN, unpublished).

* Hepatic bile flow in normal adult human beings is estimated to be between 500 and 1000 ml/day. Gall bladder bile flow is less, because 12 to 25% of the water is reabsorbed: The flow is estimated to be 450 to 900 ml/day (6.4 to 12.8 ml/kg per day for a 70-kg man). If all of the ^{241}Am in feces is assumed to have been derived from gall bladder bile, bile flow in the cynomolgus monkey would be 6 ml/kg per day, not too different from the lower range of the human estimate.

Iron in man: Secretion in bile accounts for about 40% of normal human fecal excretion of iron (0.25 mg of a total of 0.6 mg of fecal iron daily) according to GREEN et al. (1968). That group of investigators injected ^{59}Fe into normal persons and noted that biliary secretion of iron rose to a maximum on the 3rd day after injection and then declined to a negligible level by the 5th day. They suggested that the iron remaining in the liver had reacted to form insoluble forms of ferritin.

The pattern of fecal excretion of ^{241}Am , and to a lesser degree of $^{249-252}\text{Cf}$, by the beagle is similar to that of iron excretion in man, and the very stable association of ^{241}Am or $^{249-252}\text{Cf}$ with ferritin in the canine liver has been amply demonstrated (BRUENGER et al., 1969b, 1972).

2. Secretion into digestive fluids other than bile

In studies with rodents, clearance of the original liver burden in bile to the feces accounts for all or nearly all the fecal excretion up to 30 days after injection, even in the most carefully controlled balance studies. However, the possibility should not be overlooked that a portion of these nuclides might enter the gastrointestinal tract in digestive secretions other than bile, especially during the first few hours after injection while significant amounts are still circulating.

Calcium is a normal constituent of the gastrointestinal secretions of rats and is present in them at a level proportional to that of the ionized calcium in plasma (GRAN, 1960). The digestive secretions of normal human adults, which include bile, contribute to the intestinal contents 130 to 227 mg/day of endogenous calcium, of which 130 ± 47 mg/day is excreted (HEANEY and SKILLMAN, 1964).

About 40% of normal human fecal iron (0.25 mg/day) is believed to have been derived from digestive secretions other than bile (POLLYCOVE, 1966; MOORE and DUBACH, 1962).

The above observations suggest that a portion of multivalent cation in the circulation (not bound to protein) might be able to enter the gastrointestinal lumen by diffusion along with other electrolytes. Whether such a mechanism is normally operable in intact animals is not known; however, there is some evidence suggesting gastrointestinal secretion of ^{239}Pu or ^{144}Ce in rodents with obstructed bile ducts or biliary fistulas.

BALLOU and HESS (1972) found that nearly one-half of ^{239}Pu entering the perfused intestine during the first 5 hr after injection was not of biliary origin. Fluids secreted into the duodenum and jejunum accounted for nearly 40% of the ^{239}Pu in the gastrointestinal contents.

In a study of ^{144}Ce excretion, rats were injected intravenously with ^{144}Ce citrate; their bile ducts were ligated immediately thereafter. During the first hour after the ^{144}Ce injection (and obstruction of the bile duct) 0.4 and 0.6% of the dose, respectively, was secreted into the contents of the stomach and small intestine. The total ^{144}Ce recovered in the gastrointestinal contents was slightly greater than in sham operated controls (M. H. WILLIAMS, N. JEUNG, and P. W. DURBIN, unpublished).

3. Shedding of intestinal epithelium

The adult human intestine desquamates between 50 and 80 g of epithelial cells each day. Transferrin has been detected in intestinal epithelium, and CROSBY (1970) suggests that the degree of iron saturation of the transferrin in the intestinal epithelium is a major factor in the regulation of iron absorption. GREEN et al. (1968) have calculated that 0.1 mg/day of iron (17% of total fecal iron) is lost in feces with these dead cells.

The metabolic studies with lanthanide and actinide elements in which the radioactivity of the completely empty gastrointestinal tract has been measured show that the intestine always contains some nuclide (DURBIN et al., 1956 ; ZALIKIN et al., 1968; LLOYD et al., 1972d, e). Nuclide concentrations are greatest immediately after injection, and decline

at about the same rates as do the concentrations in muscle and pelt.

If some of the nuclide in intestinal tissue is present as a transferrin complex inside epithelial cells, that amount will be eliminated in feces as the cells are lost by normal attrition. The level of nuclide-transferrin complex in intestine will be proportional to the nuclide level in blood. Therefore, except for the first few days after injection when significant amounts of these nuclides are circulating, loss with shed intestinal cells would make a minor contribution to total fecal excretion.

4. Functional attrition of rodent incisors

The incisors of rodents grow, calcify, and erupt throughout the life of the animal. * They are continuously worn away at their incisal edges by gnawing, and complete replacement takes 40 to 50 days (SCHOUR and MASSLER, 1949). The ground mineral is evidently swallowed and can be completely recovered in feces (as discussed below).

Whole-body autoradiographs have demonstrated the uptake of ^{239}Pu and ^{241}Am in the incisors of adults and in the developing molars of very young rats and mice (ULLBERG et al., 1962; HAMMARSTRÖM and NILSSON, 1970a,b). DURBIN et al. (1967, 1972c,d) have shown that 4 days after intramuscular injection of the citrates of ^{241}Am or $^{249-252}\text{Cf}$, the incisors of adult rats contained 1.4 and 2.7% of the dose, respectively. The uptake of these two nuclides in incisors was 4.7 and 4.4%, respectively, of their total uptake in the edentate skeleton (Table 12).

* Rats, mice, and other rodents that eat a mixed diet have molars with limited growth and distinct roots. Those rodents that are completely herbivorous (rabbits and guinea pigs) have molars that grow from permanent pulp.

The incisors continued to take up ^{241}Am . During the first week after injection, no ^{241}Am was lost from the incisors, but the level of circulating ^{241}Am (from clearance of soft tissues and turnover of very short-lived bone structures) was high enough so that the maximum incisor content of ^{241}Am (1.6%) was not reached until the eighth day.

About 45 days are required for an externally visible label, a metabolic or dye marker, to progress from the base of the tooth to complete erosion. It can be seen from the anatomy of the rat incisors and from the autoradiographs of HAMMARSTRÖM and NILSSON (1971a,b) that although nuclide deposition on day 1 was heaviest at the base of the incisors just anterior to the odontogenic epithelium, there was some deposition over all of the surface of the pulp cavity which extends in an elongated cone of decreasing diameter from the base nearly to the tooth tip. Therefore, as expected, some nuclide loss is observed sooner than 45 days. To further complicate matters, the incisors continue to accumulate nuclide from the blood so that between 32 and 46 days, even as the bulk of the day-1 deposit at the incisor tips was being lost, the remainder of the incisors contained an amount of nuclide proportional to the integral of the plasma concentration from days 8 to 46 (BAUER, et al., 1961).

In metabolic studies with rats, if a careful collection is made not only of the feces, but also of the dust, hair, and food scraps from the cage bottoms, and the daily fecal excretion rate is plotted on a large scale (Fig. 35), a distinct "hump" can be found between days 40 and 60 after injection of any bone-seeking nuclide. The hump in Fig. 35 for $^{249-252}\text{Cf}$ is more prominent than that for ^{241}Am not only because of the larger amount of $^{249-252}\text{Cf}$ deposited in the incisors, but also because the amount of $^{249-252}\text{Cf}$ deposited in and subsequently eliminated from the liver is smaller. Graphic integration of the area between the hump in the fecal curve and a smooth curve

connecting the portions of the fecal curves before and after it results in a calculated amount of nuclide excreted in feces equal to the amount of nuclide taken up by the incisors between the time of injection and the acquisition of the maximum deposit about 8 days later.

Because the incisors continue to grow, a fraction of circulating nuclide will be deposited in them each day—to be lost some 45 days later. As indicated in the metabolic model, eventually the incisors should be accumulating and losing nuclide at the same rate at which it is being returned to circulation from long-lived bone structures. DURBIN et al. (1967) calculated by graphic integration of the incisor vs. time curve that between days 120 and 790 after injection of ^{241}Am in rats 0.37% (7.5% of total fecal nuclide passed in that interval) had been taken up and then lost by the incisors.

5. Species differences in fecal excretion patterns

Rats and mice: The livers of rats and mice eliminated their initial burdens of actinide elements in about 30 days. By the 60th day after injection the nuclide accumulated in the incisors in the first few days has been worn away and excreted (Fig. 35). This constitutes a delay of about 30 days between nuclide uptake in liver and its elimination in feces, and an approximate 45-day delay between nuclide uptake in and loss from the incisors. So, at any time, the amount of nuclide in the liver is proportional to the concentration in blood during the preceeding 30 days, and the nuclide content of the incisors represents the average blood concentration in the 45 days preceeding sampling. These delays between nuclide uptake and loss from the liver and the incisors obscure relationships between current blood concentration and fecal excretion of these nuclides by rats as long as the blood concentration is changing rapidly (for about the first 120 days after injection).

After 5 to 6 months the skeleton is almost the only source of circulating nuclide, and the rates of loss of nuclide through both the liver and incisors approach an equilibrium with the slow rate of nuclide release from bone. By then the nuclide concentration in blood is changing so slowly that the 30- to 45-day lag between liver and incisors uptake and the loss of nuclide to feces becomes relatively unimportant. The rate of excretion of nuclide in feces ultimately approaches the rate of change of the concentration in blood, and the amount of nuclide excreted daily by the gastrointestinal tract becomes almost proportional to the concentration in blood at the time of sampling of feces.

Presumably the liver continues to accumulate about 50% of circulating ^{241}Am or ^{242}Cm and about 25% of $^{249-252}\text{Cf}$ or ^{253}Es , and incisors continue to acquire 2 to 4% of circulating nuclide; so that for rats and mice the gastrointestinal tract is always the most important excretory organ. At times long after injection, the daily output of multivalent cations in feces is 2 to 5 times that excreted in urine.

Monkey: The initial deposit of ^{241}Am in the monkey liver was lost in about 200 days, and that in the baboon liver would be expected to have been reduced to 6.25% of its initial value in about 600 days (4 times the measured clearance half-time of 150 days). In the monkey the amounts of nuclide excreted daily in urine and feces were changing at the same rate at times longer than 200 days after injection. The gastrointestinal tract was the major organ of elimination of ^{241}Am by the monkey presumably because close to one-half of circulating ^{241}Am continued to be deposited in, and subsequently lost from, the liver. The daily loss of ^{241}Am in feces was 2 to 3 times that excreted in urine after 600 days (Fig. 40).

Dog: At injected doses low enough to avoid significant radiation damage (less than $0.1 \mu\text{Ci/kg}$ of ^{241}Am) most of the initial liver burden of ^{241}Am or $^{249-252}\text{Cf}$ left the liver very slowly. Excretion of these nuclides by the

beagle has been reported only for the first 3 weeks after injection. It seems likely that during the life-time of the nuclide reservoir in the liver, fecal excretion would be unrelated to the concentration in blood at the time of fecal sampling.

C. Acceleration of the excretion of actinide elements

It was noticed in the first metabolic studies of the fission products and radioactive heavy elements that the behavior of many of these newly-made radionuclides was similar to that of ^{226}Ra (STONE, 1944; COPP et al., 1947). These early workers were aware of the toxicity of ^{226}Ra , and the problem of removal of long-lived radionuclides from bone was given prompt attention (COPP et al., 1946; PAINTER et al., 1946; SCHUBERT, 1947).

The intravenous injection of zirconium citrate soon after nuclide administration was found to reduce the bone uptake of ^{239}Pu or of lanthanide nuclides (SCHUBERT, 1949; KAWIN et al., 1950; see also the reviews of ROSENTHAL, 1955, 1959).

Prompt administration of the aminopolycarboxylic acid, EDTA, was found to be effective in preventing accumulation of ^{239}Pu or the radioactive lanthanides in bone, and prolonged treatment promoted elimination of these multivalent cations from soft tissues (FOREMAN, 1950; FOREMAN and HAMILTON, 1951; HAMILTON and SCOTT, 1953; FOREMAN et al., 1955; FOREMAN and FINNEGAN, 1957). The results of animal studies were sufficiently encouraging to lead to the use of EDTA in the treatment of several persons accidentally exposed to ^{239}Pu or ^{241}Am (FOREMAN et al., 1954, 1958; R. L. DOBSON, 1955). However, it was soon learned that EDTA produced nephrosis at the dosage levels and over the prolonged treatment schedules required for significant enhancement of radionuclide excretion (R. L. DOBSON, 1955; FOREMAN, 1959).

At a conference on radioelement removal, KROLL (1955) reported briefly that a newly synthesized aminopolycarboxylic acid, diethylenetriamine-

pentaacetic acid (DTPA), chelated multicharged cations, and that the stability constants of the DTPA chelates were about 100 times greater than those of the corresponding EDTA chelates. Shortly thereafter, intravenously injected DTPA chelates with ^{90}Y and ^{140}La were found to be quantitatively excreted in the urine of human subjects (KROLL et al., 1957), and V. H. SMITH (1958a,b) reported that in rats DTPA was superior to EDTA in preventing initial bone deposition of ^{239}Pu and in promoting excretion of deposited ^{239}Pu . Since that time the effectiveness of DTPA in accelerating excretion of ^{239}Pu and the trivalent transplutonium elements has been amply demonstrated in animals (V. H. SMITH, 1959, 1972a; SOWBY and TAYLOR, 1960; SCHUBERT et al., 1961; see also the references listed in Tables 30 and 31). DTPA is the treatment of choice in reducing the burden of ^{239}Pu or ^{241}Am of contaminated persons (NORWOOD, 1960; LAGERQUIST et al., 1967; BRODSKY et al., 1966, 1969; FASISKA et al., 1971).

1. Some pharmacological characteristics of EDTA and DTPA

Although this review cannot explain all of the phenomena associated with in vivo chelation with EDTA and DTPA, some of their general properties have been summarized in order to provide a better understanding of the mechanisms of action.

Both EDTA and DTPA form stable complexes with calcium, consequently their rapid introduction into the blood causes a precipitous and dangerous fall in serum calcium. They are commonly administered as the mixed salts, CaNa_2EDTA or CaNa_3DTPA . The British group administer H_5DTPA simultaneously with an equimolar quantity of calcium gluconate (SOWBY and TAYLOR, 1960; D. M. TAYLOR AND SOWBY, 1962; D. M. TAYLOR, 1967; D. M. TAYLOR et al., 1971; JAMES and TAYLOR, 1971).

FOREMAN (1959) studied the distribution and excretion of ^{14}C -labeled EDTA and DTPA in rats and their disappearance from the circulation, and the renal excretion of ^{14}C -EDTA in man. Absorption of these compounds

from the gastrointestinal tract was low -- only 2 to 4% was absorbed in 24 hr. In rats, for either compound the rates of clearance from the blood to urine were not different after intravenous, intraperitoneal, or intramuscular injection. Both compounds were excreted rapidly by the kidneys -- 61 to 85% of EDTA or DTPA in 90 min and 96 to 99% of EDTA in 24 hr; there was some residual DTPA (8 to 13%) in the rats after 24 hr. Renal clearance calculations indicated that both compounds were excreted by the renal tubules as well as being filtered through the glomeruli.

Half-times of EDTA and DTPA clearance from the blood and of renal excretion ranged from 33 to 44 min in rats. Clearance of EDTA from the blood of human subjects was slower; the half-time was 66 to 96 min. In the human subjects, 60% of intravenously administered EDTA and 30% of intramuscularly administered EDTA was excreted in the urine within 90 min after injection. Excretion of EDTA was nearly complete in 12 to 24 hr.

Immediately after injection in the rats, EDTA or DTPA left the plasma compartment and was diluted in body fluid volumes equal to 26.5 and 30% of the body weight, respectively. The most recent estimate of the volume of ECF in the rat is 27.7% of the body weight (bromide space measured by R. N. PIERSON, JR., and D. C. PRICE, unpublished). The amounts of either compound present in tissues were low at all postinjection times, and erythrocytes were found to be impermeable to them. These observations led FOREMAN (1959) to conclude that EDTA and DTPA were able to pass through the capillaries and to equilibrate with ECF, but were not able to penetrate cells. It follows, then, that neither chelating agent can act on metals inside cells such as the ^{239}Pu , ^{241}Am , or ^{252}Cf associated with ferritin in the hepatic cells of the beagle (STOVER et al., 1970, 1972; BRUENGER et al., 1972) or colloidal ^{239}Pu confined within liver phagocytes (LINDENBAUM and ROSENTHAL, 1972).

Large and frequent doses of EDTA in rats have been found to produce degeneration of the proximal renal tubules: After 16 daily doses of 0.67 mM/kg of EDTA the tubular lesions were reversible, but were apparently irreversible after 16 daily doses of 8 mM/kg (FOREMAN, 1959). Similar lesions were apparently also induced by DTPA, but the dosages and severity of the lesions were not reported. However, there were no reports of grossly visible lesions in later studies in which as many as 50 daily doses of 0.46 mM/kg of DTPA were administered to rats (FOREMAN, 1962), or after a series of intermittent doses of 3 mM/kg of DTPA, totaling 27 mM/kg (D. M. TAYLOR and SOWBY, 1962). Amounts of DTPA ranging from 3 to 7 g/week have been tolerated by human beings under treatment for extended periods for removal of ^{239}Pu or ^{241}Am (LAGERQUIST et al., 1967; FASISKA et al., 1971).

FOREMAN (1959) also studied the in vivo stability in rats of EDTA and DTPA chelates with selected metals. The chelates with yttrium, cobalt, chromium, zinc, and lead were stable in the body and were excreted almost completely in the urine within 48 hr. The EDTA chelate with Fe(III) was not stable; 84% of the Fe(III)-EDTA chelate dissociated and was fixed in the body. The Fe(III)-DTPA chelate has been reported to be stable to dissociation in vivo (M. RUBIN and J. V. PRINCIOTTO, unpublished, quoted by BRICK and RATH, 1963). Chelation with DTPA is regarded as a fairly efficient method of accelerating iron excretion in various iron-storage diseases, but is not the treatment of choice (BRICK and RATH, 1963). The ability of DTPA to compete with the normal plasma iron-carrier, transferrin, for ferric ion suggests a mechanism by which DTPA, even though excluded from cells, might be able to promote elimination of metals from intracellular deposits in liver and spleen. By chelating some iron in serum, DTPA may act indirectly to mobilize iron from ferritin and hemosiderin in storage depots and promote its subsequent release in soluble form into body fluids. It is reasonable to assume that other metals, such as ^{239}Pu or ^{241}Am ,

when combined with ferritin, would be released into body fluids simultaneously with the iron and would then be amenable to chelation.

2. General description of animal studies of DTPA effectiveness

For the most part, rats and mice have been used to assess the effectiveness of EDTA and DTPA in reducing bone burdens of the trivalent actinides. Studies with EDTA have been abandoned since the demonstration by V. H. SMITH (1958a, b) and D. M. TAYLOR and SOWBY (1962) of the much greater effectiveness of DTPA in reducing bone burdens of ^{239}Pu and ^{241}Am . The rodent studies of DTPA treatment for removal of transplutonium elements, summarized in Tables 30 and 31, can be divided into two general categories, which for the purposes of this review have been designed prompt nuclide deposition studies and persistent reservoir studies.

(a) Prompt nuclide deposition studies. Nuclides usually have been administered ascitrate complexes, which accomplished prompt and complete distribution. The three exceptional experiments in which the nuclide was administered in a form other than a citrate complex were: (1) $^{241}\text{AmCl}_3$ injected intraperitoneally (BELYAEV, 1969); (2) $^{253}\text{Es}(\text{NO}_3)_3$ injected intramuscularly (V. H. SMITH, 1972a); and (3) $^{241}\text{Am}(\text{NO}_3)_3$ given by inhalation* (NÉNOT et al., 1971c). In all of these experiments DTPA was given by intraperitoneal or intramuscular injection. In some studies DTPA injections were started as soon as 1 hr after the nuclide injection to assess the ability of DTPA to prevent nuclide deposition in bone. In other experiments DTPA injections were delayed as long as 25 days to examine the ability of DTPA to remove trivalent nuclides already deposited in the skeleton.

*This inhalation study was included in Table 30 because by the time DTPA was begun, 20 days after exposure, nearly all of the ^{241}Am had been absorbed.

Treatment intervals varied from daily to weekly, and the amounts of DTPA given in a single treatment ranged from 0.11 mM/kg in the mouse studies (PARKER et al., 1962, 1972) to 3 mM/kg in the experiments with growing rats (SOWBY and TAYLOR, 1960; D. M. TAYLOR and SOWBY, 1962).

(b) Persistent reservoir studies. In the French experiments (summarized in Table 31), ^{241}Am or ^{242}Cm nitrates or sulfates were administered intramuscularly or as aerosols. The aim of the studies was to find the optimal treatment of persons accidentally contaminated with transplutonium elements by puncture wound or by inhalation. In either case -- contaminated muscle or lung -- a reservoir was established that continuously fed radioactivity into the circulation over periods lasting from a few days to several months. DTPA treatment was given either by intramuscular injection (0.12 mM/kg per injection) or as an aerosol. The investigators estimated that the amount of DTPA aerosol deposited in the lung was about 1% of the intramuscular DTPA dose. DTPA treatments were started 1 or 21 days after the nuclide administration and were repeated bi-weekly or weekly for intervals of 10 to 120 days.

3. Chelation of actinides in soft tissues

The amounts of actinide nuclides initially deposited in the soft tissues of rodents are small, and the soft tissues are cleared quickly (see Section X and Fig. 33). In the absence of a chelating agent, some of the nuclide released from soft tissue is redeposited in bone. As discussed in Section VIII, the trivalent actinides, when administered at low doses to rodents, are cleared promptly from the liver without therapeutic intervention.

DTPA has been found to hasten the clearance of actinide nuclides from soft tissues. A short course of DTPA injections reduced the soft tissue contents of ^{241}Am , ^{252}Cf , or ^{253}Es in the mouse, and the ^{241}Am content of rat tissues to 10% of control levels, and accelerated liver clearance

(D. M. TAYLOR and SOWBY, 1962; PARKER et al., 1962, 1972). Less frequent DTPA treatments or smaller amounts of DTPA per treatment were less effective in promoting loss of ^{241}Am or ^{242}Cm from the soft tissues and livers of rats (SEIDEL and VOLF, 1972).

4. Chelation of circulating nuclide

Shortly after DTPA became available, it was recognized that if treatment were initiated within a few minutes to a few hours after parenteral injection of soluble $^{239}\text{Pu(IV)}$, DTPA chelated and promoted efficient excretion of the large amount of ^{239}Pu still circulating in the body fluids, and effectively prevented its deposition in liver and bone (V. H. SMITH, 1958a,b). V. H. SMITH (1959) also showed that a minimum dose of 0.2 mM/kg of DTPA given 1 hr after intravenous injection of ^{239}Pu citrate into rats could limit the ^{239}Pu uptake in bone to the amount taken up before the DTPA injection (20% of the ^{239}Pu content of bones of control rats).

The ability of DTPA to prevent skeletal deposition of the trivalent actinides is more restricted, because like the lanthanide and alkaline earth elements, they are deposited very quickly after injection. It is apparent from Figs. 6 through 9 and from Table 10 that 1 hr after injection of soluble ^{241}Am or ^{242}Cm only 3 to 10% of the dose was still circulating and 28% was in soft tissues and ECF. It can be seen from Figs. 10, 11, and 13 that 1 hr after injection the deposition of ^{241}Am in bone was 76% complete; deposition in the liver was 68% complete.

5. Chelation of transplutonium elements in marrow or loosely associated with bone

In a short-term single-dose study, BELYAEV (1969) gave DTPA to rats 1 day after administration of ^{241}Am ; the rats were killed 2 days later. Even though deposition of ^{241}Am was complete at the time of the DTPA injection, the DTPA treatment reduced the ^{241}Am content of bone to 50% of the control value.

Several studies involve a short series of intermittent DTPA treatments begun 1 to 24 hr after administration to rats of ^{241}Am (BELYAEV, 1969; SOWBY and TAYLOR, 1962), or ^{253}Es (V. H. SMITH, 1972a), or after administration to mice of ^{241}Am , ^{252}Cf , or ^{253}Es (PARKER et al., 1962, 1972). In all cases the amount of actinide remaining in the skeleton 14 to 21 days after the nuclide injection was less than the amount expected. If, at the time of the first DTPA injection, all of the nuclide in bone were firmly fixed, the only expected loss from bone would have been the quantity of nuclide released from bone that was resorbed during the DTPA treatment (see paragraph 6 below) plus any nuclide in tissue fluids or soft tissues that was prevented from depositing in bone. The dose-response study of V. H. SMITH (1959) showed that if the amount of DTPA (given 1 hr after a ^{239}Pu injection) were increased above 0.2 mM/kg, the bone content was reduced to less than the amount of ^{239}Pu deposited in 1 hr (20% of control). A single dose of 4 mM/kg of DTPA reduced the ^{239}Pu in bone to 10% of the control value. Apparently about one-half of the ^{239}Pu in bone 1 hr after injection could be removed, if the DTPA dose were large.

These results suggest that for 24 to 48 hr after nuclide injection, up to one-half of trivalent actinide considered to be deposited in bone (based on analysis of whole long bones including marrow) is either in the marrow or is only loosely bound to the bone surfaces and is still amenable to chelation by DTPA. Some of the 1-hr deposit of ^{239}Pu in bone appears also to be amenable to chelation, if the amount of DTPA is large enough.

6. Chelation of actinides deposited in bone

At times longer than 1 to 2 days after nuclide injection, any nuclide that is still in the marrow has been deposited in bone, and nuclide initially only loosely bound at bone surfaces has become more firmly fixed. Growing surfaces are covered by new bone. In rapidly growing rats some of the nuclide deposited on metaphyseal trabeculae has already been resorbed and redistributed (D. M. TAYLOR et al., 1961).

The effect of delayed DTPA treatment on removal of ^{241}Am or ^{242}Cm from the bones of young adult rats, estimated to be 60 to 90 days old at the time of nuclide injection, has been the subject of several investigations (FOREMAN, 1962; BELYAEV, 1969; SEIDEL and VOLF, 1972; NÉNOT et al. 1971c; Table 30). Delayed DTPA treatment of ^{241}Am deposited in the bones of 7-week-old rats has been studied by SOWBY and TAYLOR (1960) and D. M. TAYLOR and SOWBY (1962).

JAMES and TAYLOR (1971) used quantitative autoradiography to investigate the influence of DTPA on the microscopic distribution of ^{239}Pu in the ends of the long bones of growing rats. Five treatments of DTPA (1.5 mM/kg each) were given during a 14-day period beginning 7 days after injection of a solution of 85% ultrafilterable $^{239}\text{Pu}(\text{NO}_3)_4$ to 7-week-old rats. They concluded that the observed reduction in the ^{239}Pu bone burden was due to chelation of ^{239}Pu released into tissue fluids during osteoclastic resorption of labeled bone surfaces in the normal course of growth remodeling.

In young rats, resorption of trabeculae elaborated by centers of endochondral ossification in ribs, vertebrae, and the ends of long bones appears to proceed fast enough and to involve a large enough fraction of the total bone nuclide to account for the amount of nuclide lost from bone during the first 10 to 30 days of a course of DTPA treatments begun 7 to 14 days after nuclide injection. Using quantitative autoradiography, D. M. TAYLOR et al. (1961) showed that ^{241}Am deposited on the metaphyseal trabeculae in the ends of the femora of 7-week-old male rats was almost completely resorbed within 21 days after injection -- equivalent to a constant removal rate of 5% /day. The rate of resorption of labeled metaphyseal trabeculae of older rats appears to be slower. The autoradiographs shown by DURBIN et al. (1967) can be interpreted to represent about 80% resorption in 42 days leading to a calculated resorption rate of about 2% /day (see Figs. 14 and 15).

These estimates of bone surface resorption agree with the rate of resorption of calcium in adult rat bone. BAUER et al. (1961) calculated from ^{45}Ca kinetic data that calcium in the tibia of the 90-day-old rat was being resorbed at a rate of 0.13 mg/hr, which is equivalent to resorption of 3% /day of the mass of the tibia. *

Assuming that 3 and 4%, respectively, of the labeled surfaces of the bones of adult and growing rats is resorbed daily, the calculated amounts of nuclide remaining in bone agree with the amounts measured by FOREMAN (1962), SEIDEL and VOLF (1972), SOWBY and TAYLOR (1960), and D. M. TAYLOR and SOWBY (1962), in which DTPA treatments were begun 6 to 14 days after nuclide injection and lasted for 7 to 23 days. In the studies of BELYAEV (1969) and NÉNOT et al. (1971c), in which DTPA treatment was delayed for 20 days or longer after nuclide administration, the amounts of nuclide lost from bone were less than expected at a constant resorption rate of 3% /day. Apparently, by the time the DTPA treatments were started in the latter experiments, a large fraction of the initially labeled trabecular surfaces had already been resorbed, and the nuclide had been redistributed to other surfaces with lower probabilities of resorption during the short course of treatments. The studies of NÉNOT et al. (1971c) indicated however, that if DTPA treatments were continued long enough (in this case 104 days), enough bone surface, even though with low nuclide concentration, would eventually be resorbed to reduce the nuclide burden in the whole skeleton to about 25% of the control level.

*The ash weight of the tibia of the 90-day-old female Sprague-Dawley rat is 260 mg (DURBIN et al., 1972e), and bone ash is about 40% calcium by weight. Therefore,

$$\text{Resorption (\% /day)} = \frac{0.13 \text{ mg Ca/hr} \times 24 \text{ hr/day} \times 100}{260 \text{ mg ash} \times 0.4 \text{ mg Ca/mg ash}} = 3\% / \text{day}$$

The average rate of resorption of surfaces in the adult human skeleton has been estimated to be about 5% /year or 0.014% /day (DURBIN, 1972). Thus, as was pointed out by JAMES and TAYLOR (1971), DTPA therapy can be expected to have only a marginal effect in removing deposited nuclides from the human skeleton. Consequently, prevention of the systemic distribution of nuclides in contaminated wounds or in the lungs appears to be the only realistic therapeutic approach.

7. Diversion of nuclide from a persistent reservoir

The studies of LAFUMA et al. (1970) and NÉNOT et al. (1970, 1971a, b, c, 1972), in which DTPA was administered intermittently while ^{241}Am or ^{242}Cm was being absorbed from a reservoir in muscle or lung, are practical demonstrations of the usefulness of DTPA in chelating nuclides as they enter the circulation; the nuclides are diverted to urinary excretion, and are effectively prevented from being deposited in bone and liver. DTPA (0.12 mM/kg in each treatment) administered intramuscularly to rats every fifth day or twice weekly starting 1 day after nuclide administration and continued for 2 to 4 months, prevented deposition of 75 to 90% of the administered nuclide.

BALLOU and MORROW (1972, and unpublished) determined that DTPA effectively removes ^{253}Es ($^{253}\text{EsCl}_3$ instilled intratracheally in rats) from the lung and prevents deposition of ^{253}Es in bone. The DTPA was given as a single injection (0.2 mM. kg) 1 hour after the nuclide administration. The rats were killed 1 week after the instillation at which time the lungs contained 4% of the instilled ^{253}Es (18% of untreated controls) and the skeleton contained 3% of the ^{253}Es (7% of untreated controls based on absorbed dose).

Not only did DTPA efficiently prevent the nuclides from depositing in bone and tissues, but the radioactivity was cleared more rapidly from both

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the lung and muscle reservoirs* reducing the potential radiation dose in those tissues.

It is of interest to note that although the amount of DTPA administered as an aerosol was too small to have a significant effect on the behavior of intramuscularly injected ^{241}Am , it was very effective in chelating ^{241}Am deposited in the lungs. In fact, repeated inhalation of small amounts of DTPA (about 0.0012 mM/kg in each treatment) was almost as effective in clearing ^{241}Am from the lungs and diverting it from bone as a similar series of intramuscular injections of 0.12 mM/kg of DTPA (NÉNOT et al., 1971a).

8. DTPA treatment of persons exposed to ^{241}Am

In general, human experience agrees with the above experimental findings. In the case of a wound contaminated with ^{241}Am (described in Section IV.B. and Table 7) it was calculated that nearly two-thirds of the ^{241}Am in the wound site was chelated and excreted in urine during a 60-day course of EDTA injections (R. L. DOBSON, 1955). It appears from Fig. 2 that mobilization of ^{241}Am from the wound site declined at about the time EDTA treatments were stopped.

BRODSKY et al. (1969) and FASISKA et al. (1971) have reported the prolonged treatment with DTPA of a man who had inhaled ^{241}Am oxides over a period of several years before his contamination was discovered. Weekly injections of 1g DTPA for 15 months removed about one-half of the body burden which, measured by whole-body counting, was 2 μCi at the start of the DTPA treatments. A combination of partial-body and whole-body measurements indicated that the DTPA treatments had removed about 1 μCi of ^{241}Am , mostly from the lungs and liver, leaving about 1 μCi in the skeleton. Weekly

*The intramuscular injection site could be cleared even more rapidly, if the DTPA were injected into the same location as the nuclide. See Section IV.B.

or bi-weekly DTPA treatments of 0.5 g each were continued for another year, and an additional 0.15 μCi was removed.

Some preliminary results have been reported of the metabolism in human subjects of an isotope of the artificially produced lanthanide, promethium, ^{143}Pm (PALMER et al., 1968a,b). Since the initial tissue distribution of ^{241}Am in rats most closely resembled that of the lanthanide of the same ionic radius, ^{147}Pm (see Section V.A.6), the behavior of ^{143}Pm in human beings is expected to resemble that of ^{241}Am . Well-characterized experiments with ^{143}Pm should provide insight into the problems of dealing with persons contaminated with ^{241}Am or isotopes of the other trivalent actinides. The stability constant of the ^{241}Am -DTPA chelate is greater than that of the ^{143}Pm -DTPA chelate (see the references in Section VII.A.6, and Chapter 17 of this volume). Chelates of ^{241}Am in bone, blood, and tissue constituents may also be more stable than those of ^{143}Pm , so there may be some small differences in the in vivo chelation behavior of these two, otherwise similar, elements.

In the study of PALMER et al. (1968a,b) single or multiple injections of 1 g each of DTPA (equivalent to 0.014 mM/kg in a 70 kg man) were given at various times after intravenous injection of 0.1 μCi of $^{143}\text{PmCl}_3$. Retention of ^{143}Pm was measured by whole-body counting 6 days after its injection. A single DTPA injection given 5 min prior to the ^{143}Pm completely prevented deposition; given 30 min afterwards, the body content was reduced to 14% of the control, while at 5 or 24 hr the reduction was 58 or 85%, respectively. When given 80 days afterwards, only 5% of the body content of ^{143}Pm was eliminated in the ensuing week. Three DTPA injections 1, 5, and 24 hr after the ^{143}Pm injection reduced the body content to 24% of control, and four DTPA injections, 1, 24, 48, and 72 hr after the ^{143}Pm removed all but 12% of the control body content.

As one would expect from the 100-fold difference in the amount of DTPA administered, the single injection of 0.014 mM/kg at 24 hr was not as effective in removing ^{143}Pm from man as was a single dose of 1.5 mM/kg of DTPA in removing ^{241}Am from rats; 58% of the control body content of the ^{143}Pm remained, compared with 38% of the control body content of the ^{241}Am in the rats (BELYAEV, (1969). Four injections of DTPA starting at 1 hr were more effective in reducing the body content of ^{143}Pm in man (88% removed) than was a comparable course of DTPA treatments in removing ^{241}Am from rats, which had been reduced by 82% after 7 daily injections of 0.46 mM/kg of DTPA starting 2 hr after the ^{241}Am administration (FOREMAN, 1962).

9. Suitability of ^{241}Am as a tracer for ^{239}Pu

In the plutonium processing industry, wounds of the hands and fingers are frequently contaminated with metallic plutonium or $^{239}\text{PuO}_2$. Assessment of the level of contamination and of the efficacy of treatment is difficult and often inaccurate, and requires special sophisticated detection equipment because low-energy L x-rays are the only photons emitted by an ordinary mixture of plutonium isotopes. Americium-241, the radioactive daughter of ^{241}Pu and a contaminant of all modern plutonium (Section IV.D.9), emits a 60 keV γ -ray which is accurately and easily measured in vivo by currently available photon detecting equipment. The ^{241}Am γ -ray has been used to monitor suspected contaminations of plutonium workers (HAMMOND and PUTZIER, 1964; LAGERQUIST et al., 1967).

The question of whether ^{241}Am was a good tracer for ^{239}Pu in the body was examined in a series of experiments with beagles (L. J. JOHNSON, 1969, which contains all of the original data; L. J. JOHNSON et al., 1970a,b, 1972; WATTERS and LEBEL, 1972). A colloidal suspension of

$^{239}\text{PuO}_2$ * (mean count diameter, 7 μm) was implanted subcutaneously above the left metacarpus of each of 40 beagles. Twenty of these beagles also each received DTPA by intravenous injection (0.05 mM/kg per treatment) at 2 hr, on days 1 through 6, days 9, 12, and 14, and then on three consecutive days each month for up to 1 year after the $^{239}\text{PuO}_2$ injection. Groups of dogs were killed at intervals from 2 weeks to 1 year postinjection.

The migration and/or solubilization of the implanted particles appeared to be characteristic of the $^{239}\text{PuO}_2$. External measurement of the photons of energy greater than 10 keV (those reaching the detector were chiefly the 60 keV γ -rays of ^{241}Am) demonstrated that a fraction of the implanted nuclides migrated to the superficial cervical lymph nodes (the major nodes draining the implant area). During the first 2 weeks, about 3% of the implanted nuclides migrated to the lymph nodes, and by the end of one year, the cervical lymph nodes contained an average of 17% of the implanted dose. Later, separate measurements of the alpha radioactivity of the two nuclides in the dissected nodes showed that 100 days after implantation they contained about 8% of each nuclide. In the DTPA-treated beagles the externally measurable radioactivity of the lymph nodes was less at all times after injection than in the untreated controls, but the differences were not always significant.

* In the discussion of these experiments the designation ^{239}Pu represents the mixture of plutonium isotopes with a composition by weight of 0.035% ^{238}Pu , 86.63% ^{239}Pu , 11.69% ^{240}Pu , 1.51% ^{241}Pu , and 0.135% ^{242}Pu . All of the isotopes except ^{241}Pu , which is a beta emitter, contribute to the alpha radioactivity of the mixture.

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On the average, 0.65% of the implanted ^{241}Am and 0.27% of the ^{239}Pu migrated in soluble form out of the implant site and/or the lymph nodes and were distributed through the body. The average amounts implanted were 0.55 μCi of ^{241}Am and 5.8 μCi of ^{239}Pu . At autopsy 100 days after implantation, the lymph nodes contained 0.044 μCi of ^{241}Am and 0.464 μCi of ^{239}Pu , and the measured tissues contained 0.0036 μCi of ^{241}Am and 0.016 μCi of ^{239}Pu .

Any changes occurring in the nuclide content of the tissues between 2 weeks and 1 year after the $^{239}\text{PuO}_2$ implantation were obscured by the great variability of the data and by the net flow of nuclide into and out of the tissues. The experimenters concluded that there were no well-defined trends in the tissue distributions with time after injection. The data were pooled, without regard for the length of time between injection and sacrifice, to form two large groups -- untreated and DTPA-treated.

The measured body content of ^{241}Am , expressed as percent of body content 100 days after implantation (excluding lymph nodes and neglecting unmeasured soft tissues), was distributed 60% in liver, 34% in bone, *

*The total ^{241}Am or ^{239}Pu in the skeleton was calculated using the proportionality factor of 20 times the nuclide content of one femur (L. J. JOHNSON et al., 1972). According to the data of LLOYD et al. (1972a) based on analyses of complete skeletons of beagles injected intravenously with either ^{241}Am or ^{239}Pu , one femur contains 3 or 4% of total skeletal ^{241}Am or ^{239}Pu , respectively, and the appropriate proportionality factors are 33.3 or 25, respectively. The tabulated values of ^{241}Am and ^{239}Pu in the skeleton were recalculated for this review using these proportionality factors.

2% in lung, 1.7% in kidneys, 0.8% in spleen, 0.43% in thyroid (equivalent to 430% /kg), and 0.12% in the adrenals. The distribution of ^{239}Pu was 44% in liver, 51% in skeleton, 2% each in spleen and lung, 0.5% each in kidneys and adrenal glands, and 0.03% in the thyroid gland. These tissue distributions are about what one would expect from the studies of beagles intravenously injected with ^{241}Am or ^{239}Pu (STOVER et al., 1959, 1967, 1971; LLOYD et al., 1970, 1972a, c). In the untreated beagles, a greater fraction of the implanted ^{241}Am than ^{239}Pu was absorbed in the body and of the absorbed ^{241}Am , a greater fraction was deposited in the liver, kidneys, thyroid gland and other soft tissues; while a smaller fraction of the absorbed ^{241}Am was deposited in the skeleton.

The average ^{241}Am contents of the livers, bones, kidneys, and thyroid glands of the DTPA-treated dogs were 36, 52, 55, and 61%, respectively, of those tissues in untreated controls. The DTPA treatment did not change, or actually seemed to increase the ^{241}Am content of spleens, lungs, and adrenal glands, which were 167, 92, and 200%, respectively, of the amounts in the control tissues. Although the DTPA treatments significantly increased the amounts of ^{239}Pu excreted in urine (as well as increasing urinary excretion of ^{241}Am), the amounts of ^{239}Pu in the livers and bones of the DTPA-treated beagles were almost the same as those of the controls.

The concentration of ^{241}Am in the blood of untreated beagles was highest during the first few weeks after the ^{241}Am -labeled PuO_2 was implanted, and the DTPA treatments were given almost daily during the first 2 weeks after the implantation, so it is reasonable to assume that the major action of the DTPA was to prevent deposition of some of the ^{241}Am as it was being absorbed.

The experimenters concluded, that, except for early external monitoring of the wound site itself and possibly of the major lymph nodes draining the

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site, ^{241}Am was not a suitable tracer for the metabolism of absorbed ^{239}Pu , and that the differential behavior of the two elements was exaggerated still further by the administration of DTPA.

XII. Toxicity of the transplutonium elements

A. Lethal radiation injury

The mean lethal dose (LD_{50}), which is the injected amount required to kill one-half of the animals at some specified time, has been determined in adult rats at times from 2 weeks to 1 year after injection of ^{239}Pu , ^{241}Am , or ^{244}Cm ; in growing rats after injection of ^{239}Pu or ^{241}Am ; and in Chinese hamsters and dogs after injection of ^{241}Am . The LD_{50} 's expressed as $\mu\text{Ci/kg}$ injected or inhaled are shown in Table 32 (rodents) and in Table 33 (dogs) as are the toxicities of the β -emitting bone-seekers, ^{90}Sr - ^{90}Y and ^{144}Ce - ^{144}Pr .

1. Acute toxicity

The acutely toxic doses at 30 days ($LD_{50/30}$) of the three long-lived actinides, ^{239}Pu , ^{241}Am , and ^{244}Cm , were about the same for rodents, 100 $\mu\text{Ci/kg}$, on the average. Pilot experiments with $^{253}\text{EsCl}_3$ indicated that in rats injected as adults, 21-day-old weanlings, or on the day of birth, 150 $\mu\text{Ci/kg}$ was 50% lethal in 90 to 100 days (MAHLUM and SIKOV, 1972 and unpublished). If one takes into account the high initial urinary excretion of $^{253}\text{EsCl}_3$ (about 40% is excreted in the urine in the first week after injection, HUNGATE et al., 1972) and the 20.5-day physical half-life of ^{253}Es , the total amount of α -particle energy available per μCi of ^{253}Es at 30 and 60 days after injection is only about 40 and 25%, respectively, of that available from the long-lived actinides. Therefore, the $LD_{50/30}$ of ^{253}Es is probably more than 250 $\mu\text{Ci/kg}$.

At post-injection times of 60 through 350 days, the LD_{50} 's of ^{239}Pu , ^{241}Am and ^{253}Es were greater in the young rats than in the adults, suggesting a greater resistance of the growing animals to the lethal effects of these nuclides. The LD_{50} of ^{241}Am , determined 120 to 180 days after injection,

was less in the Chinese hamsters than in the adult rats. Multivalent cations were eliminated rapidly from the rat liver, but were retained in the liver of the hamster where additional injury very likely contributed to the greater lethality of ^{241}Am in the hamsters.

The acute LD_{50} of ^{241}Am or ^{239}Pu is not well defined in the dog; injection of 10 to 60 $\mu\text{Ci/kg}$ of either nuclide was 100% lethal in less than 30 days (Table 33). The $\text{LD}_{50/30}$ of ^{241}Am or ^{239}Pu in dogs seems to be about one-half that for adult rats.

Deaths occurring earlier than 60 days after injection of a large dose of an actinide were associated primarily with bone marrow injury. Delayed deaths (those occurring 120 to 180 days after injection of somewhat lower doses) also appeared to be associated with bone marrow depression. The radiation damage that accumulated in the livers of Chinese hamsters and dogs, as well as in the lungs of those animals exposed by inhalation or intratracheal instillation, probably also contributed to the delayed deaths. Late deaths, 1 year or more after exposure, appeared to involve radiation injury in several organs--bone marrow, liver, kidneys, and lungs (after inhalation exposure)--or the consequences of radiation injury--myelogenous leukemia and bone tumors.

2. Toxicity relative to β -emitting bone seekers

The distribution of ^{144}Ce - ^{144}Pr is sufficiently similar to that of the actinides, ^{241}Am , ^{244}Cm , and ^{239}Pu , to provide a basis for comparing the toxicities of α -emitting and β -emitting nuclides that are deposited primarily on bone surfaces. The average $\text{LD}_{50/30}$ of the α -emitters in the rodents was about 100 $\mu\text{Ci/kg}$, and in the dog the median acute lethal dose was about 35 $\mu\text{Ci/kg}$. The $\text{LD}_{50/30}$ of ^{144}Ce - ^{144}Pr for Chinese hamsters, rats, and dogs, was 3750, 1830, and 110 $\mu\text{Ci/kg}$ respectively; on the basis of

injected doses, the relative effectiveness* for acute lethality was, respectively, 38, 18, and 3.

If acute lethality is due primarily to radiation damage of the bone marrow, a better estimate of relative effectiveness would be one based on the amount of radiation absorbed in bone. The path length of α -particles is less than 100 μ m in soft tissue or bone, and all of the energy of α -emitters deposited in bone is absorbed in bone. However, some of the energy of the long-range β -emitters such as ^{90}Sr - ^{90}Y and ^{144}Ce - ^{144}Pr is dissipated outside of bone. PARMLEY et al. (1964) measured the energy absorption in the skeleton of ^{90}Sr - ^{90}Y as a function of skeletal size. They found that 32, 48, and 79% of the β -particle energy of deposited ^{90}Sr - ^{90}Y was absorbed in the skeletons of mice (nearly the same size as Chinese hamsters), rats, and dogs, respectively. The average energy of the α -particles emitted by ^{241}Am , ^{244}Cm , and ^{239}Pu was 5.5 MeV. The average energy of the β -particles ($\bar{E}$) emitted by the ^{144}Ce - ^{144}Pr pair was 1.1 MeV and that of the ^{90}Sr - ^{90}Y pair was 1.0 MeV. The average energy absorption in the skeletons of Chinese hamsters, rats, and dogs, from the β -particles of ^{144}Ce - ^{144}Pr was 0.41, 0.53, and 0.87 MeV, respectively. The relative effectiveness for direct cell killing (acute lethality) based on energy absorbed in bone** was 2.8 for Chinese hamsters,*** 1.8 for rats, and

* For the purposes of this discussion relative toxicity or relative effectiveness in producing some biological endpoint is defined as the inverse of the ratio of the injected doses of the α -emitter and the β -emitter.

** For example, the relative effectiveness of the α -emitters based on approximate energy absorbed in bone of rats was $[(100 \times 5.5)/(1830 \times 0.53)]^{-1} = 1.8$.

*** MCKAY et al. (1972) calculated more precisely using Chinese hamster tissue distribution data, that the relative effectiveness was 3.2 for acute lethality of ^{241}Am compared with ^{144}Ce - ^{144}Pr or ^{90}Sr - ^{90}Y .

0.5 for dogs. The relative effectiveness for bone marrow damage of the α -emitting bone-surface seekers appeared to be inversely related to body size, suggesting that in the animals with larger bones some marrow cells escape irradiation by the short-range α -particles. Marrow that was apparently intact was found in the shafts of the long bones of mice and rats injected with lethal doses of ^{239}Pu (BLOOM, 1948; LANGHAM and CARTER, 1951), ^{241}Am (LANGHAM and CARTER, 1951), and ^{223}Ra (DURBIN et al., 1958).

3. Delayed lethality

In the adult rats, the relative effectiveness for lethality of the α -emitters was 1.8, at 120 to 180 days after injection, the same as it was for acute lethality. This concurs with the view that delayed deaths were also associated with bone marrow injury. In the Chinese hamsters 120 to 180 days post-injection, the relative effectiveness of ^{241}Am was greater, (7.3) than it was for acute lethality, suggesting the introduction of another mode of radiation injury for which the more densely ionizing α -particles were more efficient: most likely cell death in the liver. At times longer than 1 year the α -emitters were eight times more efficient than the β -emitters in inducing deaths among adult rats. Except for myelogenous leukemia and bone tumors, the causes of the late deaths among rats were not specified; however, it seems clear that for these endpoints the α -emitters were more effective than they were for direct killing of bone marrow cells.

Some late deaths among the dogs were attributable to accumulated damage in the liver and kidneys. If it is assumed for simplicity that one-half of the injected dose of either the α -emitting or the β -emitting nuclides was deposited in soft tissues where absorption of the β -particle energy was complete, and one-half was deposited in bone where 79% of the β -particle energy was absorbed, the average relative effectiveness of the α -emitters was about 9 for late deaths in the dog.

B. The formed elements of the blood

The hemorrhagic syndrome (pancytopenia and massive internal bleeding caused by bone marrow destruction, LORENZ and CONGDON, 1954) was the apparent cause of death of rats, Chinese hamsters, or dogs given large doses of transplutonium nuclides. Bone marrow aplasia and severe internal hemorrhage were observed in rats and Chinese hamsters dying within 30 days after injections of 50 $\mu\text{Ci/kg}$ or more of ^{241}Am or ^{244}Cm , and in dogs dying within 3 weeks after injection of 10 to 60 $\mu\text{Ci/kg}$ of ^{241}Am (LANGHAM and CARTER, 1951; ZALIKIN et al., 1968, 1969; SEMENOV, 1971a; MCKAY et al., 1972).

With sublethal injected doses, bone marrow was still being irradiated, but at a lower dose rate, by nuclides deposited on the inner surfaces of bone. Depletion of the marrow, especially the erythropoietic elements, was a major contributor to lethality in mice continuously exposed to external radiation at dose rates greater than 10 R/day (SACHER, 1963). Marrow depletion was likely to be the most important factor in the later deaths of animals bearing moderate burdens of actinide elements in their bones.

The depression of erythrocytes, polymorphonuclear leukocytes (PMN), and thrombocytes (platelets) was the result of radiation damage of stem cells in the marrow. The cause of the reduction in the number of circulating lymphocytes is less clear. The concentrations of transplutonium elements in lymphatic tissues were low, and the depression of lymphocytes was, therefore, presumed to be due primarily to irradiation of mature cells circulating through organs with high nuclide deposits—bone, liver, and lung (in the case of inhalation exposure).

The hematological effects of ^{241}Am were generally similar to those observed with equal doses of ^{239}Pu in growing rats (LANGHAM and CARTER, 1951) or in young adult beagles (J. H. DOUGHERTY, 1972a). In beagles, in the long-term low-dose studies, both ^{241}Am and ^{239}Pu were 2 to 6 times more effective than ^{226}Ra in reducing the numbers of circulating leukocytes (J. H. DOUGHERTY, 1972a,b). * Preliminary observations in beagles injected with ^{249}Cf or ^{252}Cf suggest that for long-term hematological effects the toxicity of the californium isotopes may equal or exceed that of ^{239}Pu (J. H. DOUGHERTY, 1971).

1. Leukocytes

- a. Acutely lethal doses in rodents. Injected doses of ^{241}Am or ^{244}Cm greater than 100 $\mu\text{Ci/kg}$ elicited maximum hematological effects in rodents. Within 7 to 10 days postinjection, the numbers of circulating PMN's and lymphocytes fell to 10 to 20% of preinjection levels and recovered to only 25 to 40% of control levels at the time of death (LANGHAM and CARTER, 1951; ZALIKIN et al., 1968); SEMENOV, 1971a). Immature PMN's and immature and unusual forms of lymphocytes considered to be characteristic of radiation damage (binucleated,

* J. H. DOUGHERTY (1972a,b) calculated relative hematological effectiveness from the ratio of skeletal dose rates from various radionuclides and ^{226}Ra at a time when the various leukocytes had been depressed to 50% of their pre-injection levels.

enlarged, or vacuolated cells) were present in the peripheral blood 2 to 3 weeks after injection (LANGHAM and CARTER, 1951; ZALIKIN et al., 1968).

b. Acutely lethal doses in dogs. Dosages of 10 to 60 $\mu\text{Ci/kg}$ of ^{241}Am were acutely lethal in dogs. The numbers of PMN's and lymphocytes declined immediately after injection, and at death 10 to 20 days later, they were only 20% of preinjection values (ZALIKIN et al., 1969).

c. Intermediate doses in rats. Dosages in the range of 10 to 60 $\mu\text{Ci/kg}$ of ^{241}Am or ^{244}Cm were 50% lethal to rats in 60 to 300 days. Within 10 to 14 days the numbers of PMN's and lymphocytes fell to between 20 to 30% and 40 to 60%, respectively, of control levels. Recovery was variable. In 6-month survivors, the PMN's and lymphocytes had recovered to 50 and 75% of preinjection levels, respectively. The numbers of PMN's and lymphocytes were within the lower limits of normal in rats that survived for 1 year (LANGHAM and CARTER, 1951; ZALIKIN et al., 1968, 1969; SEMENOV, 1971a).

d. Moderate to low doses in beagles and rats. Doses of ^{241}Am or ^{249}Cf ranging from 2 to 10 $\mu\text{Ci/kg}$ severely depressed the leucocyte levels of beagles, and 2 to 10 $\mu\text{Ci/kg}$ of ^{241}Am or ^{244}Cm reduced these levels by about 50% in adult rats.

In beagles, by 30 days after injection of 2.8 $\mu\text{Ci/kg}$ of ^{241}Am (100% lethal in 15 months) the PMN's had fallen to about 15% of the preinjection value. There was only partial recovery; after 3 months the PMN's were 35 to 50% of control values, and they remained at that low level for the next 12 months. The same dose of ^{249}Cf depressed the PMN's to less than 10% of the control value within 2 to 3 weeks after injection. By 8 weeks after injection the PMN's had recovered to 30% of their initial value.

The lymphocytes of the beagles were less affected. Thirty days after injection of 2.8 $\mu\text{Ci/kg}$ of ^{241}Am , the lymphocytes had declined to 50% of

the control level, and remained well below normal until the deaths of the dogs at 13 and 15 months. After injection of 2.8 $\mu\text{Ci/kg}$ of ^{249}Cf , the level of lymphocytes decreased slowly and steadily, and by 8 weeks was only 30% of the preinjection level (J. H. DOUGHERTY, 1970, 1971).

Doses of 5 to 10 $\mu\text{Ci/kg}$ of ^{241}Am or ^{244}Cm (lethal to 50% of the rats within 1 year) depressed the PMN's to 40 to 50% of preinjection levels within 10 to 14 days. Recovery was variable: In the ^{241}Am study, PMN's returned to within normal limits by 6 months after injection. Lymphocytes declined gradually so that 1 year after injection they were only 50% of the control value (ZALIKIN et al., 1968, 1969). In the ^{244}Cm study, the PMN's were still only 60 to 70% of normal 1 year after injection. Lymphocytes declined to 70% of the control value by the 10th day, and there was only a slight recovery, to 80% of normal by 1 year (SEMENOV, 1971a).

e. Low doses in dogs and rats. Doses of ^{241}Am or ^{244}Cm less than 2.5 $\mu\text{Ci/kg}$ had little consistent effect on the leukocytes levels of rats up to 18 months after injection (ZALIKIN et al., 1969; SEMENOV, 1971a; DURBIN et al., 1972c).

In the beagles the effects on the leukocytes of 0.9 $\mu\text{Ci/kg}$ of ^{241}Am were about the same as those of the larger dose of 2.8 $\mu\text{Ci/kg}$. There were no early changes in the numbers of circulating lymphocytes or PMN's after injection of 0.1 or 0.3 $\mu\text{Ci/kg}$ of ^{241}Am ; however, by 18 months after injection, both types of leukocytes had declined to 75 to 80% of preinjection levels (J. H. DOUGHERTY, 1970). The hematological effects of 0.28 $\mu\text{Ci/kg}$ of either ^{249}Cf or ^{252}Cf have been reported up to 8 weeks after injection. The

average energy per decay of ^{252}Cf is nearly twice that of ^{249}Cf . * The decline in PMN's and lymphocytes occurred sooner after injection of ^{252}Cf , but the effects on the white cell counts were not significantly different over the short observation period. The numbers of PMN's and lymphocytes decreased to 50 and 85% of preinjection levels, respectively, 8 weeks after injection of either californium isotope (J. H. DOUGHERTY, 1971).

At the one low dose level, 0.28 to 0.3 $\mu\text{Ci/kg}$, for which there is hematological data for ^{241}Am , ^{249}Cf , and ^{252}Cf , it appears that the californium isotopes were much more effective in depressing the leukocytes than was ^{241}Am .

2. Erythrocytes

a. Acutely lethal doses of ^{241}Am or ^{244}Cm . In dogs, at death 10 to 21 days after injection of 10 to 60 $\mu\text{Ci/kg}$ of ^{241}Am , red cell counts were only 50% of normal, presumably because of massive internal bleeding (ZALIKIN et al., 1969). In rats, within 2 to 3 weeks after injection of 100 $\mu\text{Ci/kg}$ or more of either isotope, the number of red cells fell 20 to 40% below the control level, apparently also because of hemorrhage. Red cell counts remained low or continued to decline until death (LANGHAM and CARTER, 1951; ZALIKIN et al., 1968, 1969; SEMENOV, 1971a). Unusually large numbers of reticulocytes were observed in peripheral blood 2 to 4 weeks after injection of a large dose of ^{241}Am in rats (Zalikin et al., 1968).

b. Intermediate doses of ^{241}Am or ^{244}Cm . In rats the early decline in the red cell count was only 10 to 15% below the control level after injection of 10 to 60 $\mu\text{Ci/kg}$ of either isotope. Following an early recovery between 2 and 3 months after the injection, red cell counts declined again to 20 to 25% below normal between 3 to 6 months after injection. A long period

* Californium-249 decays by the emission of α -particles with an average energy of 5.93 MeV. Californium-252 has two modes of decay; 97% by α -particle emission and 3.2% by spontaneous fission. Including the energy of the fission fragments, the average energy per disintegration of ^{252}Cf is 11.76 MeV (LLOYD et al., 1972b).

of recovery was seen in the 6-month to 1-year survivors which was characterized by periodic wide fluctuations. In the 1-year survivors, red cell counts were within 10% of normal (LANGHAM and CARTER; 1951; ZALIKIN et al., 1968, 1969; SEMENOV, 1971a).

c. Low doses of ^{241}Am or ^{249}Cf . In beagles, 2.8 $\mu\text{Ci/kg}$ of ^{241}Am depressed the volume of packed red cells (VPRC) to about 15% below normal within 1 to 3 months after injection, where it remained for 7 to 9 months. After that time a more severe anemia developed and was progressive until death at 13 to 15 months (J. H. DOUGHERTY, 1970). A comparable dose of ^{249}Cf affected the red cells more drastically. Both the VPRC and the hemoglobin fell to 55 to 60% of the preinjection levels by 4 weeks after injection; by 8 weeks they had recovered to 75 to 80% of preinjection levels. During the 4th week the number of reticulocytes in the peripheral blood rose sharply, reaching twice the normal level at 6 weeks, followed by a decline, so that by 8 weeks reticulocytes were present in normal numbers (J. H. DOUGHERTY, 1971).

In rats injected at doses lower than 10 $\mu\text{Ci/kg}$ of ^{241}Am , red cell counts fluctuated about the normal level for 3 to 5 months. By 9 months the red cell counts began to decline, and at 18 months they were 70% of the preinjection level. At dosages of 2.5 $\mu\text{Ci/kg}$ red cell counts were depressed after about the 6th month (ZALIKIN et al., 1968, 1969).

3. Thrombocytes

The effects of injected transplutonium elements on the numbers of circulating platelets has been studied in beagles. Injection of 2.8 $\mu\text{Ci/kg}$ of ^{241}Am reduced the platelets to 50% of the preinjection level within 2 to 4 weeks. By the third month after injection the platelets had recovered to 60% of normal. Eighteen months after injection of 0.9 $\mu\text{Ci/kg}$ of ^{241}Am , the platelet count was still only 60% of the preinjection level. No significant effects on the platelets were observed in the first 18 months after injection

of 0.1 or 0.3 $\mu\text{Ci/kg}$ of ^{241}Am (J. H. DOUGHERTY, 1970).

Platelets were more severely affected by ^{249}Cf . Within 3 to 5 weeks after injection of 2.8 $\mu\text{Ci/kg}$, the platelet count was less than 10% of the pre-injection level and had recovered only to 40% at 8 weeks. The platelet count was depressed after injection of 0.28 $\mu\text{Ci/kg}$ of either ^{249}Cf or ^{252}Cf : It fell sharply after injection of ^{252}Cf and was 80% of the preinjection level within 1 to 2 weeks; the depression continued through 8 weeks. After injection of ^{249}Cf , the platelet count declined gradually and at 8 weeks was 80% of the preinjection value (J. H. DOUGHERTY, 1971).

4. Bone marrow

Bone marrow biopsies of dogs injected with 10 to 60 $\mu\text{Ci/kg}$ of ^{241}Am showed fewer than 20% of the normal number of nucleated cells by the third day, and complete aplasia by 14 days (ZALIKIN et al., 1969). The marrow of four beagles was variable 127 to 1022 days after inhalation of an average ILB of 2.7 $\mu\text{Ci/kg}$ of an $^{241}\text{AmO}_2$ aerosol. Foci of complete acellularity, hypoplasia, and occasionally of hyperplasia, were found in the marrow taken from ribs, vertebrae, or long bones. The spleens of all four dogs contained foci of extramedullary hematopoiesis (R. G. THOMAS et al., 1972).

One year or more after injection of 7 $\mu\text{Ci/kg}$ of ^{241}Am into 7-week-old rats, foci of aplasia were seen in the marrow of the femoral metaphysis, and the marrow in the epiphysis was aplastic (BENSTED and TAYLOR, 1969). The marrow of Chinese hamsters was hypoplastic one year after injection of 5 $\mu\text{Ci/kg}$ of ^{241}Am (MCKAY et al., 1972).

BENSTED et al. (1965) reported a case of myelogenous leukemia among 19 rats that survived more than one year after an injection of 2.5 $\mu\text{Ci/kg}$ of ^{241}Am . Two of 48 rats given 10.7 $\mu\text{Ci/kg}$ of $^{252}\text{EsCl}_3$ by intratracheal instillation developed myelogenous leukemia within 350 days (BALLOU and MORROW, 1972, and unpublished).

5. Hematological effects of inhaled ^{241}Am

Radiation dose rates in bone and liver are highest within a few hours after injection of an actinide isotope. Because of the delayed absorption after inhalation of these nuclides (Section IV. D.), maximum radiation dose rates do not occur in bone and liver until several weeks after exposure. Therefore, the prompt depressions of leukocytes and platelets characteristic of large doses of injected actinides are not observed when comparable amounts are inhaled. R. G. THOMAS et al. (1972) have described the hematological effects in 4 beagles 127 to 1022 days after inhalation of an $^{241}\text{AmO}_2$ aerosol (average ILB was $2.7 \mu\text{Ci/kg}$). Lymphocytes were depressed to 40% of the preexposure level by 80 days, declined further to 20% by 512 days, and remained at that low level for the next 500 days. By 80 days the PMN's were reduced to 40% of the preexposure level. By 512 days the PMN's had recovered to 60% of the preexposure value; there was no further recovery. The VPRC gradually declined and was 85% of the preexposure level by 1022 days. Platelets decreased to 40% of the preexposure level by 256 days, but had recovered to 80 to 90% of normal by 1022 days.

BULDAKOV et al. (1972) reported leukopenia, depressed myelopoiesis, and reticulocytosis in dogs observed for up to two years after inhalation of $1.5 \mu\text{Ci/kg}$ of an $^{241}\text{Am}(\text{NO}_3)_3$ aerosol.

Except for the absence of the early decreases, the effects of inhalation of $2.7 \mu\text{Ci/kg}$ of $^{241}\text{AmO}_2$ on red cells, PMN's and platelets of beagles were generally similar to those seen after injection of a comparable dose of ^{241}Am citrate. After parenteral administration of ^{241}Am , lymphocytes are exposed to the radiation sources in liver and bone. Americium present in the lung constitutes an additional source of exposure. Later, loss of function of the tracheobronchial lymph nodes contributed further to the depressant effect.

C. Effect on growth and body weight

Growth or weight gain ceased or was retarded in rats injected with ^{241}Am or ^{244}Cm at dosages greater than $5\text{ }\mu\text{Ci/kg}$ or after intratracheal instillation of $^{253}\text{EsCl}_3$. After an acutely lethal dose (more than $50\text{ }\mu\text{Ci/kg}$ of ^{241}Am or ^{244}Cm) the body weights of adult rats declined and were 85% of control weights at the time of death (ZALIKIN et al., 1968; SEMENOV, 1971a). A high percentage of rats injected at 35 days of age with $32\text{ }\mu\text{Ci/kg}$ or more of ^{241}Am failed to gain weight (LANGHAM and CARTER, 1951). Weight gain of male rats was severely impaired after intratracheal instillation of $^{253}\text{EsCl}_3$; 150 days after instillation of $47.2\text{ }\mu\text{Ci/kg}$, body weights were 60 to 70% of age controls and 275 days after instillation of $10.7\text{ }\mu\text{Ci/kg}$ body weights were 80% of the controls (BALLOU and MORROW, 1972, and unpublished).

D. Effects of inhaled transplutonium elements in the lung

Four beagles were exposed to an aerosol of $^{241}\text{AmO}_2$; the average ILB was $2.7\text{ }\mu\text{Ci/kg}$ (R. G. THOMAS, 1970; R. G. THOMAS et al., 1972), and the dogs were killed 127, 256, 512, and 1022 days after exposure. Partial-body γ -ray counting and radiochemical analyses of lung tissue dissected at necropsy permitted estimation of the radiation doses absorbed in the lungs, which were 3000, 3200, 3800, and 5300 rad, respectively, (the investigators stated that these were rough estimates). After 50 days the two dogs killed at 127 and 256 days exhibited increased respiratory rates and decreased tidal volumes.

Two dogs were euthanized because of their deteriorating physical condition. The 256-day dog exhibited progressive respiratory distress. The 512-day dog was killed because of general debility which included loss of weight and liver insufficiency. At necropsy the lungs of these two dogs showed striations of the pleural surface with alternating regions of greater radiation damage

associated with the ribs (BARNES, 1970). Microscopic examination of the lungs of the 127-day dog revealed a few isolated areas of inflammation and some minor structural alterations in bronchiolar and alveolar duct epithelium. Microscopic findings in the other dogs were similar, but more pronounced. Lung pathology was most evident in the 256-day dog and included foci of dense fibrosis, which was mostly subpleural and was associated with thickening of the pleura. Small foci of mineralization were also present on the lungs of the dogs killed at 512 and 1022 days. Other pathology included local proliferation of alveolar cells, obliterative fibrosis of small arteries, and some dense parabronchiolar fibrosis. In all four dogs the tracheobronchial lymph nodes, which had the highest ^{241}Am tissue concentrations through 512 days, were small and showed medullary fibrosis and lymphoid depletion.

Two brief reports have appeared on a large series of dogs exposed to aerosols of soluble $^{241}\text{Am}(\text{NO}_3)_3$ or polymeric $^{239}\text{Pu}(\text{NO}_3)_4$ at the Institute of Biophysics in Moscow (BULDAKOV et al., 1972; NIFATOV et al., 1972).^{*} Respiratory insufficiency was the stated cause of death in those dogs that succumbed within 6 months of the exposure to either nuclide. The dogs that inhaled the ^{239}Pu aerosol exhibited more pronounced clinical signs of altered lung function (increased density of lung fields in radiographs, higher respiratory rates, poorer O_2 saturation of arterial blood, and a greater difference in arterial-venous O_2 saturation) than the dogs exposed to an equal amount of the ^{241}Am aerosol.

^{*} These reports are essentially abstracts; experimental details are scanty, and some of the information content may have been obscured in translation. The amounts of radioactivity inhaled by individual dogs, the ranges of IBB or ILB, and the numbers of dogs in the dose-level or nuclide groups were not reported.

Of those dogs exposed to an ^{241}Am aerosol, five died of a fibrinous purulent pneumonia 74 to 181 days after inhalation; the accumulated radiation doses in the lungs of these dogs were reported to be 655 to 4050 rad. Four dogs succumbed after 414 to 1108 days with signs of a moderate pulmonary sclerosis, but lung damage was apparently not the primary cause of death; the accumulated radiation dose in the lungs of these dogs was reported to be 2660 to 2990 rad.

BALLOU and MORROW (1972, and unpublished) studied the effects of $^{253}\text{EsCl}_3$ instilled in the lungs of rats. Median survival time was 180 days after instillation of 47.2 $\mu\text{Ci/kg}$, and was associated with respiratory distress. By 275 days there were only 28% (8/29) survivors at this dose level. The accumulated radiation dose to the lungs was reported to be 15,000 rad at 275 days (decay of this 20.5-day nuclide is 99% complete by 150 days). By 275 days after exposure no deaths attributable to pulmonary difficulties had occurred in rats at the 10.7 $\mu\text{Ci/kg}$ level; their individual accumulated lung dose, 3000 rad.

E. Radiation injury in the skeleton

The skeletal effects of the transplutonium elements have not been thoroughly studied. However, based on the extensive experience with ^{239}Pu , one would expect gross damage to be dependent on the accumulated radiation dose in bone and the growth status of the skeleton. (For descriptions of the effects of ^{239}Pu in the skeleton, the interested reader is referred to: HELLER, 1948; LANGHAM and CARTER, 1951; FABRIKANT and SMITH, 1964; the appropriate chapters in T. F. DOUGHERTY et al., 1961; MAYS et al., 1967; STOVER and JEE, 1972; and Chapter 10 of this volume.) For ^{239}Pu , and presumably for the other surface-seeking α -emitters, gross structural abnormalities (stunting, fractures, altered radiographic densities and altered bone thicknesses) and

microscopic changes (death of bone and cartilage cells, peritrabecular fibrosis, and obliteration of cortical vascular channels) would be expected to be more dramatic and to appear sooner in growing animals and in short-lived animals with more rapid bone turnover in adulthood.

1. Alterations of growth and structure of bone

Cessation of growth of long bones and limb deformities were noted as early as 8 weeks after injection of 32 to 63 $\mu\text{Ci/kg}$ of ^{241}Am into 35-day-old male rats (LANGHAM and CARTER, 1951). Skeletal radiographs revealed fractures of the long bones, generalized osteoporosis, dense bars of bone along epiphyseal growth lines, and marked cortical thinning with occasional fibrocystic changes in the long bones. These skeletal abnormalities were similar to those seen in rats of the same age injected with ^{239}Pu at the same dose levels. Histological examination revealed extensive areas of bone necrosis. Skeletal anomalies similar to those just described were observed several months after injection of 5.8 to 7 $\mu\text{Ci/kg}$ of ^{241}Am into 7-week-old male rats (FABRIKANT and SMITH, 1964; D. M. TAYLOR and BENSTED, 1967; BENSTED and TAYLOR, 1969). Bone growth was reduced, and by 8 to 10 months after injection all long bones were stunted. Humeri and tibiae were 10% shorter and femora 15% shorter than in age controls. Radiographs at 10 months showed osteoporosis in the ends of the long bones and sclerosis in the femoral shaft. Bilateral symmetrical thinning of the cortex of the femoral metaphysis led to fractures of the knee. Thinning of the cortex was apparently not the result of an increase in the diameter of the marrow cavity, but rather the net result of continued periosteal resorption in the absence of the normal compensatory apposition of new bone on the endosteal surface.

Gross damage has also been noted in the growth apparatus of the upper incisors (D. M. TAYLOR and BENSTED, 1967; BENSTED and TAYLOR, 1969). By 400 days postinjection the upper incisors had stopped growing; some were loosened and others were lost altogether, resulting in overgrowth of the lower incisors.

Growth retardation, spontaneous fractures, and loss of teeth have been observed within a few months after injection of 10 to 150 $\mu\text{Ci/kg}$ of $^{253}\text{EsCl}_3$ into either adult or 21-day-old rats. These effects were more pronounced in the rats injected as weanlings (MAHLUM and SIKOV, 1972).

Fairly extensive bone damage was observed in four beagles that inhaled an average ILB of 2.7 $\mu\text{Ci/kg}$ of an $^{241}\text{AmO}_2$ aerosol and were killed from 127 to 1022 days later (R. G. THOMAS et al., 1972). The effects in bone were reminiscent of those seen in beagles injected with ^{239}Pu . (See ^{239}Pu references cited above.) A series of radiographs (the first taken 1 year after exposure) of the skeletons of the 512-day and 1022-day dogs showed progressively decreasing bone density, coarsening and attenuation of trabecular patterns in vertebrae and the ends of long bones, and roughening of the endosteal surfaces of the long bones. Rib fractures were first noted in the 1022-day dog 550 days after exposure, and there were several unhealed fractures at the time of death. Microscopically, in the femora, ribs, and vertebrae, there was extensive endosteal fibrosis associated with focal osteoid thickening, focal resorption of spicules, irregular cortical thickening, and periosteal fibrosis. In the ribs, in addition to the ununited fractures, there were small areas of degeneration in the central cartilage of the costochondral junctions.

2. Induction of bone tumors

Tumors of bone, mostly osteogenic sarcomas, have been recognized for more than 40 years as a probable late consequence of radiation accumulated

in bone from deposited ^{226}Ra (MARTLAND and HUMPHRIES, 1929). Osteogenic sarcomas have been observed in experimental animals injected with ^{239}Pu : mice (LISCO et al., 1947; FINKEL and BISKIS, 1962); growing and adult rats (LANGHAM and CARTER, 1951; FABRIKANT and SMITH, 1964; RUDNITSKAYA and MOSKALEV, 1970); and young adult beagles (references cited in Section 1 above). Osteogenic sarcomas have also been induced by ^{241}Am and ^{253}Es .

a. Estimation of radiation dose in rat bone. The range of radiation doses in the bones of ^{241}Am -injected rats was calculated from the dose rate (based on the $\mu\text{Ci/kg}$ injected) and the burden time (time of appearance of the first bone tumor and either the time of appearance of the last bone tumor or the time of death of the last rat in an experimental group). Radiation dose rate is given by the general equation

$$\text{Dose rate (rad/day)} = 51.2EC \quad \text{Eq. (27)}$$

where E is the α -particle energy, 5.5 MeV, and C is the ^{241}Am concentration in bone which is given by the expression,

$$C(\mu\text{Ci/g}) = \frac{k(\mu\text{Ci/kg} \times 10^{-3}) (\text{Body weight, g})}{(\text{Bone weight, g})} \quad \text{Eq. (28)}$$

For these approximate calculations, the fraction of injected ^{241}Am deposited in the skeleton, k , was assumed to be 0.3 of the administered dose on the average, and the weight of the rat skeleton was assumed to be 10% of the body weight. Substituting these values in Eq. 28 and combining terms, Eq. 28 reduces to

$$C(\mu\text{Ci/g}) = 3 \times 10^{-3} D, \quad \text{Eq. (29)}$$

where D is the injected dose in $\mu\text{Ci/kg}$ of body weight. The accumulated radiation doses were calculated directly from the injected dose, D, and the time after injection, t days:

$$\text{Dose}_t \text{ (rad)} = 0.845Dt. \quad \text{Eq. (30)}$$

b. Bone tumors induced in rats. In LANGHAM and CARTER's (1951) pioneer study of the biological effects of ^{241}Am , it was found that 19% (6/32) of rats that survived more than 290 days after injection of 32 to 63 $\mu\text{Ci/kg}$ of ^{241}Am at 35 days of age developed osteogenic sarcomas between 290 and 350 days. The accumulated radiation doses calculated from Eq. 30 ranged from 7800 to 16,000 rad. In a series of experiments also using growing male rats (7 weeks old), but much lower injected doses of ^{241}Am : 16% (5/32) of rats injected with 2.5 $\mu\text{Ci/kg}$ developed bone tumors between 475 and 671 days after injection, estimated dose range, 1000 to 1400 rad (FABRIKANT and SMITH, 1964); 25% (5/20) of rats injected with 2.5 $\mu\text{Ci/kg}$ developed bone tumors 400 to 525 days after injection, estimated dose range, 800 to 1100 rad (BENSTED and TAYLOR, 1965; D. M. TAYLOR and BENSTED, 1967; BENSTED and TAYLOR, 1969); 17% (5/30) of rats injected with 5.8 $\mu\text{Ci/kg}$ developed bone tumors 365 to 510 days after injection, estimated dose range 1800 to 2500 rad (FABRIKANT and SMITH, 1964); and 47% (15/32) of rats injected with 7 $\mu\text{Ci/kg}$ developed bone tumors between 287 and 525 days after injection, estimated dose range, 1700 to 3100 rad (D. M. TAYLOR and BENSTED, 1967; BENSTED and TAYLOR, 1969).

In adult rats the incidence of osteogenic sarcomas has been reported to be 13.5% (7/52) among rats that lived longer than 300 days after injection of 2.5 to 10 $\mu\text{Ci/kg}$ of ^{241}Am (ZALIKIN et al., 1969; MOSKALEV and RUDNITSKAYA, 1970). Accumulated radiation doses in bone, estimated from Eq. 30, were

600 and 2500 rad 300 days after injection. They agreed reasonably well with the dose range calculated by the investigators, 500 to 5000 rad.

No bone tumors were found among 52 rats that were observed for longer than 500 days after injection of $0.37 \mu\text{Ci/kg}$ of ^{241}Am at 110 days of age (DURBIN et al., 1967, 1972c). The bone doses estimated from Eq. 30 were 190 rad by 390 days post-injection and 250 rad by 800 days, the maximum survival time of this group of rats.

Although the results are preliminary, it is clear that osteogenic sarcomas in adult rats can also be induced by ^{253}Es . As of 280 to 350 days after intratracheal instillation of $10.7 \mu\text{Ci/kg}$ of $^{253}\text{EsCl}_3$ into adult male rats, 4/48 rats had developed bone tumors. The accumulated radiation dose in bone was 300 rad at 20.5 days (one-half-life of the ^{253}Es isotope) and a maximum of 600 rad by 150 days after exposure (BALLOU and MORROW, 1972, and unpublished).

In the young rats bone tumors arose about equally in the axial and the appendicular skeleton. Combining all of the data from the studies of FABRIKANT and SMITH (1964), BENSTED et al. (1965), D. M. TAYLOR and BENSTED (1967), and BENSTED and TAYLOR (1969), bone tumors were distributed as follows: long bones, 16; vertebrae, 10; pelvis, 1; and jaw, 2. In the LANGHAM and CARTER (1951) study four tumors developed in long bones and one each in the spine and pelvis. The distribution of bone tumors induced in the young rats by ^{239}Pu was reported to be the same, but has not been reported for adult rats.

Much of the radiation dose absorbed in the skeletons of the growing rats from very high doses of ^{241}Am was wasted, perhaps by dissipation in bone that had already been killed by the continuous irradiation. The lowest dose associated with a bone tumor in the high-level injection study was 7800 rad. In the low-dose experiments the smallest tumorigenic dose was 800 rad, only one-ninth as large.

Although the range of doses required to elicit bone tumors was about the same in the growing and mature rats, tumors were induced more fre-

quently in the growing rats. If all of the data in the low-dose studies are combined in such a fashion that equal numbers of rats are represented at the 2.5, 5.8, and 7 $\mu\text{Ci/kg}$ dose levels, the overall incidence of tumors is 29% (25/86) compared to an overall incidence in the adult rats (2.5 to 10 $\mu\text{Ci/kg}$ of ^{241}Am) of 13.5%. This finding is expected from the results of FABRIKANT and SMITH (1964) who found that after injection of 2.95 $\mu\text{Ci/kg}$ of ^{239}Pu the incidence of bone tumors in growing rats (7 weeks old at injection) and adult rats (7 months old at injection) was 25 and 5%, respectively. These investigators also indicated that the ^{239}Pu -induced tumors in the adult rats grew more slowly, were more confined, and had a lower tendency to invade surrounding tissue.

c. Bone tumors induced in dogs. Osteogenic sarcomas have been induced in beagles and mongrel dogs by ^{241}Am . Bone tumors developed in 10 mongrels* that survived 1044 to 1433 days after inhaling an $^{241}\text{Am}(\text{NO}_3)_3$ aerosol (BULDAKOV et al., 1972; NIFATOV et al., 1972). Accumulated radiation doses in the skeleton were stated to be less than 2000 rad. Some dogs developed more than one tumor. Tumors were located in both the appendicular and axial skeleton, including the head; the most common location of tumors was in vertebrae.

Several groups of beagles have been injected with ^{241}Am , ^{249}Cf , or ^{252}Cf at various dose levels for long-term study at the University of Utah. Each dose level group will eventually contain 12 to 13 dogs, but they are introduced into the experiment at different times depending on the rate of production of the breeding colony. The first dogs were injected with ^{241}Am in June 1966, but only a few have been in the study long enough to achieve minimum tumorigenic doses. Of the 8 dogs injected with californium, none has been in the experiment long enough to develop a bone tumor. All of the results described below are as of March 1972 (LLOYD et al., 1972a; T. F. DOUGHERTY, 1972).

*Numbers of dogs and exact nuclide dosages were not reported.

At the 0.9 $\mu\text{Ci/kg}$ level of ^{241}Am , 2 dogs developed bone tumors at 1132 and 1779 days after injection (accumulated radiation doses in bone were 1360 and 2220 rad, respectively). The accumulated radiation doses in the skeletons of 6 dogs in this group each exceeded 1360 rad. At the 0.3 $\mu\text{Ci/kg}$ level 2 dogs developed bone tumors at 1510 and 1917 days after injection (accumulated radiation doses in bone were 547 and 660 rad, respectively). The accumulated radiation doses in the skeletons of 4 dogs in this group exceeded 500 rad. At the 0.1 $\mu\text{Ci/kg}$ level one dog developed a bone tumor at 1847 days after injection (accumulated radiation dose in bone was 190 rad). The accumulated radiation dose in the skeletons of only 2 dogs in this group exceeded 190 rad.

The results obtained so far suggest that in beagles ^{241}Am will be about as effective for inducing bone tumors as is ^{239}Pu . The long-term studies in beagles of the higher dose levels of ^{239}Pu are complete. All of the dogs that accumulated more than 550 rad in their skeletons developed an osteogenic sarcoma. Osteogenic sarcomas were found in 10 of 12 dogs with accumulated bone doses of 230 to 460 rad, and in 9 of 13 dogs with accumulated bone doses of 170 to 220 rad (T. F. DOUGHERTY, 1972). At the highest dose levels (0.9, 0.3, and 0.1 $\mu\text{Ci/kg}$) of ^{241}Am and ^{239}Pu for which there were long-term survivors, the minimum accumulated radiation doses in bone associated with bone tumor development were, respectively: for ^{241}Am 1360, 546, and 190 rad; for ^{239}Pu 1560, 550, and 230 rad.

In beagles, based on time from injection to death, ^{241}Am seems to be lethal sooner than ^{239}Pu , because of the greater amount of accumulated radiation damage in the soft tissues of ^{241}Am -injected animals. The 2 dogs injected with 2.8 $\mu\text{Ci/kg}$ of ^{241}Am died by 448 days of liver and kidney failure. At the same dose level of ^{239}Pu , 9 dogs died between 499 and 2059 days. Six deaths were related to bone only, two to soft tissue degeneration only, and one to a combination of both. At the 0.9 $\mu\text{Ci/kg}$ level of ^{241}Am , the first of 5 deaths occurred at 633 days, and all five deaths have involved radiation damage in one or more soft tissues; bone tumors also developed in two or them.

At the 0.9 $\mu\text{Ci/kg}$ level of ^{239}Pu , all of the remaining dogs were euthanized between 1066 to 1724 days because of the development of bone tumors.

Although the Lawrence Berkeley Laboratory experiments with ^{241}Am in monkeys (see Section VII.D.3) are primarily metabolic, four ^{241}Am -injected monkeys have been observed for a time sufficient to permit them to accumulate significant skeletal radiation doses. All four were adults at the time of the injection (more than 6.5 years old with fully united epiphyses and fully erupted wisdom teeth). The accumulated radiation doses, based on the retention of ^{241}Am and the measured skeletal weight of each animal, range from 237 to 1023 rad accumulated during intervals of 735 to 2087 days after injection of an average dose of 0.65 $\mu\text{Ci/kg}$ of ^{241}Am . None of the four developed a bone tumor that could be discerned from skeletal radiographs or gross examination of defleshed bones.

F. Cytogenic effects in liver and bone marrow

The late effects of radiation, especially neoplastic changes, are believed to be the end result of the proliferation of genetically altered cells. The liver of the Chinese hamster, in which cell division has been stimulated by partial hepatectomy, has proven to be a useful model system in which to study the relationships between chromosome aberration frequencies and radiation dose or dose rate (MCKAY et al., 1970, 1972; BROOKS et al., 1971, 1972).

Single doses of ^{241}Am citrate ranging from 0.0006 to 5 $\mu\text{Ci/kg}$ and of ^{252}Cf citrate ranging from 0.56 to 45 $\mu\text{Ci/kg}$ were injected into adult Chinese hamsters. Groups of hamsters were killed at intervals from 6 to 362 days after injection of ^{241}Am , and 6 to 42 days after injection of ^{252}Cf . Fifty-four hours before sacrifice a partial hepatectomy was performed to stimulate cell division, and four hours before sacrifice colchicine was administered to block cellular division at metaphase. Cells from livers or bone marrow of several animals were scored for chromosome aberrations (50 to 200 cells were scored at each possible postinjection time-dose level combination).

The following types of chromosome changes were reported: isochromatid or chromatid deletions, chromosome exchanges, and dicentric, multicentric, or ring forms. Results were also expressed as total aberrations per cell. The accumulated radiation doses in the livers were calculated from tissue distribution data obtained in companion experiments.

After injection of ^{241}Am or ^{252}Cf the total number of metaphase chromosome aberrations in the liver was proportional to the accumulated radiation dose. The aberration frequency for ^{241}Am was 7.1×10^{-3} aberrations/cell/rad; for ^{252}Cf it was 3.3×10^{-3} , if radiation doses were calculated from the total energy per disintegration (fission fragments plus α -particles). If only the dose contributed by the α -particles was considered, the frequency of liver chromosome aberrations was the same as for ^{241}Am . (See footnote in Section XII. B. 1. e.). The investigators considered the following possibilities: (a) the energy of the fission fragments was so great that struck cells were probably killed outright and, therefore, did not divide and could not be scored; (b) the low frequency of emission of fission fragments (3.2% of decays) or their very short range in tissue might limit the number of cells hit, and these could have been overlooked by the scoring system, or (c) fission fragments had such a high linear energy transfer (LET) that for many biological effects much of their energy might have been wasted. They concluded that the fission fragments of ^{252}Cf were not contributing to the measured endpoint.

Based on accumulated radiation dose the frequency of liver cell aberrations after injection of the β -emitter, ^{144}Ce - ^{144}Pr , was 3.1×10^{-4} . The effect was about 1/20 of that produced by ^{241}Am or ^{252}Cf . For the α -emitters, aberration frequency increased with total accumulated dose but was independent of the dose rate.

In the bone marrow studies, chromosome aberrations were scored only in the animals injected at levels greater than $5 \mu\text{Ci/kg}$ of ^{252}Cf . Aberrations in

chromosomes of marrow cells appeared to be related to dose rate. The average frequency of aberrations regardless of dose level or time after injection was 0.07 aberrations/cell, which was about four times the measured value in normal controls. The total scored aberration frequency was low; the frequency of chromatid and isochromatid deletions (which are usually reported as a function of dose rate) was high, as was the proportion of symmetrical to asymmetrical (dicentric) chromosome exchanges compared with that found in the liver. These results suggested to the investigators that certain chromosome aberrations were produced but not seen, because cell division in the rapidly dividing bone marrow cells placed a selective disadvantage on cells with certain types of chromosome aberrations, and the cells carrying them had been eliminated in successive cell divisions.

G. Effects on reproduction and offspring

A large study in rats of (a) the transfer of ^{237}Np , ^{239}Pu , and ^{241}Am via the placenta and the milk from injected mothers to their offspring, and (b) the effects of these nuclides on fertility, reproductive capacity, and development of offspring has been made at the Institute of Biophysics in Moscow. Only brief summaries of the results have been published (MOSKALEV et al., 1969; OVCHARENKO, 1970, 1972).

In the studies on maternal transfer, female rats were injected intravenously with doses of 3 or 15 $\mu\text{Ci/kg}$ of ^{241}Am citrate at times from day 1 to day 19 of gestation and killed 48 hours later. As was observed by HOLLINS and DURAKOVIC (1972) in lactating rats, the livers of the pregnant rats contained a greater fraction, and the skeletons a smaller fraction of the injected ^{241}Am , than was found in non-pregnant controls.

The amounts of ^{241}Am transferred from the mothers were greatest on the 19th day of gestation. Fetuses, placentas, and uterus contained 0.1, 0.9, and 0.27% of the mother's dose, respectively, when 3 $\mu\text{Ci/kg}$ was injected on the 13th day of gestation, and 0.45, 1.22, and 0.7%, respectively, when the dam was injected on the 19th day of gestation. The amounts of ^{241}Am transferred were less after injection of a larger dose, 15 $\mu\text{Ci/kg}$. In a comparable experiment, the amounts of ^{239}Pu transferred to the fetuses, placentas, and uterus were three to six times greater than for ^{241}Am . A total of 1% of the mother's ^{241}Am dose was transferred to the offspring via the milk.

Radiation effects on the estrus cycle, embryonic deaths, and fertility of ^{241}Am -injected males and females were studied in rats injected with 2 to 96 $\mu\text{Ci/kg}$ of ^{241}Am at 1 to 180 days before mating. The number of implantations was normal (10.6 per pregnant female) when less than 4 $\mu\text{Ci/kg}$ of ^{241}Am was given 1 to 10 days before mating, but was only 6.6 per female at the 96 $\mu\text{Ci/kg}$ level. At the lower doses the numbers of embryonic deaths 14 or 17 days after conception (10% and 17%, respectively) were the same as in normal controls. At the highest dose level (96 $\mu\text{Ci/kg}$ of ^{241}Am , equal to the $\text{LD}_{50/30}$) embryonic deaths were 40 and 82% at 14 and 17 days of gestation, respectively. The intrauterine deaths were attributed to altered placental development and radiation stresses in the mothers (MOSKALEV et al., 1969).

In experiments in which ^{241}Am -injected males were mated to control females, intrauterine deaths were also increased.

Altered postnatal development of the offspring of ^{241}Am -injected mothers included poor survival, delayed development, variable weight, blood dyscrasias, altered radiosensitivity, and depressed reproductive capacity. The effects on the offspring were reported to depend on the dose administered to the mother.

SIKOV and MAHLUM, (1972b) injected female rats with $^{253}\text{EsCl}_3$ on the 15th or 19th day of gestation, and the animals were killed 24 hours later. The concentrations of ^{253}Es in the fetuses were 0.002 and 0.007% of the mother's dose per gram of fetal tissue in the 16-day and 20-day fetuses, respectively. The ^{253}Es concentrations in placentas were about 100 times greater than in the fetuses. In the dams, ^{253}Es concentrations in liver, spleen, and femur ranged from 1.3 to 1.9%/g of wet tissue. Radiochemical analysis and autoradiography demonstrated that nearly all of the transferred ^{253}Es was in the fetal skeletons.

The average size of a litter was 9.5 fetuses, and the average weights of the fetuses were 0.5 and 4g at 16 and 20 days, respectively (D. MAHLUM, personal communication). The total amounts of ^{253}Es transferred to the fetuses were 0.01 and 0.7% of the mother's dose at 16 and 20 days, respectively, in agreement with the extent of placental transfer of ^{241}Am given above.

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Research and progress reports of several Laboratories have been rich sources of material. In order to conserve space these report citations have been abbreviated to the initials of the Laboratory followed by a report number.

ANL- Argonne National Laboratory Report.

BNWL- Battelle Northwest Laboratory.

CH- Metallurgical Laboratory (Manhattan Project) usually followed by a USAEC declassification number, MDDC- or AECD.

COO-119- University of Utah, Department of Anatomy, Radiobiology Project.

HW- Hanford Biology Research Reports.

LA- Los Alamos Scientific Laboratory.

LF- Lovelace Foundation Fission Product Inhalation Program.

UCRL- University of California, Lawrence Radiation Laboratory.

USNRDL- U. S. Naval Radiological Defense Laboratory Research Reports.

All of the numbered documents, progress reports, and English translations of French and Russian language publications are listed in the Cumulative Report Indexes of Nuclear Science Abstracts. The introductory pages of these Indexes include information on the availability for purchase from the USAEC Technical Information Center, Oak Ridge, Tennessee, and on the availability for loan from the several repository libraries in the United States; the National Lending Library, Boston Spa, England, the International Atomic Energy Agency, Vienna, Austria, and the Zentralstelle für Atomkernenergie-Dokumentation, Karlsruhe, W. Germany.

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Appendix A: Calculation of ILB in intratracheal intubation studies with rats

ZALIKIN et al. (1968) and TSEVELEVA and YEROKHIN (1969) reported the results of their intratracheal intubation studies with $^{241}\text{AmCl}_3$ or $^{241}\text{Am}(\text{NO}_3)_3$ as percent of amount introduced into the lungs, i. e., percent of administered dose. In both experiments 25 to 30% of the administered dose was missing from rats killed from $t = 0$ to $t = 1$ hr after administration--the ^{241}Am was not in the lungs nor had it been absorbed into the body. Excreta were not collected in either study, however, ZALIKIN et al. (1968) measured ^{241}Am in the upper respiratory and gastrointestinal tracts--they found 7% of the administered dose in the trachea and gastrointestinal contents 1 hr after administration. The ^{241}Am content of lungs and body changed very little in the succeeding 24 hr.

Clearance of a kinetic compartment in 1 hr requires a half-time of about 10 min. The best available lung model does not include a pulmonary clearance mechanism coupled to gastrointestinal tract elimination with a half-time shorter than 1 day (for man). However, the N-P and T-B compartments are cleared via the gastrointestinal tract with half-times of 4 to 10 min (ICRP, 1966). One must conclude that the missing 25 to 30% of the instilled ^{241}Am solutions was not actually administered, or remained in the upper airways and never reached the lung, or was drawn from the lung into the upper airways as the tracheal cannula was being removed. In the latter cases the ^{241}Am in the upper respiratory tract would be promptly cleared to the gastrointestinal tract. In these studies the ILB was assumed to be equal to the dose recovered at $t = 0$ to $t = 1$ hr less the ^{241}Am content of the upper respiratory and gastrointestinal tracts.

HUNGATE et al. (1972) expressed the results of their study of intratracheally instilled $^{253}\text{EsCl}_3$ in rats as percent of the administered dose.

All of the administered ^{253}Es could be accounted for, if allowance were made for urinary excretion of the absorbed ^{253}Es . The ILB was assumed to be equal to the stated amount administered (IBB).

APPENDIX B

Calculation of the total amount of actinide that is transferred to rat liver after instillation into the lung, and calculation of the total amount of actinide absorbed from the rat lung

A large fraction of administered actinide is deposited in the liver of the rat whether the nuclide is introduced directly into the blood, or is absorbed from an intramuscular injection or from the lungs. The actinide deposited in the rat liver is promptly excreted in the feces. But, after administration by lung instillation some of the nuclide may at the same time be cleared from the lung into the gastrointestinal tract and excreted in feces also. If the rate at which the nuclide is absorbed from the lung is not very different from the rate at which the nuclide deposited in liver is simultaneously excreted into the feces, the total transfer of nuclide from lung to liver cannot be measured directly.

The laws of radioactive decay provide an appropriate mathematical expression that describes the simultaneous growth and decay of a radioactive isotope (daughter) being formed from the decay of a parent isotope with a comparable half-life (SIRI, 1949):

$$N_2 = \frac{T_2}{T_1 - T_2} N_0 \left(e^{-0.693t/T_1} - e^{-0.693t/T_2} \right). \quad \text{Eq. A1}$$

N_2 is the amount of daughter present at time t ($N_2 = 0$ at $t = 0$); N_0 is the amount of parent present at $t = 0$; and T_1 and T_2 are the radioactive half-lives of the parent and daughter, respectively. When appropriate subscripts are inserted, Eq. A1 becomes

$$N_{li} = \frac{T_e}{T_a - T_e} f_{li} N_{lu} \left(e^{-0.693t/T_a} - e^{-0.693t/T_e} \right). \quad \text{Eq. A2}$$

N_{li} is the amount of actinide in the liver at time t ($N_{li} = 0$ at $t = 0$); N_{lu} is the ILB, equal to 100%; f_{li} is the fraction of ILB absorbed and transferred to the liver; T_a is the half-time of absorption from the lung, and T_e is the half-time of transfer of actinide from liver to feces. It is assumed that f_{li} , T_a , and T_e are constant over the period of interest, and that T_a , the half-time of absorption from lung to liver, is the same as the half-time of transfer of nuclide from lung to bone.

As shown in Fig. 5, deposition of ^{241}Am in the skeleton reached an equilibrium value (Sk_{eq}) in about 10 days. This is an example of accumulation of a tracer in a long-lived phase, and its accumulation rate can be obtained by the method of COMAR (1955). The skeleton accumulation data from the three studies of inhalation or intratracheal instillation of ^{241}Am (ZALIKIN et al., 1968; TSEVELEVA and YEROKHIN, 1969; and NÉNOT et al., 1971a,b,c) were plotted linearly, and smooth curves (not shown) were drawn by eye. Several values for the amount of ^{241}Am in the skeleton at various times (Sk_t) were obtained for each experiment; from these it was possible to evaluate the expression $(1 - Sk_t/Sk_{eq})$ at each time t . Semilogarithmic plots (not shown) of $(1 - Sk_t/Sk_{eq})$ as functions of time indicated skeletal-uptake half-times of 3.2 days (ZALIKIN et al., 1968), 3.1 days (TSEVELEVA and YEROKHIN, 1969), and 3.4 days (NÉNOT et al., 1971a,b,c) with a mean of 3.2 ± 0.2 days.

It was assumed that during the first 30 days after exposure, the rate of elimination of ^{241}Am from the rat liver was the same as it would have been had the entire liver deposit been acquired on the first day (as it is after an intravenous or intraperitoneal injection). The results of several determinations of the half-time in the rat liver of parenterally administered ^{241}Am are given in Table 21; the mean half-time is 7.5 ± 0.5 days.

When appropriate substitutions are made, $T_a = 3.2$ days, $T_e = 7.5$ days, $N_{lu} = 100\%$, $\frac{T_e}{T_a - T_e} = -1.74$; and the terms are rearranged; an

expression is obtained for f_{li} :

$$f_{li} = \frac{-N_{li}}{(1.74) (e^{-0.216t} - e^{-0.092t})} \quad \text{Eq. A3}$$

N_{li} and t were obtained from the results of the three experiments and f_{li} was evaluated for each: Five sets of data from 1 to 16 days after intratracheal instillation of $^{241}\text{AmCl}_3$ yielded a mean f_{li} of 59.6% of the ILB (ZALIKIN et al., 1968); five sets of data from 6 hr to 15 days after intratracheal instillation of $^{241}\text{Am}(\text{NO}_3)_3$ yielded a mean f_{li} of 52.2% of the ILB (TSEVELEVA and YEROKHIN, 1969); and two sets of data, 10 and 20 days after inhalation of an $^{241}\text{Am}(\text{NO}_3)_3$ aerosol yielded a mean f_{li} of 53.8% of the ILB (NÉNOT et al., 1971a,b,c). These calculated values of f_{li} compare favorably with total liver deposition of ^{241}Am administered parenterally (in the form of these same compounds) by these same investigators as shown in Table 18.

Absorption of ^{241}Am from the rat lung (shown in Table 9) was calculated at the time when the lung burden had been reduced to about 10% of the ILB (LB_{10}). Total absorption was assumed to equal the sum of the amounts of ^{241}Am (expressed as percent of the ILB) present at $t = \text{LB}_{10}$ in skeleton, liver, residual soft tissues, urine, and fecal excretion derived from the liver (Fe_{end}). Fe_{end} was calculated by difference,

$$\text{Fe}_{\text{end}}(\%) = f_{li} - L_t, \quad \text{Eq. A4}$$

where L_t is the amount of ^{241}Am in the liver at $t = \text{LB}_{10}$. Urinary excretion in rats of absorbed ^{241}Am was estimated to be 27% of the maximum skeletal deposition based on the quantities of ^{241}Am in bone and urine 1 to 4 days after intramuscular injection of $^{241}\text{AmCl}_3$ (SCOTT et al., 1948a) or ^{241}Am citrate (DURBIN et al., 1967, 1972c).

Appendix C

Tissue and organ weights and percent of body weight of Standard Man and laboratory animals that have been used in studies of the metabolism and toxicity of the transplutonium elements^a

	Standard Man ^b		Cynomolgus monkey		Beagle dog		Albino rat		Chinese hamster		Mouse (LAF-1)		Mouse (BALB/c)	
Tissue	Weight (g)	% of body wt.	Weight (g)	% of body wt.	Weight (g)	% of body wt.	Weight (g)	% of body wt.	Weight (g)	% of body wt.	Weight (g)	% of body wt.	Weight (g)	% of body wt.
Muscle	30,000	43	1300	43	4300	43	110	44	—	—	(10) ^c	(42)	—	—
Skin	6100	23	410	14	1510	15	30	12	—	—	3.4	14	—	—
Skeleton ^d	10,000	14	540	18	720	7.2	23	8.2	—	—	2.0 ^e	8.3	—	—
Blood ^b	5400	7.7	—	5.4	—	9.2	—	5.1	—	—	—	5.0	—	—
G. I. tract	3600	5.1	270	8.9	430	4.3	22	9.0	2.6	9.6	2.6	9.6	—	—
Liver	1700	2.4	74	2.5	400	4.0	7.6	3.1	1.4	5.2	1.6	6.7	1.5	5.5
Brain	1500	2.1	80	2.7	80	0.8	2.0	0.8	0.66	2.4	0.44	1.8	0.46	1.7
Lungs	1000	1.4	33	1.1	90	0.9	1.8	0.7	0.33	1.2	0.3	1.2	—	—
Kidneys	300	0.43	18	0.6	50	0.5	1.6	0.65	0.33	1.2	0.32	1.3	0.35	1.3
Heart	300	0.43	12	0.4	90	0.9	1.2	0.5	0.15	0.56	0.13	0.54	0.13	0.47
Spleen	150	0.21	5	0.17	20	0.2	0.6	0.24	0.33	1.2	0.14	0.55	0.071	0.26
Urinary bladder	150	0.21	—	—	15	0.15	—	—	—	—	0.025	0.1	—	—
Pancreas	70	0.10	3.8	0.12	20	0.2	—	—	—	—	0.19	0.76	—	—
Salivary glands	50	0.071	—	—	—	—	—	—	—	—	0.17	0.7	—	—
Testes	40	0.057	—	—	15	0.15	(2.8)	(1.1)	0.16	0.59	—	—	0.16	0.58
Eyes	30	0.043	7.2	0.024	—	—	—	—	—	—	0.047	0.19	—	—
Thyroid	20	0.029	0.5	0.016	0.9	0.01	0.025	0.009	—	—	0.0028	0.011	—	—
Prostate	20	0.029	—	—	—	—	—	—	—	—	—	—	—	—
Adrenals	20	0.029	1.1	0.037	1.0	0.01	0.065	0.023	0.0057	0.021	0.012	0.049	0.0033	0.012
Thymus	10	0.014	—	—	—	—	0.27	0.10	0.021	0.078	0.051	0.21	0.046	0.17
Ovaries	(8)	(0.011)	0.34	0.011	1.0	0.01	0.07	0.025	—	—	0.012	0.047	—	—
Pituitary	0.6	0.0009	0.05	0.002	—	—	0.014	0.005	—	—	0.0023	0.0093	—	—
Uterus	—	—	5.5	0.18	—	—	—	—	—	—	0.093	0.38	—	—
Total body ^f	70,000	—	3000	—	10,000	—	250	—	27	—	24.5	—	27	—

^aData sources: Standard Man (ICRP, 1959); cynomolgus monkey, female (P. W. DURBIN and M. H. WILLIAMS, unpublished); beagle dog, male and female (ANDERSEN and JOHNSON, 1962; CUDDIHY et al., 1970; ATHERTON et al., 1969b); rat, Charles-River (Sprague-Dawley) female (DURBIN et al., 1972e), male (R. N. PIERSON and D. C. PRICE, unpublished); Chinese hamster, male, 100 days old (A. L. BROOKS, unpublished), male more than 1 yr old, 39g (G. A. SACHER, unpublished); mouse, LAF-1 female (P. W. DURBIN, unpublished), BALB/c male (G. A. SACHER, unpublished).

^bTissue weights of Standard Man are free of blood. Tissue weights of the animals include contained blood present after routine dissection.

^cPITTS and BULLARD (1968).

^dSkeleton includes cartilages, periosteum, and marrow.

^eWeight of mouse skeleton calculated to be 8.3% of the body weight (PARMLEY et al., 1961).

^fFat can be calculated by difference of sum of all tissues from body weight.

Appendix D

Adult body weight (BW), glomerular filtration rate (GFR),^a filtered volume (GFR $\times$ BW), plasma volume (V_p)^b, and total plasma volume ($\Sigma V_p = V_p \times BW$) of several mammals

	Body weight (kg)	GFR (ml/min/kg)	Filtered volume (ml/min)	V_p (ml/kg)	ΣV_p (ml)
Rat	0.25	6.0	1.5		
Cynomolgus monkey	3.3	(3.6)	11.9	36.4	120
Beagle	10	4.3	43	49.3	493
Man	70	1.7	120	42.8	3000
Cat	3.3	3.2	10.6	39	130
Rabbit	3.7	3.1	11.5	35.1	130

^aReferences for GFR: rat, dog, cat, rabbit, man, H. W. SMITH (1951); dog also DELLA ROSA et al. (1961). GFR for monkey estimated to be the mean for rabbit, cat and dog.

^bReferences for V_p : rat, EVERETT et al. (1956); monkey, GREGERSON et al. (1959); beagle, J. H. DOUGHERTY and SEYMOUR (1957); man, ICRP (1959); cat and rabbit (TEKLAD, INC.).

Table 1. Uptake of ^{141}Ce and ^{91}Y from sea water by a crab
and a mollusc. Data of ZESENKO (1966)

Percent of body isotope content					
Carcinus meanes			Mytilus galloprovincialis		
Tissue	^{144}Ce	^{91}Y	Tissue	^{144}Ce	^{91}Y
Muscle	2.6	0.6	Muscle	0.1	0.3
Liver	0.1	0.3	Viscera	4.7	9.8
Stomach	0.3	0.02	Foot	0.03	0.03
Heart	0.004	0.001	Mantle	1.1	0.2
Gonads	0.005	0.3	Gills	0.6	3.0
Gills	12.0	24.2			
Total soft tissues	12.8	25.7	Total soft tissues	7.4	12.5
Chitin	87.3	74.1	Byssus ^a	17.7	39.1
			Shell	75.5	47.9

^a A tuft of filaments by which a bivalve mollusc attaches itself to a surface.

Table 2. Distribution of lanthanide fission products in tissues and eggs of laying hens^a 4 days after intramuscular injection. Calculated from isotope concentrations reported by MRAZ et al. (1964) and organ weights of Leghorn chickens reported by MITCHELL et al. (1931).

Tissue	Percent administered dose						Percent of body content					
	¹⁴⁰ _{La}	¹⁴⁴ _{Ce}	¹⁴² _{Pr}	¹⁴⁷ _{Nd}	¹⁴⁷ _{Pm}	⁹¹ _Y	¹⁴⁰ _{La}	¹⁴⁴ _{Ce}	¹⁴² _{Pr}	¹⁴⁷ _{Nd}	¹⁴⁷ _{Pm}	⁹¹ _Y
Blood	1.6	0.07	0.22	1.1	1.0	0.87	3.5	0.97	4.4	5.2	4.2	3.7
Liver	10.2	0.26	0.71	1.6	1.7	3.7	22.3	3.4	14.2	7.4	6.7	16.0
Kidneys	0.71	0.08	0.09	0.21	0.35	0.26	1.6	1.1	1.8	0.98	1.4	1.11
Spleen	0.12	0.06	0.04	0.14	0.08	0.08	0.26	0.83	0.80	0.65	0.32	0.34
Heart	0.08	0.18	0.01	0.26	0.06	0.05	0.18	2.5	0.20	1.2	0.24	0.20
Lungs	0.30	0.06	0.03	0.33	0.10	0.11	0.66	0.83	0.60	1.5	0.40	0.47
Brain ^b	0.02	<0.01	<0.01	0.01	0.01	0.01	0.04	<0.14	<0.20	0.05	0.04	0.04
Gizzard	1.0	0.16	0.06	0.29	0.19	0.22	2.2	2.2	1.2	1.4	0.76	0.94
Muscle ^c	0.81	0.81	0.32	0.97	0.64	0.73	1.7	10.7	6.4	4.5	2.5	3.1
Ovaries ^d	0.48	0.04	0.04	0.15	0.17	0.13	1.0	0.55	0.80	0.70	0.68	0.55
Repr. tract ^{d,e}	0.84	0.14	0.21	0.39	0.26	0.25	1.8	1.9	4.2	1.8	1.0	1.1
Bone ^f	22.2	3.9	2.1	12.7	18.0	14.8	48.5	51.3	42.0	59.0	72.0	63.2
Residue ^g	<u>7.2</u>	<u>1.8</u>	<u>1.2</u>	<u>3.4</u>	<u>2.3</u>	<u>2.2</u>	15.8	23.7	24.0	15.8	9.2	9.4
Body	45.7	7.6	5.0	21.5	25.0	23.4						
Egg components (total of 4 eggs)												
Shell	0.01	<0.01	0.03	<0.01	<0.01	0.07						
Albumin	<0.01	<0.01	0.02	<0.01	0.03	<0.01						
Yolk	18.1	2.7	1.8	6.1	5.0	6.1						

^a Body weight 1800 g.

^b Weight not given by MITCHELL et al. (1931); assumed to be 10 g.

^c Concentration used was the average for pectoral and gastrocnemius muscles.

^d MITCHELL et al. (1931) reported the weight of the entire reproductive tract as 44 g; ovary is assumed to be 5% or 2.2 g, and the rest of the tract, 42 g.

^e Concentration used was the average for infundibulum, magnum, isthmus, and uterus which were assayed separately.

^f Concentration of isotopes was assayed only in tibia shaft, which weighs 5.5 g. ²⁴¹Am in tibia shaft of the rat is 0.01 of ²⁴¹Am in whole skeleton (DURBIN et al., 1972 c). Skeleton isotope = (conc. %/g) x 5.5 g x 100.

^g MITCHELL et al. (1931) reported the weight of skin, pancreas, and intestine as 330 g. Concentration used was the average of blood, gizzard, muscle, and reproductive tract (excluding ovaries)

Table 3. Summary of experimental conditions for mammalian studies with isotopes of the transplutonium elements: Parenteral and oral administration

Isotope and chemical form	Dose adm. (μ Ci/kg)	Routes of administration ^a	Animal data				Objectives and length of study	References ^c
			Strain ^b	Sex	Age	Wt		
					AMERICIUM STUDIES			
RAT								
²⁴¹ AmCl ₃ , pH=5	3.6	i.m., s.t.	W.	F	- ^d	275 g	Metabolism, 256 days	SCOTT et al. (1948a), HAMILTON (1947, 1948)
²⁴¹ AmCl ₃ , pH=5	30	i.v.	S.D.	M	47 day	150 g	Metabolism, 48 days	{ LANGHAM and CARTER (1951)
²⁴¹ AmCl ₃ , pH=5	32-189	i.v.	S.D.	M	35 day	95 g	Toxicity, 315 days	
²⁴¹ Am citrate	69	i.m.	-	F	-	225 g	Bone autoradiographs, 1 day	ASLING et al. (1952)
²⁴¹ Am citrate	0.5-7	i.v.	M.A.	M	49 day	105 g	Metabolism, 18 months Toxicity, life span	D. M. TAYLOR et al. (1961), FABRIKANT and SMITH (1964), BENSTED et al. (1965), BENSTED and TAYLOR (1969), D. M. TAYLOR and BENSTED (1967)
²⁴¹ Am citrate	1.0-1.9	i.v.	M.A.	M	49 day	105 g	Removal by tetracycline, DTPA, ^e desferrioxamine, 21 days	D. M. TAYLOR and SOWBY (1962), SOWBY and TAYLOR (1960)
²⁴¹ Am citrate, 5%	0.4	i.v.	alb.	-	-	~250 g	Removal by DTPA, ^e 30 days	D. M. TAYLOR (1967) D. M. TAYLOR et al. (1971) FOREMAN (1962)
²⁴¹ Am citrate, 0.4%	1-3	i.v., s.t.	M.A.	M	49 day	105 g	Metabolism, 4 days	{ D. M. TAYLOR (1962)
²⁴¹ Am(NO ₃) ₃ , pH=1.7	-	i.v., s.t.	M.A.	M	49 day	105 g	Metabolism, 4 days and bone uptake, 1 day	
²⁴¹ AmCl ₃	5-10	i.v., s.t.	alb.	F	~150 day	200 g	Metabolism, 64 days	{ ZALIKIN et al. (1968, 1969)
²⁴¹ AmCl ₃	0.25-200	i.v.	alb.	F	~150 day	200 g	Toxicity, life span	
²⁴¹ Am citrate, 0.6%	0.37	i.m.	C.R.	F	110 day	275 g	Metabolism, life span	DURBIN et al. (1967, 1972c)

Table 3 (cont. b)

Isotope and chemical form	Dose adm. ($\mu\text{Ci/kg}$)	Routes of administration	Animal data				Objectives and length of study	References
			Strain	Sex	Age	Wt		
			AMERICIUM STUDIES (cont.)					
			RAT (cont.)					
$^{241}\text{Am}(\text{NO}_3)_3, \text{pH}=3.8$	5.9	i.p.	W.	—	—	170 g	Metabolism, 9 months	TSEVELEVA and YEROKHIN (1969)
$^{241}\text{AmCl}_3, \text{pH}=4$	7	i. p., i. v.	—	M	—	170 g	Removal by DTPA ^e and other chelating agents, 180 days	BELYAEV (1969)
^{241}Am citrate	40	i.p.	S.D.	—	10 day	~25 g	Autoradiographs, 4 days	HAMMARSTRÖM and NILSSON (1970b)
^{241}Am citrate	variable	i.v.	W.	M,F	adult	—	Reproductive transfer, to F ₁ and F ₂ generations	OVCHARENKO (1970,1972) MOSKALEV et al. (1969)
$^{241}\text{AmCl}_3$	2.5-25	i.v.	W.	M,F	—	180 g	Toxicity, life span	RUDNITSKAYA and MOSKALEV (1970) MOSKALEV and RUDNITSKAYA (1970)
$^{241}\text{Am}(\text{NO}_3)_3, \text{pH}=2$	~1 $\mu\text{Ci/rat}$	i.m.	S.D.	M	~60 day	300 g	Metabolism and removal by DTPA, ^e 4 months	LAFUMA et al(1970), NÉNOT et al(1971b,1972)
^{241}Am citrate, pH=7	—	i.v., i.p.	S.D.	F	—	—	Metabolism in pregnancy and lactation, 43 days	HOLLINS and DURAKOVIC (1972)
^{241}Am citrate, 1%	1.0	i. v.	H.	F	—	190 g	Removal by DTPA, ^e 13 days	SEIDEL and VOLF (1972)

Table 3 (cont. c)

Isotope and chemical form	Dose adm. (μ Ci/kg)	Routes of administration	Strain	Sex	Age	Wt	Objectives and length of study	References
<u>AMERICIUM STUDIES (cont.)</u>								
<u>CHINESE HAMSTER</u>								
^{241}Am citrate, pH=6	1-100	i.p.	—	—	adult	—	Metabolism and toxicity, 362 days	MCKAY et al. (1969, 1972)
<u>MOUSE</u>								
^{241}Am citrate, 3%	0.7	i.m.	Swiss	M	adult	30-35 g	Metabolism and removal by DTPA, 14 days	PARKER et al. (1962)
$^{241}\text{Am}(\text{NO}_3)_3$	50	i.v.	CBA	M, F	adult	20-35 g	Autoradiographs, 60 days	HAMMARSTRÖM and NILSSON (1970a)
^{243}Am citrate	5	i.m.	Swiss	F	30-35 day	21-25 g	Metabolism, 14 days	WRIGHT (1972)
^{241}Am citrate, pH=3.5	0.00179-4.49	i.v.	beagle	<u>DOG</u> M, F	~15 mo	11 kg	Metabolism and toxicity, life span	LLOYD et al. (1970, 1967a, b, 1968, 1969), STEVENS et al. (1969a, b) G. N., TAYLOR et al. (1969a, b), ATHERTON et al. (1968, 1969a) J. H. DOUGHERTY (1970)
$^{241}\text{AmCl}_3$	up to 60	i.v.	—	—	—	—	Toxicity, > 30 days	ZALIKIN et al. (1969)
<u>PRIMATE</u>								
Cynomolgus monkey (<u>Macaca fascicularis</u>)								
^{241}Am citrate, 3%	0.44-0.87	i.m., i.v.	—	F	>6.5 yr	2.5-4.5 kg	Metabolism, 973 days	DURBIN et al. (1961, 1972c)
Baboon (<u>Papio anubis</u>)								
^{241}Am citrate, pH=3.5	0.2	i.v.	—	F	7-9 yr	—	Metabolism, 3 months	ROSEN et al. (1972)
<u>SWINE</u>								
$^{241}\text{Am}(\text{NO}_3)_3$	—	cut.	—	—	56 day	—	Skin absorption, 168 hr	OSANOV et al. (1971)
<u>SHEEP</u>								
^{241}Am citrate, pH=4	150 μ Ci/ewe	i.v.	Suffolk	F	adult	—	Milk secretion, 10 days	MCCLELLAN et al. (1962b)

Table 3 (cont. d)

Isotope and chemical form	Dose adm. (μ Ci/kg)	Routes of administration	Animal data				Objectives and length of study	References
			Strain	Sex	Age	Wt		
			CURIUM STUDIES					
RAT								
$^{242}\text{CmCl}_3$, pH=5	4.4	i.m., s.t.	alb.	F	>120 day	225 g	Metabolism, 256 days	SCOTT et al(1949), HAMILTON(1947,1948)
$^{242}\text{CmCl}_3$, pH=3-5	5.0	i.m., i.v.	alb.	M, F	50-120 days	185-250 g	Removal by EDTA, ^e 40 days	K. G. SCOTT (unpublished)
$^{242}\text{CmCl}_3$, pH=4	1.8	i.m., i.v.	S.D.	F	>110 day	250 g	Metabolism, 1 day	{ WILLIAMS et al. (1961)
^{242}Cm citrate, 1.5%	1.8	i.m., i.v.	S. D.	F	>110 day	250 g	Metabolism, 1 day	
$^{242}\text{Cm}(\text{NO}_3)_3$, pH = 1.5	8.3-83	i.m., i.v.	W.	M	~60 day	~300 g	Metabolism and removal by DTPA, ^e 4 months	NENOT et al (1970,1972) LAFUMA et al (1970)
^{242}Cm citrate, 1%	1.0	i.v.	H.	F	—	190 g	Removal by DTPA, ^e 13 days	SEIDEL and VOLF (1972)
$^{244}\text{CmCl}_3$, pH=3	5-400	i.v., s.t.	alb.	M	—	190 g	Metabolism and toxicity, 360 days	SEMENOV (1971a, b)
SHEEP								
^{244}Cm citrate, pH=4	140 μ Ci/ewe	i.v.	Suffolk	F	adult	—	Milk secretion, 10 days	MCCLELLAN et al. (1962b)
BERKELIUM STUDIES								
RAT								
$^{249}\text{BkCl}_3$, pH=2	6.25	i.v., s.t.	W	M	3 mo	400 g	Metabolism, 21 days	HUNGATE et al. (1972)
DOG								
^{249}Bk citrate	—	i.v.	beagle	M, F	15 mo	9-13.5 kg	Autoradiographs	G. N. TAYLOR et al. (1972)

Table 3 (cont. e)

Isotope and chemical form	Dose adm. ($\mu\text{Ci/kg}$)	Routes of administration	Animal data				Objectives and length of study	References
			Strain	Sex	Age	Wt		
CALIFORNIUM STUDIES								
RAT								
^{249}Cf citrate, 0.6%	0.33	i.m.	C.R.	F	136 day	275 g	Metabolism, 95 days	DURBIN (1962), DURBIN et al. (1972d)
^{252}Cf citrate, pH=6	7.7	i.p.	-	M	-	130 g	Metabolism, 64 days	MEWHINNEY et al. (1971, 1972)
MOUSE								
^{252}Cf citrate, 3%	0.7	i.m.	Swiss	M	adult	30-35 g	Metabolism and removal by DTPA, ^e 14 days	PARKER et al. (1962)
^{252}Cf citrate	4.0	i.m.	Swiss	F	35-42 day	25 g	Metabolism, 122 days	S. R. WRIGHT (unpublished)
CHINESE HAMSTER								
^{252}Cf citrate, 1.2%	0.056-45	i.p.	-	-	80-120 day		Metabolism and toxicity	MEWHINNEY et al (1972), BROOKS et al (1972)
DOG								
^{249}Cf citrate, pH=3.5	0.28, 2.8	i.v.	beagle	M, F.	>15 mo	9-13.5 kg	Metabolism and toxicity	{ LLOYD et al (1972b, e), ATHERTON et al. (1972), G. N. TAYLOR et al. (1972)
^{252}Cf citrate, pH=3.5	0.29	i. v.	beagle	M, F.	> 15 mo	9-13.5 kg	Metabolism and toxicity	
EINSTEINIUM STUDIES								
RAT								
$^{253}\text{EsCl}_3$, pH=2	6.25	i.v., i.p.	W	M, F	3 mo	400 g	Metabolism, reproductive transfer, skin absorptions, 21 days	HUNGATE et al. (1972)
$^{253}\text{Es}(\text{NO}_3)_3$, pH = 2	3.3	i. v. , i. m. , s. c.	W	F	-	285 g	Metabolism and removal by DTPA, ^e 24 days	V. H. SMITH (1972a, b)
MOUSE								
^{253}Es citrate, 4.6%	1.3	i.m.	Swiss	F	30-35 day	21-25 g	Metabolism and removal by DTPA, ^e 14 days	PARKER et al. (1972)

^a Intravenous, i.v.; intraperitoneal, i.p.; intramuscular, i.m. subcutaneous, s.c.; oral intubation, s.t.; skin application, cut.

^b Wistar, W.; Sprague-Dawley, S.D.; Marshall-August, M.A.; albino unstated strain, alb.; Charles River Sprague-Dawley, C.R.; Heiligenberg, H.

^c Reference cited first contains original or most detailed description of study; others provide ongoing or ancillary information about the same or similar groups of animals.

^d Dash indicates information not available. This convention is followed in all tables.

^e DTPA, diethylenetriaminepentaacetic acid; EDTA, ethylenediaminetetraacetic acid.

Table 4. Summary of experimental conditions for mammalian studies with isotopes of the transplutonium elements: Inhalation and intratracheal administration

Isotope	Chemical form	Particle size	Method of administration	Strain ^a	Sex	Age	Wt	Initial body burden	References ^b
AMERICIUM STUDIES									
RAT									
²⁴¹ Am	citrate, 5%	solution	intubation	alb.	F	—	~250 g	0.1 µCi	FOREMAN (1962)
²⁴¹ Am	chloride	solution	intubation	alb.	F	~150 day	200 g	0.6 µCi	ZALIKIN et al. (1968)
²⁴¹ Am	nitrate, pH=3.8	solution	intubation	W.	—	—	170 g	0.3 µCi	TSEVELEVA and YEROKHIN (1969)
²⁴¹ Am	nitrate, pH=0.6	mist	inhalation	S.D.	M	~60 day	~300 g	4-6 µCi	NÉNOT et al. (1971a, b, c, 1972) LAFUMA et al. (1970)
DOG									
²⁴¹ Am	oxide	0.82-0.99µm AMAD	inhalation	beagle	M-F	446 day	8.4-10.6 kg	38-51 µCi	MCCLELLAN and RUPPRECHT (1968), R. G. THOMAS (1970), R. G. THOMAS et al. (1969, 1972), BARNES (1970)
²⁴¹ Am	nitrate, pH=1.5-2.0	—	inhalation	mongrel	M-F	—	—	≤ 1.5 µCi/kg	BULDAKOV et al (1972), NIFATOV et al (1972)
CURIUM STUDIES									
RAT									
²⁴² Cm	chloride, pH=0.6	mist	inhalation	S.D.	M	~60 day	~300 g	4-6 µCi	{ NÉNOT 1971a, 1972) LAFUMA et al. (1970)
²⁴² Cm	nitrate, pH=0.6	mist	inhalation	S. D.	M	~60 day	~300 g	—	
DOG									
²⁴⁴ Cm	chloride, CsCl carrier	1.6 µm AMAD	inhalation	beagle	M-F	11-47 mo	5.7-12.8 kg	1.4-3.4 µCi	{ MCCLELLAN et al. (1972), GALLEGOS et al. (1970)
²⁴⁴ Cm	oxide (CmO _{1.73})	0.5 µm AMAD	inhalation	beagle	M-F	11-47 mo	5.7-12.8 kg	0.8-1.8 µCi	
EINSTEINIUM STUDIES									
RAT									
²⁵³ Es	chloride, pH=2	solution	intubation	W.	M	3 mo	400 g	0.21-47.2µCi	{ BALLOU and MORROW (1972) HUNGATE et al. (1972)
²⁵³ Es	hydroxide, pH=12	suspension	intubation	W.	M	3 mo	400 g	2.5 µCi	

^a Albino unstated strain, Alb.; Wistar, W.; Sprague-Dawley, S.D.^b Reference cited first contains original or most detailed description of study; others provide ongoing or ancillary information about the same or similar groups of animals.

Table 5. Absorption of various salts of trivalent actinides following intramuscular injection in rats.

Administered nuclide and injection conditions					Absorption at days after injection (percent of administered dose)												Reference
Compound	Activity (μCi)	Mass (μg)	Volume (ml)	pH	1	4	7	10	16	20	30	64	90	120	256		
$^{241}\text{AmCl}_3$	1.0	0.3	1.0	5	58	84	—	—	92	—	—	93	—	—	98	SCOTT et al. (1948a)	
$^{241}\text{Am}(\text{NO}_3)_3$	0.01-5.0	0.03-1.5	0.1	0.5-2.5	10	—	46	55	—	—	57	—	84	85	—	LAFUMA et al. (1970) NÉNOT et al. (1971a, 1972) NÉNOT et al. (1971a)	
$^{241}\text{Am}(\text{SO}_4)_3$	0.1	0.03	0.1	0.5-2.5	24	—	—	—	—	—	—	—	92	—	—		
$^{242}\text{CmCl}_3$	1.0	0.0003	1.0	5.0	90	92	—	—	92	—	—	98	—	—	95		SCOTT et al. (1949)
$^{242}\text{Cm}(\text{NO}_3)_3$	5.0	0.0015	—	1.5	18	—	50	—	—	83	—	89	—	—	—	NÉNOT et al. (1972)	
$^{242}\text{Cm}(\text{NO}_3)_3$ + $\text{La}(\text{NO}_3)_3$	0.1-1.6	≤ 200 (of La)	0.1	0.5-2.5	6.5	—	—	—	—	30	—	55	—	—	—	LAFUMA et al. (1970; NÉNOT et al. (1970, 1972)	
$^{253}\text{Es}(\text{NO}_3)_3$	0.95	<0.001	0.2	2.0	—	—	—	—	—	5	—	—	—	—	—	V. H. SMITH (1972b)	
$^{239}\text{PuCl}_3$	1.0	15	1.0	2.5	—	33	—	—	42	—	—	60	—	—	76	SCOTT et al. (1948b)	

Table 6. The effect of DTPA on absorption of intra-muscularly injected $^{241}\text{Am}(\text{NO}_3)_3^a$ and $^{242}\text{Cm}(\text{NO}_3)_3^b$

Isotope	<u>Absorption at time after isotope injection</u> <u>(Percent of administered dose)</u>							Reference
	0 min	1 min	30 min	1 day	10 days	20 days	90 days	
$^{241}\text{Am}(\text{NO}_3)_3^a$	-	-	-	-	65.1	-	95.7	LAFUMA et al. (1970) NENOT et al. (1971a)
$^{242}\text{Cm}(\text{NO}_3)_3 +$ $\text{La}(\text{NO}_3)_3^b$	100	92	61.6	57	-	74	-	LAFUMA et al. (1970) NENOT et al. (1970)

^a Compare with experiment from Ref. b in Table 5; 50 mM/kg of CaNa_3 DTPA injected into leg opposite ^{241}Am -injected leg beginning 24 hr after the ^{241}Am and 2 times each week thereafter. Rats killed 24 hr after the last DTPA injection.

^b Compare with experiment from Ref. f in Table 5; 50 mM/kg of CaNa_3 DTPA injected into the ^{242}Cm injection site; 0-, 1-, and 30-min and 1-day groups were each given one DTPA injection at those times after the ^{242}Cm injection and were killed 24 hr later. The 20-day group received the first DTPA injection 24 hr after the ^{242}Cm , and two DTPA injection each week thereafter.

Table 7. Calculation of initial rate of absorption
of ^{241}Am from a puncture wound

^{241}Am activity at time following accident (dis/min)		
	<u>3 days</u>	<u>134 days</u>
Removed surgically (on day 3)	21×10^5	(21×10^5)
Hand	4.5×10^5	2.0×10^5
Body	2.3×10^5 (calc.)	0.8×10^5 (meas.)
Urine	<u>$<1 \times 10^5$</u>	<u>4.0×10^5</u>
Total in wound at $t = 0$	27.8×10^5	27.8×10^5

Fraction absorbed in 2.5 hr before surgery

$$\frac{2.3 \times 10^5}{27.8 \times 10^5} = 0.083$$

Calculated absorption rate, k

$$k = \frac{0.083 \times 24 \text{ hr/day}}{2.5 \text{ hr}} = 0.8/\text{day}$$

Calculated absorption half-time, $T_{1/2}$

$$T_{1/2} = \frac{0.693}{0.8/\text{day}} = 0.87 \text{ day}$$

Table 8. Deposition of actinide aerosols in the respiratory tract of rat and beagle dog compared to the deposition predicted by the report of the Task Group on Lung Dynamics (ICRP, 1966)

<u>Compound</u>	<u>Animal</u>	<u>Particle size</u> <u>AMAD(μm)</u>	<u>IBB^a</u> <u>Inhaled</u> <u>(%)</u>	<u>ILB^b</u> <u>Inhaled</u> <u>(%)</u>	<u>ILB</u> <u>IBB</u> <u>(%)</u>	<u>Reference</u>
²⁴¹ Am(NO ₃) ₃	rat	<5 ^c	-	-	37	NENOT et al. (1971 a,b,c)
ICRP, predicted ^d		2.5	82	19	24	
²⁴¹ AmO ₂	dog	0.9	75	45	60	R. G. THOMAS et al. (1972)
ICRP, predicted		1.0	42	26	62	
²⁴⁴ CmCl ₃	dog	1.6	64	33	52	MCCLELLAN et al. (1972)
ICRP, predicted		1.5	62	25	41	
²⁴⁴ CmO _{1.73}	dog	0.5	35	27	77	MCCLELLAN et al. (1972)
ICRP, predicted		0.5	38	28	73	

^aIBB, initial body burden; the total amount in the animal at t = 0.

^bILB, initial lung burden; the total amount deposited in the lungs, less (by convention) the fraction cleared promptly via pathway f (ICRP, 1966).

^cParticles stated to be less than 5 μ m in diameter.

^dPredicted value is the average of the top and bottom of the range of the appropriate curve of deposition vs. particle diameter shown in Fig. 11 of the ICRP report (1966).

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Table 9. Fate of the initial lung burden (ILB) of ^{241}Am , ^{244}Cm , and ^{253}Es compounds administered to rats or dogs by intratracheal instillation or by inhalation expressed in terms of the time required to eliminate 90% of ILB (LB_{10}) and the fractions of ILB leaving the lung by absorption (pathways e and h, Fig. 3) and by clearance (pathway g) ICRP (1966).

Compound	Animal	Mode of exposure	LB_{10} (days)	Absorbed (% ILB) ^a						Retained or cleared (% ILB)		
				Skeleton	Liver	Kidney & spleen	Urine	Fe_{end}	Total	Lung	Cleared ^b	Reference
^{241}Am citrate	rat	instilled ^c	-	-	-	-	-	-	>76	-	-	FOREMAN (1962)
$^{241}\text{AmCl}_3$	rat	instilled ^c	30	13	5.5	0.49	4 ^d	54	77	9.4	<13	ZALIKIN et al. (1968)
$^{241}\text{Am}(\text{NO}_3)_3$	rat	instilled ^c	<30	31	10.5	0.83	8.8 ^d	42	86	5.6	<2.0	TSEVELEVA and YEROKHIN (1969)
$^{253}\text{EsCl}_3$	rat	instilled ^c	20	30	2.0	1.4	35 ^d	4.4	88 ^c	11	0	HUNGATE et al. (1972)
$^{241}\text{Am}(\text{NO}_3)_3$	rat	inhaled	40	22	3.3	-	12	39	76	10	13.4	NENOT et al. (1971 a,b,c)
$^{241}\text{AmO}_2$	beagle	inhaled	<127	36	31	0.3	17	-	>85	7.4	<7.8	R. G. THOMAS et al. (1972)
$^{244}\text{CmCl}_3$	beagle	inhaled	50	38	31	1.5	13	-	>84	10	<5.6	MCCLELLAN et al. (1972)
$^{244}\text{CmO}_{1.73}$	beagle	inhaled	64	34	36	1.3	13	-	>84	10	<5.4	MCCLELLAN et al. (1972)

^a The absorbed fraction is the sum of the radioactivity in the tissues (except lung), the urine, and, in the case of the rat studies, the fecal excretion (of absorbed nuclide (Fe_{end})). See Appendix B.

^b Slow pathway (g) only. The prompt clearance pathway (f) is, by convention, not included in ILB in inhalation experiments.

^c In the instillation studies ILB is assumed to equal IBB. In two of the three studies cited here (ZALIKIN et al., 1968; TSEVELEVA and YEROKHIN, 1969) it was necessary to correct the data for the 25 to 35% of the administered dose that leaked out of the lung immediately after administration. See Appendix A.

^d Estimated from parenteral administration of same compound.

^e Absorbed total includes a soft tissue component of about 16%.

Table 10. Protein-bound fraction of intravenously injected ^{241}Am , ^{244}Cm , and ^{239}Pu in the blood of rats, and ^{241}Am in the blood of dogs.

Data of TURNER and TAYLOR (1968b) and BRUENGER et al. (1969a)

Dose distribution (%)	^{241}Am citrate		$^{241}\text{Am}(\text{NO}_3)_3$	$^{244}\text{Cm}(\text{NO}_3)_3$	^{239}Pu citrate
at time following injection	(rat)	(dog)	(rat)	(rat)	(rat)
<u>1 minute</u>					
% dose in plasma	14.9	65	45.4	45.2	92.4
% dose bound	5.6	36.4	5.9	26.0	67.0
% dose unbound	9.3	28.6	39.5	19.2	25.4
<u>10 minutes</u>					
% dose in plasma	-	28.0	-	-	-
% dose bound	-	17.9	-	-	-
% dose unbound	-	10.7	-	-	-
<u>1 hour</u>					
% dose in plasma	2.2	9.82	1.4	4.3	68.9
% dose bound	2.1	(9.3) ^a	(1.3) ^a	4.3	58.4
% dose unbound	0.1	(0.52) ^a	(0.1) ^a	0	10.5
<u>Initial rate of clearance (1 min to 1 hr)</u>					
bound (%/min)	1.6	2.3	2.5	3.0	0.22
unbound (%/min)	7.5	6.7	6.8	>10.	1.5

^aEstimated from ^{241}Am citrate in rat.

Table 11. Distribution of ^{45}Ca , ^{144}Ce , $^{152,154}\text{Eu}$, ^{241}Am , and ^{239}Pu

5 minutes after intravenous injection in the rat

Nuclide (Form administered)	$^{45}\text{Ca(II)}^{\text{a}}$ chloride	$^{144}\text{Ce(III)}^{\text{b}}$ citrate	$^{152,154}\text{Eu(III)}^{\text{b}}$ citrate	$^{241}\text{Am(III)}^{\text{c}}$ chloride	$^{239}\text{Pu(IV)}^{\text{d}}$ citrate
(Percent of injected dose in tissue)					
Blood volume	9	5	11	37	52
Skeleton ^e	26	.13	17	6	4
Liver ^e	0	29	16	14.5	3
Excreted	0	0.8	0.7		0.1
Extracellular fluid and soft tissue ^f	65	52	55	43	40

^a ^{45}Ca , 60-day-old, female, Long-Evans (THOMSON, 1953)

^b ^{144}Ce and $^{152,154}\text{Eu}$, 3- to 4-month-old, female, Sprague-Dawley (DURBIN et al., 1955)

^c ^{241}Am , 170-g male, Wistar (BELYAEV, 1969). Skeleton and liver weights assumed to be 9 and 3% of the body weight, respectively.

^d ^{239}Pu , 250-g female, Sprague-Dawley (SCHUBERT et al., 1950; recalculated by DURBIN et al., 1972a)

^e Nuclide content of skeleton and liver corrected for nuclide in contained plasma as described by DURBIN et al. (1972a).

^f Calculated by difference from 100%.

Table 12: Distribution of isotopes of the transplutonium elements^a in the adult rat after intravenous or intramuscular injection

Tissue	Percent of injected or absorbed dose ^b at days after injection										
	²⁴¹ Am ^b			²⁴² Cm ^b			²⁴⁹ Bk	²⁴⁹⁻²⁵² Cf ^b		²⁵³ Fs	
	4 days	15 days	64 days	4 days	16 days	64 days	21 days	4 days	90 days	7 days	24 days ^b
Skeleton ^c	33.8	34.0	32.7	30.7	30.2	27.2	38.0	61.6	62.3	68.8	56.9
Incisors(four)	1.4	1.4	0.1	-	-	-	-	2.7	0.2	-	-
Liver	41.8	10.5	0.6	35.8	20.0	2.3	4.0	13.9	1.2	7.8	1.7
Kidneys	1.2	0.7	0.6	1.5	1.1	0.8	1.3	1.3	0.5	-d	-d
Soft tissue balance	1.5	1.0	0.7	6.8	5.1	2.5	11.5	2.2	1.8	2.0	9.4
G.I. tract and contents	2.1	1.7	0.2	5.7	1.6	0.2	-d	1.7	0.4	-d	-d
Urine	10.0	10.2	11.5	1.2	3.6	67.0	12.6	7.3	10.7	10.9	16.4
Feces	7.5	36.2	53.8	18.2	38.4	-	12.6	9.5	22.7	10.5	15.6
Recovered	96.7	94.1	103.6	107.3	96.6	97.6	80.0	99.3	99.3	-	-
Unabsorbed	1.9	1.9	1.2	7.5	7.0	2.4	-	2.1	0.5	-	4.7
Femur, tibia-fibula(one each) ^e	3.1	2.6	2.4	3.1	3.0	2.6	-	5.2	5.1	5.4	4.2

^a ²⁴¹Am: DURBIN et al. (1967,1972c); ²⁴²Cm: SCOTT et al. (1949);

²⁴⁹Bk: HUNGATE et al. (1972); ²⁴⁹⁻²⁵²Cf: DURBIN et al. (1972d); ²⁵³Es: V. H. SMITH (1972b).

^b Results of intramuscular studies are expressed as percent absorbed dose and are corrected to 100% recovery.

^c Includes incisor teeth unless incisors are shown as a separate sample.

^d Included in soft tissue balance.

^e Included in total skeleton.

Table 13: Distribution of isotopes of the transplutonium elements^a in the immature rat after intravenous or intraperitoneal injection

Tissue	Percent of injected dose at days after injection										
	²⁴¹ Am(high dose)			²⁴¹ Am(low dose)			²⁴² Cm ^b		²⁵² Cf		
	4 days	16 days	48 days	4 days	21 days	62 days	15 days	50 days	4 days	16 days	64 days
Skeleton ^c	30.8	34.7	45.5	47.8 ^d	41.6 ^d	39.4 ^d	34.3	34.5	56.3 ^e	55.6 ^e	53.4 ^e
Liver	38.3	12.6	11.9	21.9	12.8	12.7	18	5.5	4.3	2.5	0.6
Kidneys	2.7	1.6	2.5	1.0	0.5	0.5	1.0	0.9	1.6	0.6	0.6
Soft tissue balance	5.9	6.4	6.2	-	-	-	4.0	3.5	5.0	4.3	4.3
G.I. tract and contents	2.7	0.9	1.1	-	-	-	1.5	0.6	1.4	0.9	0.9
Urine	5.6	8.0	9.9	11.8	30.7	44.5	7.9	11.3	-	-	-
Feces	10.1	27.6	20.6	-	-	-	33.2	43.6	-	-	-
Recovered	96.5	91.7	97.6	82.2	87.3	94.1	88.0	100.5	-	-	-
Femur, tibia-fibula (one each)	-	-	-	4.1	3.5	3.3	3.0	3.5	5.5	5.4	5.2

^a ²⁴¹Am(high dose): LANGHAM and CARTER (1951); ²⁴¹Am(low dose): D. M. TAYLOR et al. (1961); ²⁴²Cm: K. G. SCOTT, M. H. WILLIAMS, and H. I. JOHNSON (unpublished); ²⁵²Cf: MEWHINNEY et al. (1972).

^b Results corrected to 100% recovery.

^c Includes incisor teeth.

^d Estimated from the average of the following relationships between isotope content of whole skeleton and of leg bones: ²⁴¹Am, adult skel(%)//fem(%)= 23.1 and skel(%)//fem-tib(%)=11.8; ²⁴²Cm, 45 days old, skel(%)//fem-tib(%)=10.8; ⁴⁵Ca, 43 days old, skel(%)//fem(%)= 22.2.

^e Estimated by author, skel(%)//fcm(%)=18.7

Table 14. Distribution of isotopes of the transplutonium elements^a in the adult mouse after intramuscular injection

Tissue	Percent of absorbed dose at days after injection					
	²⁴³ Am		²⁵² Cf		²⁵³ Es	
	4 days	14 days	4 days	14 days	4 days	14 days
Skeleton and teeth	~44 ^b	~39 ^b	~43 ^b	~45 ^b	46.5	39.7
Liver	29	19	7.5	1.5	3.3	1.8
Kidneys	1.4	0.3	-	-	-	0.2
Residual soft tissues ^c	~3 ^b	~3 ^b	~6 ^b	~5 ^b	3.2	3.9
Urine	21	22	5.8	6	30	26.7
Feces	6.6	16	18	21	1.4	2.0
Unabsorbed	0.5	0.8	~2.5 ^d	~2.5 ^d	3.5	2.7
Recovered	105.4	98.9	82.8	81	87.9	77.0
Hind leg bones	1.6	1.8	~2.5 ^d	~2.5 ^d	2.3	1.8
Carcass	46.9	41.8	49.0	50.0	49.7	43.6

^a ²⁴³Am: WRIGHT (1972); ²⁵²Cf: PARKER et al. (1962); ²⁵³Es: PARKER et al. (1972).

^b Skeleton and residual soft tissues were assayed as a unit. Their separate ²⁴³Am and ²⁵²Cf contents were estimated assuming $Sk_{est}(\%) = (Carc-ST)$, where soft tissue (including G.I. tract) was assumed to be the mean of the measured soft tissue values in rats and hamsters; 3.3 and 2.7% of ²⁴³Am, and 5.7 and 4.7% of ²⁵²Cf at 4 and 14 days, respectively.

^c Other soft tissues including G. I. tract and contents.

^d Data available for injected leg only, and one-half each assigned to the hind-leg bones and the unabsorbed fraction.

Table 15. Distribution of isotopes of the transplutonium elements^a
in the adult Chinese hamster after intraperitoneal injection

Tissue	Percent of injected dose at days after injection					
	²⁴¹ Am			²⁵² Cf		
	4 days	16 days	64 days	4 ^b days	16 days	64 days
Skeleton ^c	19	22	26	28	34	29
Liver	55	53	52	27	18	18
Kidneys	6	1	<1	7.7	1.5	0.9
Soft tissue balance	3	3	3	6 ^d	5 ^d	8 ^d
G. I. tract and contents	-	-	-	1.5	2.3	1.3
Whole body ^e	83	79	81	70	61	57
Femur (one)	-	-	-	1.7	2.3	1.9

^a²⁴¹Am: MCKAY et al. (1969, 1972) ²⁵²Cf: MEWHINNEY, et al. (1972).

^bValues shown for 4 days are means of the published values for 2 and 8 days.

^cIncludes incisor teeth.

^dSoft tissue balance = (whole body) - (measured tissues).

^eMeasured by whole-body counting.

Table 16. Distribution of isotopes of ^{241}Am and $^{249-252}\text{Cf}$ in the young adult beagle after intravenous injection

Tissue	Percent of injected dose at days after injection			
	$^{241}\text{Am}^a$		^{249}Cf or $^{252}\text{Cf}^b$	
	1 to 22 days	1510 to 1917 days	7 to 13 days	21 to 36 days
Skeleton	31.0	32.7	46.6	54.7
Liver	48.7	46.4	17.4	17.4
Kidneys	0.6	0.6	1.1	0.8
Spleen	0.03	0.06	0.2	0.1
Soft tissue balance	3.7	1.8	10.1	5.4
G. I. tract and contents	0.6	0.1	1.6	0.6
Urine	9.7	9.7 ^c	15.9	16.4 ^c
Feces	1.4	1.4 ^c	7.3	7.5 ^c
Recovered	95.7	93.5	100.2	102.9

^a ^{241}Am : LLOYD et al. (1970, 1971, 1972c,d); 1 to 22 days, 4 dogs (T15W5.5, T32W5.5, T33W5.5, T16W5) 2.8 to 4.5 $\mu\text{Ci/kg}$; 1510 to 1917 days, 3 dogs (F6W3, F7W2, M5W3) 0.095 to 0.31 $\mu\text{Ci/kg}$.

^b ^{249}Cf or ^{252}Cf : ATHERTON and LLOYD (1972); LLOYD et al. (1972b,e): 7 to 13 days, 2 dogs (T2G5, T2F5) 2.8 $\mu\text{Ci/kg}$; 21 to 36 days, 2 dogs (T3G5, T1F5) 2.8 $\mu\text{Ci/kg}$.

^cExcretion collections to 21 days only.

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Table 17: Distribution of ^{241}Am in adult female primates^a after intramuscular or intravenous injection

Tissue	Percent of injected or absorbed dose at days after injection				
	Cynomolgus monkey ^b			Baboon	
	8 days	21 to 42 days	81 to 112 days	32 days	86 days
Skeleton ^c	27.2	35.5	42.2	44.2 ^d	36.8 ^d
Liver	54.4	44.7	29.0	13.6 ^d	22.2 ^d
Kidneys	0.2	0.06	0.2	0.1	0.08
Soft tissue Balance	6.6	4.0	3.6	11.0	9.0
G.I. tract and contents	1.3	0.9	0.4	0.9	1.6
Urine	8.3	11.0	11.6	9.6	13.8
Feces	1.0	3.0	12.6	6.5	14.4
Recovered	100.2	101.2	100.5	86.4	98.3
Unabsorbed	1.6	0.6	0.4	-	-
Femur, tibia, and fibula(one each)	1.8	2.3	2.6	2.5	2.6
Humerus (one)	0.9	1.2	1.2	1.6	1.0

^a Cynomolgus monkey: DURBIN et al. (1972c); baboon: ROSEN et al. (1972).

^b Results of intramuscular studies are expressed as percent absorbed dose corrected to 100% recovery.

^c Includes teeth.

^d Apparent decrease in ^{241}Am contents in skeleton and its increase in liver are the results of greater initial skeleton uptake and less initial liver uptake by the animal sampled at 32 days. Partial-body counting and liver biopsies demonstrated constant skeleton retention and declining liver retention of ^{241}Am by both animals over the 86-day period of observation.

Table 18. Summary of initial bone and liver deposition of ^{241}Am in rats

Experiment	Chemical form and mode of administration ^a	Sex and age (days)	Days after injection	Percent injected or absorbed dose $\pm$ S. D.	
				Bones and teeth	Liver+ feces + G. I. contents
SCOTT et al. (1948a)	Chlor., i.m.	F >120	1 ^b	23.2 ^c	62.3
LANGHAM and CARTER (1951)	Chlor., i.v.	M 47	4 ^b	31.9 ^c	53.0
D.M. TAYLOR et al. (1961)	Citr., i.v.	M 49	4 ^b	58.1 $\pm$ 5.2 ^c	32.8 $\pm$ 9.1
DURBIN et al. (1967)	Citr., i.m.	F 110	1 ^b	35.7 $\pm$ 4.1 ^c	49.4 $\pm$ 4.6
ZALIKIN et al. (1968)	Chlor., i.v.	F 150	1 ^b	20.3	68.6
BELYAEV (1969)	Chlor., i.v.	M ~49 ^d	1	30.4	61 ^e
BELYAEV (1969)	Chlor., i.p.	M ~49 ^d	1 ^b	22.4	68
TSEVELEVA and YEROKHIN (1969)	Nitr., i.p.	- -	1	7.1	64.8 ^e
NENOT et al. (1971b)	Nitr., i.v.	M ~60 ^d	1 ^b	10	71
NENOT et al. (1971b)	Nitr., i.m.	M ~60 ^d	10 ^b	30.6	39.8
HOLLINS and DURAKOVIC (1972)	Citr., i.v.	F 140	7	19.4 $\pm$ 3.4 ^c	-

^aChlor., chloride; nitr., nitrate; citr., citrate; i.m., intramuscular; i.v., intravenous; i.p., intraperitoneal.

^bWhole body and excreta measured, data corrected for absorption and 100% recovery (See text).

^cWhole skeleton or all bones measured. In all other studies, skeleton was apparently calculated from measurement of femur or other specific bones, but the details of those calculations were not reported.

^dAge estimated from Sprague-Dawley rat growth curve.

^eLiver only; excreta and G.I. contents not reported.

Table 19. Summary of deposition of ^{242}Cm in bone and liver of rats

Experiment	Chemical form and mode of administration ^a	Sex and age (days)	Days after injection	Percent injected or absorbed dose $\pm$ S.D.	
				Bones and teeth	Liver+ feces+ G.I. contents
SCOTT et al. (1949)	Chlor., i.m.	F, ~110	1 ^b	27.7 ^c	60.9
K.G. SCOTT and M.H. WILLIAMS(unpublished)	Chlor., i.v. Chlor., i.m.	F, >110 F, ~60	4 ^b 15 ^b	25.5 ^c 34.3 ^c	61.6 52.8
WILLIAMS et al. (1961)	Chlor., i.v.	F, $\geq$ 110	1 ^b	22.2 $\pm$ 2.0 ^c	59.6 $\pm$ 1.2
WILLIAMS et al. (1961)	Chlor., i.m.	F, $\geq$ 110	1 ^b	28.5 $\pm$ 1.2 ^c	50.0 $\pm$ 0.8
WILLIAMS et al. (1961)	Citr., i.v.	F, $\geq$ 110	1 ^b	24.3 $\pm$ 2.0 ^c	58.5 $\pm$ 3.5
WILLIAMS et al. (1961)	Citr., i.m.	F, $\geq$ 110	1 ^b	27.8 $\pm$ 1.3 ^c	53.5 $\pm$ 0.6
NENOT et al. (1970)	Nitr., i.v.	M, ~60 ^d	1	20	68
NENOT et al. (1970)	Nitr., i.m.	M, ~60 ^d	1	21	48

^aChlor., chloride; nitr., nitrate; citr., citrate, i.v., intravenous; i.m., intramuscular.

^bWhole body and excreta measured; data corrected for absorption and 100% recovery.
See text.

^cWhole skeleton measured.

^dAge estimated from Sprague-Dawley rat growth curve.

Table 20. Partition of trivalent lanthanide and actinide isotopes among bone (including teeth), liver ($L_{\max}$),^a and residual soft tissues (S. T.) 4 days after injection into rats.^b

Lanthanide series (4f)						Actinide series (5f)				
No. of f-electrons	Symbol	Ion ^c radius (Å)	Nuclide content			Symbol	Ion ^c radius (Å)	Nuclide content		
			(% normalized dose) Bone	$L_{\max}$ ^a	S. T.			(% normalized dose) Bone	$L_{\max}$ ^a	S. T.
1	Ce	1.03	30	63	8	Th	(1.08)	—	—	—
2	Pr	1.01	28	60	11	Pa	(1.05)	—	—	—
3	Nd	1.00	40	48	12	U	1.03	—	—	—
4	Pm	0.98	40	53	7	Np	1.01	—	—	—
5	Sm	0.96	38	55	7	Pu	1.00	—	—	—
6	Eu	0.95	43	43	14	Am	0.98	39	57	4
7	Gd	0.94	57	28	16	Cm	0.98	28	60	13
8	Tb	0.92	72	16	12	Bk	0.95	60	23	16
9	Dy	0.91	79	12	9	Cf	0.94	69	27	4
10	Ho	0.89	71	20	10	Es	0.93	77	20	2
11	Er	0.88	78	12	10	Fm	—	—	—	—
12	Tm	0.87	82	9	9	Md	—	—	—	—
13	Yb	0.86	72	12	16	No	—	—	—	—
14	Lu	0.85	80	12	8	Lr	—	—	—	—

^a $L_{\max}$ defined by Eq. 23 (Section VIII.A.1.)

^bData have been corrected for material recovery and absorption (intramuscular studies), and have been normalized to take account of the variable urinary excretion using Eq. 14. Four-day studies, except for ^{242}Cm , ^{249}Bk , and ^{253}Es which were 1-, 21-, and 7-day studies, respectively. Lanthanide studies are those of DURBIN et al. (1956); actinide studies, except ^{242}Cm , are those shown in Table 12; ^{242}Cm data of WILLIAMS et al. (1961).

^cIon radius calculated for the cubic sesquioxide; lanthanide series, TEMPLETON and DAUBEN (1954); Pu(III), Am(III), Cm(III), ZACHARIASEN (1954); Bk, Cf, PETERSON (1967); Es, FUJITA (1969) as calculated by B. B. CUNNINGHAM (private communication).

Table 21. Intraskkeletal distribution of ^{241}Am , $^{249-252}\text{Cf}$, ^{253}Es , and bone ash in several animal species expressed as percent total skeletal nuclide or ash content

	Adult rat				Beagle dog			Cynomolgus monkey		Baboon
	$^{241}\text{Am}^a$	$^{249-252}\text{Cf}^a$	$^{253}\text{Es}^b$	Ash ^a	$^{241}\text{Am}^c$	$^{249}\text{Cf}^c$	Ash ^c	$^{241}\text{Am}^a$	Ash ^a	$^{241}\text{Am}^d$
Skull ^e	—	—	—	14.7	7.77	8.64	17.7	15.7	15.8	15.2
Mandibles ^e	2.79	2.52	—	4.72	2.60	3.23	9.0	5.19	5.90	—
Cerv. vert.	—	—	—	—	7.91	6.41	7.6	—	—	—
Thor. vert.	23.8	23.3	24.1	20.3	18.1	13.4	6.1	30.6	21.4	29.2
Lumb. vert.	—	—	—	—	19.0	13.3	6.0	—	—	—
Caud. vert.	—	—	—	11.9	1.81	1.04	0.9	—	—	—
Scapulae	—	—	—	2.65	3.5	4.97	3.9	3.55	3.02	4.34
Clavicles	—	—	—	—	—	—	—	0.59	0.57	0.43
Ribs	3.98	3.71	4.9	5.42	8.52	12.0	8.4	5.92	4.53	7.68
Sternum	—	—	3.0	2.64	5.95	4.26	0.3	1.47	0.89	1.18
Humeri	—	—	—	—	6.19	7.62	6.2	6.46	7.17	6.42
Radii	9.64	—	—	8.63	1.11	1.29	2.7	—	—	1.89
Ulnae	—	—	—	—	1.34	1.49	2.9	15.7	23.7	2.16
Femora	8.48	8.95	8.6	8.48	5.81	7.36	6.6	—	—	8.46
Tib. -Fib.	7.61	7.35	—	6.53	3.34	3.50	6.4	—	—	4.89
Paw bones	—	—	4.6	7.25	2.02	4.56	10.0	6.16	8.60	5.97
Pelvis	5.75	—	6.7	6.77	4.88	7.00	5.3	8.43	7.68	10.7
Patellae	—	—	—	—	—	—	—	0.22	0.27	—
Teeth	3.91	4.20	—	—	—	—	—	1.32	—	—
Skeletal nuclide (%)	35.6	64.3	56.9	—	31.0	48.6	—	31.9	—	40.5
Ash wt. skeleton(g)	—	—	—	8.9	—	—	327	—	153	—

^a ^{241}Am measured in 20 adult female rats 1 to 15 days after injection. $^{249-252}\text{Cf}$ measured in 3 adult female rats 4 days after injection. Bone ash measured in 50 or more female rats killed between the ages of 100 and 300 days; total skeletal ash measured in 50 female rats 100 to 130 days old. ^{241}Am measured in 8 adult female cynomolgus monkeys killed 1 to 63 days after injection. Bone ash measured in 19 adult female cynomolgus monkeys (DURBIN et al., 1972c,d,e)

^b ^{253}Es measured in 8 adult female rats 24 days after injection (V. H. SMITH, 1972b).

^c ^{241}Am measured in 6 beagles 1 to 21 days after injection (LLOYD et al., 1971, 1972a). Skeletal ash measured in 11 adult beagles of both sexes in the same colony (B. W. = 8.47 to 13.1 kg) (ATHERTON et al., 1969b). ^{249}Cf measured in two beagles killed 7 and 21 days after injection (LLOYD et al. 1972b).

^d ^{241}Am measured in two adult female baboons killed 32 and 86 days after injection (ROSEN et al., 1972).

^eIn the studies with dogs and baboons, skull and mandibles include teeth.

Table 22. Clearance of ^{241}Am , ^{242}Cm , $^{249-252}\text{Cf}$ and
four lanthanides from the liver of the rat

Isotope	Liver clearance half-time (days)			Reference
	Injection route ^a	Liver	Fecal excretion	
²⁴¹ AmCl ₃	i.m.	7.5	7.3	SCOTT et al. (1948 a) ^b
²⁴¹ AmCl ₃	i.v.	16 ^c	-	LANGHAM and CARTER (1951)
²⁴¹ Am citrate	i.v.	-	10.8 ^c	D.M. TAYLOR et al. (1961)
²⁴¹ Am citrate	i.m.	7	7	DURBIN et al. (1972c)
²⁴¹ AmCl ₃	i.v.	8	-	ZALIKIN et al. (1968)
²⁴¹ Am(NO ₃) ₃	i.p.	10 ^c	-	TSEVELEVA and YEROKHIN (1969)
²⁴² CmCl ₃	i.m.	8.5	9.0	SCOTT et al. (1949) ^b
²⁴² CmCl ₃	i.v.	-	9.2	K.G. SCOTT, M. H. WILLIAMS and H. I. JOHNSON, unpublished ^b
²⁴⁹⁻²⁵² Cf citrate	i.m.	-	8.2	DURBIN et al. (1972d)
²⁵² Cf citrate	i.p.	8	-	MEWHINNEY et al. (1972)
²⁵³ Es(NO ₃) ₃	i.v.	5.6	-	V. H. SMITH (1972b)
¹⁴⁴ Ce citrate	i.m.	-	8.3	DURBIN et al. (1956) ^b
¹⁴⁷ Pm citrate	i.m.	-	7.0	DURBIN et al. (1956) ^b
^{152,154} Eu citrate	i.m.	-	6.5	DURBIN et al. (1956) ^b
¹⁶⁰ Tb citrate	i.m.	5.6	-	DURBIN et al. (1956) ^b

Average liver half-time:				
²⁴¹ Am, 7.5 ± 0.5 days ²⁴² Cm, 9 ± 0.3 days ²⁴⁹⁻²⁵² Cf, 8.1 days				

^ai.m., intramuscular; i.v., intravenous; i.p., intraperitoneal.

^bCalculated from the original data.

^cNot included in average because injected dose exceeded 5 $\mu\text{Ci/kg}$ (LANGHAM and CARTER 1951; D.M. TAYLOR et al., 1961), or because ^{241}Am was administered in a readily hydrolyzable form.

Table 23. Concentrations of ^{241}Am and ^{249}Cf in selected soft tissues of the beagle and the baboon, ^a at days after injection (%/kg)

Tissue	^{241}Am in beagle ^b			^{249}Cf in beagle ^c		^{241}Am in baboon ^d
	2.8 to 4.5 $\mu\text{Ci/kg}$	2.8 $\mu\text{Ci/kg}$	0.09 to 0.3 $\mu\text{Ci/kg}$	2.8 $\mu\text{Ci/kg}$	2.8 $\mu\text{Ci/kg}$	0.2 $\mu\text{Ci/kg}$
	1 to 21 days	401 to 448 days	1510 to 1917 days	7 to 13 days	21 to 36 days	32 days
Thyroid	55	110	37	46	22	3.4
Dura mater	8.5	—	5.2	20	14	—
Lymph nodes	8.5	17	1.3	12	10	6.5
Trachea	7.1	29	^e	^e	—	17
Aorta	4.8	5.2	2.0	5.0	3.5	15
Lung	4.6	4.9	3.0	12	7.6	18
Larynx	3.3	6.4	2.1	—	—	6.1
Salivary glands	3.2	—	1.2	<1.8	5.7	2.0 ^f
Adrenals	3.2	3.4	1.0	5.9	4.7	3.2
Pituitary	2.6	14.0	1.2	3.2	8.0	—
Prostate	1.9	5.1	0.7	4.2	5.4	—
Eyes	1.5	1.4	0.9	1.0	<1.4	—
Heart	0.8	1.7	2.3	1.9	1.2	4.0
Urinary bladder	0.8	—	0.7	—	—	—
Testes	0.8	1.0	0.4	1.4	0.8	—
Pelt	0.8	1.0	0.3	2.9	1.3	1.9
Pancreas	0.5	0.6	2.1	<2.5	1.4	3.1
Muscle	0.3	0.6	0.2	0.95	0.5	0.9
Fat	0.09	—	—	—	—	0.2
Thymus	<0.4	—	<1.3	<1.5	2.5	—
Brain	<0.02	0.1	0.3	<0.15	0.2	0.06
Ovaries	—	—	1.0	4.9	3.4	4.8
Uterus	—	—	—	<0.6	—	1.9
Mammary glands	—	—	—	—	—	3.9 ^f

^aTissues and organs shown in Tables 16 and 17 are not included. Nuclide concentrations in those tissues may be obtained from the nuclide data in Tables 16 and 17 and the average weights in Appendix C.

^b1 to 21 days - dogs T15W5.5, T32W5.5, T16W5, T33W5.5; 401 to 448 days - dogs T1W5, T2W5; 1510 to 1917 days - dogs F6W3, F7W2, M5W3 (LLOYD et al. 1970, 1972d).

^c7 to 13 days - dogs T2G5, T2F5; 21 to 36 days - dogs T3G5, T1F5 (LLOYD et al. 1972d).

^dBaboon #B-416 (ROSEN et al. 1972).

^eTrachea and lung combined.

^fBaboon #B-412 killed 86 days after injection.

Table 24. Deposition and retention of trivalent actinide elements in selected soft tissues of the rat

Isotope and compound	Injn. route ^a	Spleen				Lungs				Muscle				Pelt				Reference
		Days	%	Days	%	Days	%	Days	%	Days	%	Days	%	Days	%	Days	%	
²⁴¹ AmCl ₃	i.m.	4	0.10	256	0.06	1	0.23	256	0.08	1	1.5	256	1.2	1	3.3	256	0.22	SCOTT et al. (1948a)
²⁴¹ AmCl ₃	i.v.	4	0.26	48	0.45	4	0.51	48	0.50	-	-	-	-	4	1.6	48	0.92	LANGHAM and CARTER (1951)
²⁴¹ Am citrate	i.v.	4	0.38	62	0.24	4	0.22	62	0.19	-	-	-	-	-	-	-	-	D. M. TAYLOR et al. (1961)
²⁴¹ AmCl ₃	i.v.	1	0.22	64	0.30	1	0.13	64	0.10	2	1.3	64	2.6	2	0.77	32	1.12	ZALIKIN et al. (1968)
²⁴¹ Am(NO ₃) ₃	i.p.	3	0.91	270	0.22	1	1.13	270	0.17	-	-	-	-	-	-	-	-	TSEVELEVA and YEROKHIN (1969)
²⁴¹ AmCl ₃	i.p.	3	0.84	180	0.18	1	0.26	30	0.07	1	3.0	14	0.80	-	-	-	-	BELYAYEV (1969)
²⁴¹ Am citrate	i.m.	1	0.04	293	0.03	-	-	-	-	-	-	-	-	-	-	-	-	DURBIN et al. (1972c)
²⁴² CmCl ₃	i.m.	1	0.09	256	0.10	1	0.29	256	0.09	1	2.2	256	0.47	1	1.9	256	0.09	SCOTT et al. (1949)
²⁴² Cm citrate	i.v.	1	0.08	-	-	-	-	-	-	-	-	-	-	-	-	-	-	WILLIAMS et al. (1961)
²⁴⁹ BkCl ₃	i.v.	-	-	21	0.42	-	-	-	-	-	-	-	-	-	-	-	-	HUNGATE et al. (1972)
²⁵² Cf citrate	i.p.	1	0.29	64	0.10	-	-	-	-	-	-	-	-	-	-	-	-	MEWHINNEY et al. (1972)
²⁵² Cf citrate	i.m.	4	0.10	91	0.21	-	-	-	-	-	-	-	-	-	-	-	-	DURBIN et al. (1972d)
²⁵³ Es(NO ₃) ₃	i.v.	7	0.42	24	0.14	7	0.24	24	0.20	7	1.5	24	1.2	-	-	-	-	V. H. SMITH (1972b)
²⁵³ EsCl ₃	i.v.	-	-	21	0.62	-	-	-	-	-	-	-	-	-	-	-	-	HUNGATE et al. (1972)
²⁵³ Es citrate (mouse)	i.m.	4	0.03	14	0.04	-	-	-	-	-	-	-	-	-	-	-	-	PARKER et al. (1972)

^a i.m., intramuscular; i.v., intravenous; i.p., intraperitoneal.

Table 25. Concentration of transplutonium nuclides in the thyroid gland of the beagle

Days	Concentration at days after injection (%dose/kg)				Concentration at days after inhalation (% ILB/kg)		
	²⁴¹ Am citrate ^a			²⁴⁹ Cf citrate ^b	²⁴¹ AmO ₂ ^c	²⁴⁴ CmCl ₃ ^d	²⁴⁴ CmO _{1.73} ^d
	2.8-4.5 µCi/kg	0.91 µCi/kg	0.09-0.3 µCi/kg	2.8 µCi/kg	2.7 µCi/kg	0.11 µCi/kg	0.10 µCi/kg
1-2	115	—	—	—	—	130;420 ^e	110;130
7-8	42;47	—	—	58	—	42;70	80
13-16	46;56	—	—	34	—	41;42	48;49
21-22	20	—	—	16	—	—	—
36	—	—	—	28	—	—	—
64	—	—	—	—	—	52;77	—
127-256	—	—	—	—	10;37	12;15	—
401-448	80;134	—	—	—	—	—	—
512-633	—	144	—	—	28	—	—
1022-1132	—	276	—	—	35	—	—
1323-1510	—	89;157	69	—	—	—	—
1779-1917	—	67	10;31	—	—	—	—

^aData of LLOYD et al. (1972d).^bData of LLOYD et al. (1972e).^cData of R. G. THOMAS et al. (1972).^dData of MCCLELLAN et al. (1972).^eWhen two values are shown they are individual measurements from pairs of dogs.

Table 26. Excretion of trivalent actinide elements by the adult rat.

Day after injection(t)	Cumulative excretion ^a (% dose)											
	²⁴¹ AmCl ₃ ^b		²⁴¹ Am cit. ^c		²⁴² CmCl ₃ ^d		²⁴⁹ BkCl ₃ ^e		²⁴⁹⁻²⁵² Cf cit. ^f		²⁵³ Es(NO ₃) ₃ ^g	
	Σ Ur ^h	Σ Fe ⁱ	Σ Ur	Σ Fe	Σ Ur	Σ Fe	Σ Ur	Σ Fe	Σ Ur	Σ Fe	Σ Ur	Σ Fe
1	6.1	1.7	9.0	1.7	6.3	0.8	7.0	0.2	6.2	2.1	12.1	2.1
2	6.4	3.3	9.4	2.8	6.6	2.6	8.6	1.1	6.8	4.7	13.0	6.6
4	6.7	8.5	9.7	7.2	6.9	7.6	9.9	3.1	7.3	6.9	13.6	8.4
7	6.8	14.1	10.0	17.2	7.3	17.0	11.0	6.0	7.8	11.0	14.0	14.0
14	6.9	31.8	10.2	34.3	7.5	24.9	11.9	10.4	8.4	15.6	14.8	14.0
21	7.1	41.5	10.4	42.1	7.7	33.7	12.7	12.4	8.8	17.8	15.3	15.6
28	7.2	47.3	10.6	46.0	7.8	42.2			9.2	19.3		
35	7.3	50.4	10.7	47.9	7.9	47.8			9.4	20.4		
49	7.5	54.2	10.8	50.2	8.0	52.4			9.8	22.0		
63	7.6	56.6	10.9	50.8	8.1	53.8			10.1	23.2		
77	7.7	57.8	11.0	51.5	8.1	55.8			10.3	24.7		
91	7.8	59.3	11.0	51.8	8.1	56.6			10.5	25.1		
105	7.8	60.6	11.1	52.1	8.2	57.6						
133	8.0	62.0		52.4 ^j	8.4	58.5						
161	8.2	63.4		52.8	8.5	59.4						
189	8.4	65.4		53.4	8.7	60.3						
217	8.6	67.4		53.8	8.9	61.1						
245	8.8	69.4		54.0	9.1	61.6						
301				54.3								
357				54.6								
413				55.0								
469				55.4								
525				55.8								
581				56.3								
637				56.6								
693				57.1								
749				57.4								

^aThese data are readily manipulated as follows:

to calculate whole-body retention, $\text{Retention}_t = 100\% - \Sigma(\text{Ur} + \text{Fe})_{0-t}$;

to calculate excretion in an interval, $\text{Ur}(\%)_{t_2-t_1} = \Sigma \text{Ur}_{t_2} - \Sigma \text{Ur}_{t_1}$;

$$\text{Ur}(\%)_{t_2-t_1} = \frac{\Sigma \text{Ur}_{t_2} - \Sigma \text{Ur}_{t_1}}{t_2 - t_1}$$

to calculate excretion rate, $\text{Ur}(\%/day)_{t_2-t_1} = \frac{\text{Ur}(\%)_{t_2-t_1}}{t_2 - t_1}$.

^b²⁴¹AmCl₃, 3.6 μCi/kg, intramuscular (SCOTT et al., 1948a); original data recalculated.

^c²⁴¹Am citrate, 0.37 μCi/kg, intramuscular (DURBIN et al., 1967, 1972c).

^d²⁴²CmCl₃, 4.4 μCi/kg, intramuscular (SCOTT et al., 1949; K. G. SCOTT et al., unpublished); original data recalculated.

^e²⁴⁹BkCl₃, 6.25 μCi/kg, intravenous (HUNGATE et al., 1972).

^f²⁴⁹⁻²⁵²Cf citrate, 0.33 μCi/kg, intramuscular (DURBIN et al., 1972d).

^g²⁵³Es(NO₃)₃, 3.3 μCi/kg, intravenous (V. H. SMITH, 1972b).

^hUr = urine

ⁱFe = feces

^jUrine and feces combined after 106 days.

Table 27. Excretion by monkey, baboon, and dog of ^{241}Am and ^{249}Cf during the first 3 weeks after injection

Days after injection	Excretion in interval (% dose)							
	^{241}Am , monkey ^a		^{241}Am , baboon ^b		^{241}Am , beagle dog ^c		^{249}Cf , beagle dog ^d	
	Urine	Feces	Urine	Feces	Urine	Feces	Urine	Feces
1	6.01	0.10	8.70	0.71	8.03	0.22	11.36	3.22
2	0.87	0.11			0.34	0.51	1.23	1.42
3	0.41	0.12			0.34	0.14	1.50	1.15
4-7	1.10	0.42			0.51	0.33	1.14	1.07
8-14	0.70	0.96	1.25	1.50	0.33	0.14	0.76	0.41
15-21	<u>0.51</u>	<u>1.10</u>	<u>0.51</u>	<u>1.45</u>	<u>0.17</u>	<u>0.06</u>	<u>0.48</u>	<u>0.22</u>
Total	9.60	2.81	10.46	3.66	9.72	1.45	16.47	7.49

^aMean of 14 to 20 cynomolgus monkeys (DURBIN et al., 1972c).

^bData from 2 baboons (ROSEN et al., 1972).

^cMean of 4 dogs (LLOYD et al., 1970).

^dMean of 11 dogs (LLOYD et al., 1972b).

Table 28. Cumulative excretion of ^{241}Am by the cynomolgus monkey and the baboon

Days after injection	Cynomolgus monkey ^a				Baboon ^b	
	No. of animals	Urine % dose	Feces % dose	No. of animals	Urine % dose	Feces % dose
28	16	10.1	4.3	2	10.9	5.6
56	12	11.6	10.1	1	11.7	10.3
84	10	12.8	14.7	1	12.2	14.50
112	9	13.6	18.0			
140	7	14.2	20.2			
196	6	15.5	24.2			
252	6	16.3	26.7			
308	5	16.7	28.0			
364	5	17.0	29.1			
420	4	17.3	29.8			
476	4	17.7	30.8			
532	4	18.0	31.8			
588	4	18.3	32.5			
644	4	18.5	33.0			
742	4	18.8	33.8			
854	2	19.0	34.8			
966	2	19.2	35.5			
1022	1	19.3	35.7			
1078	1	19.4	35.9			
1190	1	19.5	36.6			
1302	1	19.7	36.9			
1414	1	19.8	37.1			
1526	1	19.9	37.2			
1638	1	20.0	37.4			

^aData of DURBIN et al. (1972c).^bData of ROSEN et al. (1972).

Table 29. Plasma concentrations (P_x), urinary excretion rates (U_x), renal clearances (C_x), and calculated filterable fraction in plasma of ^{241}Am , ^{249}Cf , and ^{239}Pu in several mammals.

Am, Cf, and Pu in several mammals.							
Species and nuclide	Days after injection	P _x (% dose/ml)	U _x (% dose/min)	C _x		Filterable fraction (% of plasma content)	References
				(ml/min)	(Plasma volumes per day)		
²⁴¹ Am							
Rat ^a	1	1.4×10 ⁻¹	3.4×10 ⁻³	2.4×10 ⁻²			D. M. TAYLOR et al. (1961) TURNER and TAYLOR (1968b)
	2	2.3×10 ⁻²	4×10 ⁻⁴	1.7×10 ⁻²			
	3-4	8×10 ⁻³	2.7×10 ⁻⁴	3.4×10 ⁻²			
	Mean			2.5×10 ⁻²	7.3	3.8	
Beagle	1	4.6×10 ⁻³	5.5×10 ⁻³	1.2			STEVENS and BRUENGER (1972) LLOYD et al. (1970)
	2-4	1.1×10 ⁻⁴	1.6×10 ⁻⁴	1.4			
	Mean			1.3	4.3	3.2	
Monkey	1	5.8×10 ⁻³	3.4×10 ⁻³	5.9×10 ⁻¹			DURBIN et al. (1972c)
	2	1.3×10 ⁻³	6.7×10 ⁻⁴	5.2×10 ⁻¹			
	3-4	5.4×10 ⁻⁴	2.7×10 ⁻⁴	5×10 ⁻¹			
	14-110 ^b	5.8×10 ⁻⁵	3.3×10 ⁻⁵	5.7×10 ⁻¹			
	Mean			5.4×10 ⁻¹	6.5	4.5	
²⁴⁹ Cf							
Beagle	1	5.2×10 ⁻³	7.8×10 ⁻³	1.5			STEVENS and BRUENGER (1972) LLOYD et al. (1972b)
	2-4	5.4×10 ⁻⁴	6.4×10 ⁻⁴	1.2			
	Mean			1.35	4.3	3.4	
²³⁹ Pu							
Rat ^a	2-3	5×10 ⁻¹	1.6×10 ⁻⁴	4.4×10 ⁻⁴			D. M. TAYLOR et al. (1961) TURNER and TAYLOR (1968b)
	7-14	7.1×10 ⁻²	5×10 ⁻⁵	6.9×10 ⁻⁴			
	Mean			5.7×10 ⁻⁴	1.6×10 ⁻¹	8×10 ⁻²	
Beagle	3	9×10 ⁻³	1.2×10 ⁻⁴	1.4×10 ⁻²			STOVER et al. (1959)
	60-180	1.6×10 ⁻⁴	5.2×10 ⁻⁶	3.4×10 ⁻²			
	Mean			2.4×10 ⁻²	8.5×10 ⁻²	6×10 ⁻²	
Man	1-6	—	—	3.8×10 ⁻²			LANGHAM et al. (1950); DURBIN (1972)
	19-24	—	—	1.7×10 ⁻¹			
	Mean			1.0×10 ⁻¹	5×10 ⁻²	8×10 ⁻²	

^aBody weight of 6- to 8-week-old male rats, 110 g.

^bBody weight of monkey # 72, 2.5 kg.

Table 30. Design of experiments using DTPA to promote excretion of promptly deposited trivalent actinides in rodents, and amount of nuclide remaining in bone after treatment

Isotope and route of administration ^a	Length of study (days)	DTPA Treatment					Reference
		Treatment schedule (time after nuclide injn.)	Number of treatments	DTPA per treatment ^b (mM/kg)	Total DTPA given (mM/kg)	Amount of nuclide in bone (% of control)	
Studies using rats							
²⁴¹ Am citrate, i. v. }	21	1hr, 7, 14d	3	3.0	9.0	17.5	{ SOWBY and TAYLOR (1960)
	21	6hr, 7, 14d	3	3.0	9.0	25	
	21	7, 14d	2	3.0	6.0	50	
²⁴¹ Am citrate, i. v. }	30	2hr, 1-29d	30	0.46	13.8	17 ^c	{ FOREMAN (1962)
	30	2m, 1-29d	30	0.028, s. t.	0.84	33.8 ^c	
	30	7-29d	23	0.46	10.6	36 ^c	
	30	14-29d	16	0.46	7.4	52 ^c	
²⁴¹ Am citrate, i. t. }	30	2hr, 1-29d	30	0.46	13.8	21 ^c	{
	50	2hr, 1-49d	50	0.46	23.0	14.3 ^c	
²⁴¹ Am citrate, i. v.	21	7-11, 14-17d	9	3.0	27.0	50.5	D. M. TAYLOR and SOWBY (1962)
²⁴¹ AmCl ₃ , i. p. }	3	1d	1	1.5	1.5	52	{ BELYAEV (1969)
	16	1-13d	13	0.41	5.7	22	
	40	25-37d	13	0.41	5.7	63	
²⁴¹ Am citrate, i. v.	13	6, 8, 11d	3	1.0	3.0	77	{ SEIDEL and VOLF (1972)
²⁴² Cm citrate, i. v.	13	6, 8, 11d	3	1.0	3.0	67	
²⁵³ Es(NO ₃) ₃ , i. m.	21	1h, 1-3, 5, 7, 9, 12, 15, 17d	10	0.33	3.3	42.3	V. H. SMITH (1972a)
²⁴¹ Am(NO ₃) ₃ , aer. }	40	{ 20d, 2/week	6	0.12, i. m.	0.72	82	{ NENOT et al. (1971c)
	90		20	0.12, i. m.	2.4	42	
	124		30	0.12, i. m.	3.6	26	
Studies using mice							
²⁴¹ Am citrate, i. m. }	4	2hr, 1-3d	4	0.11	0.44	34	{ PARKER et al. (1962)
	14	2hr, 1-4, 7-11d	10	0.11	1.1	34	
²⁵² Cf citrate, i. m. }	4	2hr, 1-3d	4	0.11	0.44	46	
	14	2hr, 1-4, 7-11d	10	0.11	1.1	38.5	
²⁵³ Es citrate, i. m. }	1	2hr	1	0.11	0.11	76.5	{ PARKER et al. (1972)
	4	2hr, 1-3d	4	0.11	0.44	68.5	
	14	2hr, 1-4, 7-11d	10	0.11	1.10	50	

^ai. v., intravenous; i. t., intratracheal; i. m., intramuscular; i. p., intraperitoneal; s. t., stomach tube; aer., aerosol.

^bDTPA administered by intraperitoneal injection unless otherwise specified.

^cBased on whole-body measurement at 30 days postinjection; at that time liver and soft tissues have been cleared.

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Table 31. Design of experiments using DTPA to mobilize ^{241}Am or ^{242}Cm from a persistent reservoir in muscle or lung and to prevent their deposition in bone

Isotope and route of administration ^a	Length of study (days)	DTPA Treatment				Route of administration of DTPA ^b	Amount of absorbed nuclide in bone (% of control)	Reference
		Treatment schedule (time after nuclide adm.)	Number of treatments	DTPA per treatment (mM/kg)	Total DTPA given (mM/kg)			
$^{242}\text{Cm}(\text{NO}_3)_3$, i. m. ^c	1	0.5 hr	1	0.12	0.12	{ i. m., inj. leg	3.6	{ NENOT et al. (1970)
	20	1, 5, 10, 15d	4	0.12	0.48		12	
$^{242}\text{Cm}(\text{NO}_3)_3$, i. m.	42	{ 21d, 2/week	6	0.12	0.72	{ i. m. opp. leg	45	{ NENOT et al. (1972)
	81		16	0.12	1.92		50	
	111		24	0.12	2.88		35	
$^{241}\text{Am}(\text{NO}_3)_3$, i. m.	10	1, 7d	2	0.12	0.24	{ i. m. opp. leg	21	{ NENOT et al. (1971b)
	90	1d, 1/week	13	0.12	1.56		24	
	10	1, 7d	2	0.0012	0.0024	aerosol	84	
$^{241}\text{Am}(\text{SO}_4)_3$, i. m.	90	1d, 1/week	13	0.12	1.56	i. m., opp. leg	13	
$^{241}\text{Am}(\text{NO}_3)_3$, aer.	90	{ 1d, 1/week	13	0.12	1.56	i. m.	2.8	
	90		13	0.0012	0.016	aerosol	5.8	
$^{241}\text{Am}(\text{NO}_3)_3$, aer.	60	{ 1d, 1/week	8	0.12	0.96	i. m.	9	{ NENOT et al. (1971a)
	60		8	0.0012	0.01	aerosol	18	
$^{253}\text{EsCl}_3$, i. t.	7	1 hr	1	0.2	0.2	i. m.	7	BALLOU and MORROW (1972, and unpublished)

^ai. m., intramuscular; aer., aerosol; i. t., intratracheal instillation.

^bIntramuscular injections of DTPA were given either in the same leg into which the nuclide was injected (inj. leg) or in the opposite leg (opp. leg).

^cIn the first studies with ^{242}Cm , the $^{242}\text{Cm}(\text{NO}_3)_3$ solutions contained variable amounts of stable lanthanum carrier. (See Tables 5 and 6, Section IV. B.)

Table 32. Acute and subacute toxicity of ^{241}Am and ^{244}Cm in the adult and young rat^a and the Chinese hamster compared with that of ^{239}Pu , ^{144}Ce , and ^{90}Sr .

Days after injection	LD ₅₀ (μCi/kg)						References
	≤ 17	30	60	120-150	250	300-350	
<u>Adult rat^a</u>							
²⁴¹ Am	—	110	60	43	25	—	ZALIKIN et al. (1968,1969)
²⁴⁴ Cm	—	110	60	38	18	4.4	SEMENOV (1971a)
²³⁹ Pu	125	90	60	30	—	—	FINKLE et al. (1946)
¹⁴⁴ Ce	—	1830	—	872	826	452	{ MOSKALEV et al. (1966)
⁹⁰ Sr	—	1185	—	979	629	480	
<u>Young rat^a</u>							
²⁴¹ Am	189	95	64	49	47	34	{ LANGHAM and CARTER (1951)
²³⁹ Pu	—	71	63	59	52	30	
<u>Chinese hamster</u>							
²⁴¹ Am	—	100	—	10	—	5	MCKAY et al. (1972)
¹⁴⁴ Ce	5000	—	2500	1250	—	—	BROOKS et al. (1969)
⁹⁰ Sr	3000	—	2000	—	1000	—	BROOKS and MCCLELLAN (1969)

^a Adult rat, more than 60 days old or more than 130 g body weight; young rat, 30 to 60 days old, body weight approximately 100 g.

^b Isotopes were administered intravenously or intraperitoneally as chloride, nitrate, or citrate.

Table 33. Acute and chronic toxicity of ^{241}Am in dogs compared with the toxicity of ^{239}Pu , ^{144}Ce , and ^{90}Sr . Toxicity is expressed as mean lethal dose (LD_{50}) or absolute lethal dose (LD_{100}) at varying times after exposure.

Isotope, chemical form and method of administration ^a	Dose ($\mu\text{Ci/g}$)	Mortality at days after injection		References
		LD_{50}	LD_{100}	
$^{241}\text{AmCl}_3$, i.v.	10-60	—	21	ZALIKIN et al. (1969)
^{241}Am citrate, i.v.	2.8	—	450	{ T. F. DOUGHERTY et al. (1972).
	0.9	~1800	—	
$^{241}\text{Am}(\text{NO}_3)_3$, inhal.	1.5	—	~180	BULDAKOV et al (1972), NIFATOV et al (1972).
$^{241}\text{AmO}_2$, inhal.	4.7 ^b	~ 300	—	R. G. THOMAS (1970), R. G. THOMAS et al. (1972).
$^{239}\text{Pu}(\text{VI})$ citrate, i.v.	22	—	16	{ PAINTER et al. (1946)
	13	—	90	
$^{239}\text{Pu}(\text{IV})$ citrate, i.v.	2.9	1325	—	{ T. F. DOUGHERTY et al. (1972)
	0.9	1725	—	
$^{239}\text{Pu}(\text{IV})$ nitrate, polymeric, inhal.	1.5	—	~180	BULDAKOV et al (1972), NIFATOV et al (1972)
^{144}Ce citrate, i.v.	~110	30	—	{ FRITZ et al. (1966)
	50	1200	—	
$^{144}\text{CeCl}_3$, inhal.	370 ^b	30	—	{ MCCLELLAN et al. (1970)
	120 ^b	~1600	—	
^{90}Sr citrate, i.v.	100	1225	—	T. F. DOUGHERTY et al. (1972)
$^{90}\text{SrCl}_2$, inhal.	270 ^b	30	—	{ MCCLELLAN et al (1970)
	120 ^b	150	—	

^a i.v., intravenous; inhal., inhalation

^b Initial body burden

DBL 727 5350

Fig. 1. Absorption of chlorides or nitrates of Pu(III), Am(III), and Cm(III) intramuscularly injected into rats (shown as data points), and the mean absorption of varying masses of intramuscularly injected chlorides of several lanthanides (shown as curves). Data are presented as percent of administered dose remaining at the injection site; Absorption (%) = (100% - Injection site). References: $^{241}\text{AmCl}_3$, SCOTT et al. (1948a); $^{242}\text{CmCl}_3$, SCOTT et al. (1949); $^{239}\text{PuCl}_3$, SCOTT et al. (1948b); $^{241}\text{Am}(\text{NO}_3)_3$, LAFUMA et al. (1970) and NÉNOT et al. (1971b); $^{242}\text{Cm}(\text{NO}_3)_3$, NÉNOT et al. (1972); $^{242}\text{Cm}(\text{NO}_3)_3$ + La carrier, LAFUMA et al. (1970) and NÉNOT et al. (1971b, 1972).

DBL 727-5365

Fig. 2. Absorption of ^{241}Am (in an alkaline solution) from a puncture wound in the hand. Data of R. L. DOBSON (1955) and R. L. DOBSON, H. G. PARKER, M. C. WALES, and M. CHUPP (unpublished).

Fig. 3. Kinetic model of the deposition and clearance of inhaled particles from the respiratory tract. Deposition values were read from Fig. 11 of the ICRP Task Group report (ICRP, 1966) for an aerosol of $AMAD = 1 \mu m$ and a tidal volume of 1450 ml. Transfer coefficients (a-j) and transfer half-times ($T_a - T_j$) were taken from Table 4 of the above report for poorly soluble compounds (Class W).

Fig. 4. Distribution of $^{244}\text{CmCl}_3$ inhaled by dogs (AMAD = $1.6\ \mu\text{m}$, administered with a CsCl vector). Terminal slopes were determined using later data points (not shown). Data of MCCLELLAN et al. (1972).

Fig. 5. Distribution of $^{241}\text{AmCl}_3$ instilled in the lungs of rats. Initial lung burden = initial body burden corrected for prompt regurgitation of 23% of the administered dose. Terminal slopes were determined using later data points (not shown). Data of ZALIKIN et al. (1968).

Fig. 6. Disappearance of ^{241}Am from the circulation after intravenous injection in beagles, BRUENGER et al. (1969a) and STEVENS and BRUENGER (1972); lactating ewes, MCCLELLAN et al. (1962a, b); young rats, TURNER and TAYLOR (1968b); and cynomolgus monkeys, DURBIN et al. (1972c).

DBL 727-5356 R

Fig. 7. Clearance from the blood of the actinides, ^{241}Am and ^{249}Cf , as compared to the alkaline earths, ^{47}Ca and ^{89}Sr , after intravenous injection in beagles. ^{241}Am and ^{249}Cf from BRUENGER et al. (1969a) and STEVENS and BREUNGER (1972); ^{47}Ca from COLLINS et al. (1962); ^{89}Sr from SWIFT and PROSSER (1947).

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Fig. 8. Comparison of the blood clearance of the actinides, ^{241}Am or ^{244}Cm , the lanthanides, ^{144}Ce , $^{152,154}\text{Eu}$, and ^{160}Tb , and the alkaline earth, ^{45}Ca , after intravenous injection in the rat. ^{241}Am and ^{244}Cm from TURNER and TAYLOR (1968b); ^{144}Ce , $^{152,154}\text{Eu}$, and ^{160}Tb from DURBIN et al. (1955); ^{45}Ca from COPP et al. (1951).

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Fig. 9. Comparison of the blood clearance of the actinides, ^{241}Am and ^{244}Cm , the lanthanides, ^{144}Ce and ^{147}Pm , and the alkaline earth, ^{45}Ca , after intravenous injection in the lactating Suffolk ewe. Data from MCCLELLAN et al. (1962a, b, 1963).

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Fig. 10. Comparison of the deposition in the bone of rats of intravenously injected $^{241}\text{Am}(\text{NO}_3)_3$, solid triangle -▲, D. M. TAYLOR (1962); $^{241}\text{AmCl}_3$, solid diamond -◆, BELYAEV (1969); ^{144}Ce citrate, open circle - O, and $^{152,154}\text{Eu}$ citrate, open rectangle - □, DURBIN et al. (1955); ^{45}Ca citrate, open diamond - ◇, L. PALMER and E. PALMER (unpublished); $^{45}\text{Ca}(\text{NO}_3)_2$, inverted open triangle - ▽, D. M. TAYLOR (1962); ^{90}Sr citrate, open triangle - Δ, G. D. BARR and P. W. DURBIN (unpublished); and $^{239}\text{Pu(IV)}$ citrate, SCHUBERT et al. (1950) recalculated by DURBIN et al. (1972a).

DBL 727-5357

Fig. 11. Clearance of ^{241}Am from the blood or soft tissues plus extra-cellular fluid (ECF) and accumulation of ^{241}Am in liver and bone. Young male rats injected intravenously with $^{241}\text{AmCl}_3$; data of BELYAEV (1969) recalculated as described in text.

DBL 7110-6005

Fig. 12. Kinetic model of initial transport and deposition of trivalent elements.

DBL 727-5358

Fig. 13. Accumulation of ^{241}Am in the skeleton, liver, and kidneys of rats after intravenous injection of $^{241}\text{AmCl}_3$, (BELYAEV, 1969) or intraperitoneal injection of $^{241}\text{Am}(\text{NO}_3)_3$ (TSEVELEVA and YEROKHIN, 1969). Data are expressed as percent of the maximum uptake in each tissue.

Fig. 14. Gross autoradiographs of bones from female rats injected intramuscularly with $0.37 \mu\text{Ci/kg}$ of ^{241}Am citrate at 110 days of age.

Bones and autoradiographs were prepared as described by DURBIN et al. (1967) using Kodak NTA plates. $\times 7.5$.

- a. A central longitudinal section and mid-diaphyseal cross section of the femur of a rat killed 4 days after injection. Plate exposed 1556 days.
- b. The femur of a rat killed 95 days after injection. Plate exposed 1556 days.
- c. The femur of a rat killed 739 days after injection. The perimeter of the bone at death is shown as a broken white line. Plate exposed 1620 days.

Fig. 15. Gross autoradiographs of bones from female rats injected intramuscularly with $0.33 \mu\text{Ci/kg}$ of $^{249-252}\text{Cf}$ citrate at 136 days of age. See Fig. 14 for method of preparation of plates, which were exposed 2050 days. $\times 7.5$.

- a. A central longitudinal section and mid-diaphyseal cross section of the tibia of a rat killed 4 days after injection.
- b. The tibia of a rat killed 91 days after injection.
- c. A central longitudinal section of a vertebra (L1) of a rat killed 91 days after injection.

Fig. 16. Gross autoradiographs of ^{241}Am in bones of female cynomolgus monkeys. See Fig. 14 for preparation of plates, which were exposed 1400 days.

- a. Longitudinal and cross sections from the central one-third of the 5th rib of adult #42 (more than 6 years old, killed 8 days after an intravenous injection of $0.56 \mu\text{Ci/kg}$ of ^{241}Am citrate). $\times 2$.
- b. A central section of a premolar of adult #8 (more than 6 years old, killed 8 days after an intramuscular injection of $0.56 \mu\text{Ci/kg}$ of ^{241}Am citrate). $\times 1.5$.
- c. A cross section of the calvarium of adolescent #41 (2.5 years old, killed 8 days after an intravenous injection of $0.56 \mu\text{Ci/kg}$ of ^{241}Am citrate). $\times 1.75$.
- d. A cross section of the mid-diaphysis of the humerus of adolescent #41 described in Fig. 16c. $\times 2$.
- e. A cross section of the calvarium of adult #42 described in Fig. 16a. $\times 1.75$.
- f. A cross section of the mid-diaphysis of the humerus of adult #8 described in Fig. 16b. $\times 2$.

Fig. 17. Gross autoradiographs of ^{241}Am in bones of female cynomolgus monkeys. See Fig. 14 for method of preparation of plates, which were exposed 1400 days. $\times 2.25$.

- a. A central longitudinal section of the proximal humerus of adolescent #41 described in Fig. 16c.
- b. A central longitudinal section of the proximal humerus of adult #8 described in Fig. 16b.
- c. A central cross section of vertebra (L1) of adolescent #41 described in Fig. 16c.
- d. A central cross section of vertebra (L1) of adult #42 described in Fig. 16a.

Fig. 18. Microautoradiographs of ^{241}Am in undecalcified sections of bones of female cynomolgus monkeys. Bone sections and autoradiographs were prepared as described by J. S. ARNOLD and JEE (1954) and J. S. ARNOLD (1954) using Kodak NTA liquid emulsion, which was exposed 62 days. $\times 200$.

- a. The growth cartilage of the proximal humerus of adolescent # 41 described in Fig. 16c. Americium-241 is associated with the spicules of recently calcified cartilage.
- b. A trabeculus in the vertebral body (L1) of adult # 45 (more than 6 years old, killed 48 weeks after an intramuscular injection of $0.44 \mu\text{Ci/kg}$ of ^{241}Am citrate). Americium-241 is shown on a surface unaltered during the 48-week postinjection interval.
- c. The metaphyseal cortex of the proximal humerus of adult # 45 described in Fig. 18b. New bone has been laid down during the 48-week postinjection interval.
- d. The cortex of vertebra (L1) of adult # 45 described in Fig. 18b. Labeled haversian canal surface has been filled with new bone during the 48-week postinjection interval.

Fig. 19. Retention of ^{241}Am in the femora and whole edentate skeleton of adult female rats, DURBIN et al. (1967, 1972c) and in the femora of young male rats, D. M. TAYLOR et al. (1961).

DBL 727-5367

Fig. 20. Retention of ^{241}Am in the whole body of adult monkeys after intravenous or intramuscular injection of 0.44 to 0.87 $\mu\text{Ci/kg}$ of ^{241}Am citrate. Retention was calculated by subtraction of summed excretion from 100%. Data of DURBIN et al. (1972c).

DBL 727-5361

Fig. 21. Retention of ^{241}Am in the skeleton, liver, and residual soft tissues of adult cynomolgus monkeys after intravenous or intramuscular injection of 0.44 to 0.87 $\mu\text{Ci/kg}$ of ^{241}Am citrate. Solid symbols represent pairs of monkeys, and open symbols, single animals. Data of DÜRBIN et al. (1972c).

DBL 727-5359

Fig. 22. Retention of ^{241}Am or $^{249-252}\text{Cf}$ in the whole bodies of adult female rats after intramuscular injection of $0.37 \mu\text{Ci/kg}$ of ^{241}Am citrate or $0.33 \mu\text{Ci/kg}$ of $^{249-252}\text{Cf}$ citrate. Retention was calculated by subtraction of summed excreta from 100%. Data of DURBIN et al. (1967, 1972c,d).

Fig. 23. Microautoradiographs of ^{241}Am in liver or kidneys of monkeys or rats. Autoradiographs were stained with hematoxylin-eosin and prepared as described by BOYD (1955) using Kodak NTA plates. $\times 200$.

- a. In the liver of adult monkey # 8, described in Fig. 16b, the ^{241}Am is more concentrated near the central veins 8 days after injection. Plate exposed 540 days.
- b. In the kidney of adult monkey # 45, described in Fig. 18b, single tracks and track clusters are associated with brown pigment in renal tubules and intertubular connective tissue 336 days after injection. Plate exposed 887 days.
- c. In the kidney of adult monkey # 55, (more than 6 years old, killed 21 days after intramuscular injection of $0.71 \mu\text{Ci/kg}$ of ^{241}Am citrate). Aggregates of alpha tracks can be seen in the glomerular tuft. Plate exposed 545 days.
- d. In the kidney of a rat (described in Fig. 14) killed 712 days post injection, ^{241}Am alpha tracks emanate from the surface of a renal stone. Plate exposed 274 days.

Fig. 24. Americium-241 in the liver of adult monkeys. Gross autoradiographs were prepared as described by BOYD (1955). $\times 5$.

Note: The gross autoradiographs shown in Figs. 24, 25, 28, and 29 were prepared over a 12-year interval. During that time Kodak medical x-ray film was changed and Dupont film became available. For visual comparisons Kodak (red-base) sensitivity equals 2.5, Kodak (green-base) sensitivity equals 5, and Dupont Cronar (low graininess) sensitivity equals 1.

- a. Adult # 7 (killed 1 days after intramuscular injection of $0.67 \mu\text{Ci/kg}$ of ^{241}Am citrate). Kodak single-coated (green-base) medical x-ray film was exposed 369 days.
- b. Adult # 73 (killed 168 days after intravenous injection of $0.69 \mu\text{Ci/kg}$ of ^{241}Am citrate). Dupont Cronar single-coated medical x-ray film was exposed 766 days.
- c. Adult # 54, (killed 938 days after intramuscular injection of $0.69 \mu\text{Ci/kg}$ of ^{241}Am citrate). Kodak single-coated (red base) x-ray film was exposed 1633 days.

Fig. 25. Gross autoradiographs of ^{241}Am in the livers of rats described in Fig. 14. Gross autoradiographs were prepared as described in Fig. 24. $\times 8$.

- a. At 1 day after injection random foci of high concentration are superimposed on a generally uniform distribution. Kodak single-coated (green-base) medical x-ray film was exposed 383 days.
- b. At 15 days after injection intense foci are no longer present, and slightly higher concentrations near central veins persist. Kodak single-coated (red-base) medical x-ray film was exposed 1939 days.
- c. At 32 days after injection radioactivity is barely detectable above film background. Kodak single-coated (red-base) medical x-ray film was exposed 1939 days.

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DBL 728 5442

Fig. 26. Retention of ^{241}Am in the liver of the rat. Data of DURBIN et al. (1967, 1972c). Each point represents the mean for five or more rats; bars represent the S. D.

Fig. 27. Kinetic model of the metabolism of trivalent actinide elements in mammals modified from DURBIN et al. (1967). The incisor teeth compartment is present only in rodents.

Fig. 28. Americium-241 in the kidneys of rats described in Fig. 14.

Gross autoradiographs were prepared as described in Fig. 24.

Kodak single-coated (red-base) medical x-ray film was exposed for 1957 days. $\times 5$.

- a. Four days after injection the ^{241}Am is localized in the cortex and on renal stones in the medulla.
- b. At 46 days after injection, cortical localization is much reduced, but labeling of renal stones persists.

Fig. 29. Americium-241 in the kidneys of monkeys. The gross autoradiographs were prepared as described in Fig. 24; Kodak single-coated (red-base) medical x-ray film was exposed for 805 days.

× 3.

- a. Adolescent #41, described in Fig. 16c, killed 8 days after injection. The heaviest concentrations of ^{241}Am are in the medullary rays and the papillae.
- b. Adult monkey #81 (more than 6 years old, killed 81 days after intramuscular injection of $0.56 \mu\text{Ci/kg}$ of ^{241}Am citrate). The cortical deposit is greatly reduced. Concentration in papillae is still high, and some of this deposit is associated with large numbers of small intertubular concretions.

DBL 7210-5510

Fig. 30. Retention of ^{241}Am in kidneys of rat and monkey. Female rats, 110-days old, were injected intramuscularly with $0.37 \mu\text{Ci/kg}$ of ^{241}Am citrate: solid circles (●) represent mean kidney retention of groups of 5 or more rats. Adult female cynomolgus monkeys were injected intravenously or intramuscularly with ^{241}Am citrate, 0.44 to $0.87 \mu\text{Ci/kg}$: solid triangles (▲) represent pairs of monkeys, open triangles (Δ) represent individual monkeys. Data of DURBIN et al. (1972c).

DBL 7210-5507

Fig. 31. The influence of experimental conditions on the retention of ^{241}Am by the rat kidney: $0.37 \mu\text{Ci/kg}$ ^{241}Am citrate, adults, DURBIN et al. (1969, 1972c); 5 to $10 \mu\text{Ci/kg}$ $^{241}\text{AmCl}_3$, adults, ZALIKIN et al. (1968); $3.6 \mu\text{Ci/kg}$ $^{241}\text{AmCl}_3$, adults, SCOTT et al. (1948a); $30 \mu\text{Ci/kg}$ $^{241}\text{AmCl}_3$, growing rats, LANGHAM and CARTER (1951).

DBL 7210-5508

Fig. 32. Retention of trivalent actinide elements in rat kidney: ^{241}Am citrate, DURBIN et al. (1967, 1972c); $^{242}\text{CmCl}_3$, SCOTT et al. (1949); ^{252}Cf citrate, MEWHINNEY et al. (1972); $^{253}\text{EsCl}_3$, HUNGATE et al. (1972), and BALLOU and MORROW (1972).

Fig. 33. Retention of ^{241}Am in the blood, muscle, and pelt (residual soft tissues) of the rat. Data of DURBIN et al. (1972c).

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DBL 7210-5506

Fig. 34. Early excretion rates of trivalent actinide elements in the urine of the adult rat: ^{241}Am and $^{249-252}\text{Cf}$, DURBIN et al. (1967, 1972c, d); ^{242}Cm , SCOTT et al. (1949); ^{249}Bk , HUNGATE et al. (1972); ^{253}Es , V. H. SMITH (1972b). See also Table 26.

DBL 7210-5505

Fig. 35. Early rates of excretion of trivalent actinide elements in the feces of the adult rat. Data sources are the same as given in Fig. 34.

DBL 7210-5504

Fig. 36. Long-term rates of excretion of trivalent actinide elements in the urine of the adult rat: ^{241}Am citrate, DURBIN et al. (1967, 1972c); $^{241}\text{AmCl}_3$, intramuscular injection, SCOTT et al. (1948a); $^{241}\text{AmCl}_3$, intravenous injection, ZALIKIN et al. (1968); $^{242}\text{CmCl}_3$, SCOTT et al. (1949); $^{249-252}\text{Cf}$ citrate, DURBIN et al. (1972d). See also Table 26.

DBL 7210-5503

Fig. 37. Long-term rates of excretion of trivalent actinide elements in the feces of adult rats. Data sources are the same as given in Fig. 36.

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DBL 727-5364

Fig. 38. Early excretion rates (urine and feces) and plasma content of ²⁴¹Am in cynomolgus monkey # 72. Data of DURBIN et al. (1972b, c).

See also Tables 27 and 28.

DBL 7210-5509

Fig. 39. Early excretion rates (urine and feces) of ²⁴¹Am in baboon.
Data of ROSEN et al. (1972). See also Tables 27 and 28.

DBL 727 5349

Fig. 40. Long-term rates of excretion of ^{241}Am in urine and feces of cynomolgus monkey #75. Data of DURBIN et al. (1972b,c). See also Tables 27 and 28.

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TECHNICAL INFORMATION DIVISION
LAWRENCE BERKELEY LABORATORY
UNIVERSITY OF CALIFORNIA
BERKELEY, CALIFORNIA 94720