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SOME ASPECTS OF THE BIOINORGANIC CHEMISTRY OF THE ACTINIDES

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CONTENTS

A. INTRODUCTION

All the isotopes of the actinide elements are radioactive. The radioactive properties of some of the principal transuranic isotopes produced in the nuclear power programme are presented in Table 1. The half-lives of these isotopes range from 1.405×10^{10} years for ^{232}Th to 0.38 milliseconds for ^{258}Fm. The mode of radioactive disintegration of the nucleus varies from electron capture in neutron deficient isotopes to β-decay in neutron-excess isotopes. As the atomic number of the element increases, α-decay and spontaneous fission become more important.

The chemistry of the actinides has attracted only a little interest in those

TABLE 1

Radioactive properties of some actinide isotopes

Isotope	Half-life	Mode of formation	Specific activity (Ci g^{-1})	Principal mode of decay	Energy (MeV)	M.P.B.B. [a] (μCi)
^{227}Ac	21.8y	$^{231}Pa \xrightarrow{\alpha} {}^{227}Ac$	0.8×10^{2}	α, β	α 4.95 (1.4%) β 0.04 (90%)	0.1
^{228}Th	1.91y	$^{228}Ac \xrightarrow{\beta} {}^{228}Th$	8.4×10^{2}	α	5.4 (100%)	0.09
^{230}Th	7.6×10^{4}y	$^{234}U \xrightarrow{\alpha} {}^{230}Th$	0.02	α	4.6 (100%)	0.4
^{231}Pa	3.25×10^{4}y	$^{231}Th \xrightarrow{\beta} {}^{231}Pa$	0.05	α	5.041 (c.100%)	0.1
^{233}U	1.59×10^{5}y	Naturally occurring	0.01	α	4.8 (98%)	0.07
^{238}U	4.47×10^{4}y	Naturally occurring		α	4.196 (c.100%)	0.5
^{237}Np	2.1×10^{6}	$^{238}U(n,2n)^{237}U \xrightarrow[6.7d]{\beta} {}^{237}Np$	6.9×10^{4}	α	4.79 4.77	0.06
^{238}Pu	86.4	$^{237}Np(n,\gamma)^{238}Pu$	17	α	5.49 (72%) 5.45 (28%)	0.04
^{239}Pu	24.4×10^{3}	$^{238}U(n,\gamma)^{239}U \xrightarrow[23m]{\beta} {}^{239}Np \xrightarrow[2.3d]{\beta} {}^{239}Pu$	6.2×10^{-2}	α	5.147 (73.3%) 5.134 (15.1%) 5.094 (11.5%)	0.04
^{240}Pu	6.6×10^{3}	$^{239}Pu(n,\gamma)^{240}Pu$; $^{239}Np(n,\gamma)^{240}Np \xrightarrow[67m]{\beta} {}^{240}Pu$	0.23	α	5.159 (75%) 5.115 (25%)	0.04
^{241}Pu	13.1	$^{240}Pu(n,\gamma)^{241}Pu$	1.10×10^{2}	β	0.022 (99.99%)	0.9
^{242}Pu	5.8×10^{5}	$^{241}Pu(n,\gamma)^{242}Pu$	3.9×10^{-3}	α	4.903 (76%) 4.863 (24%)	0.05
^{241}Am	458	$^{240}Pu(n,\gamma)^{241}Pu$; $^{241}Pu \xrightarrow{\beta} {}^{241}Am$	3.2	α	5.486 (86%) 5.443 (12.7%) 5.389 (1.3%)	0.05
^{242}Cm	0.45	$^{241}Am(n,\gamma)^{242}Am \xrightarrow[16h]{\beta} {}^{242}Cm$	3.3×10^{3}	α	6.12 (74%) 6.07 (26%)	0.05
^{244}Cm	17.6	$^{243}Pu \xrightarrow[5h]{\beta} {}^{243}Am(n,\gamma)^{244}Am \xrightarrow[10h]{\beta} {}^{244}Cm$	8.2×10	α	5.81 (c.100%) 5.31	0.1

[a] Maximum permissible body burden, International Commission on Radiological Protection, Publication 2, Pergamon, Oxford, 1959.

scientists who work outside the atomic energy industry. Quite obviously most of the interest in the chemistry of the actinides has been directed at uranium and plutonium, and to a lesser extent americium and curium. However, investigations into the chemistry and behaviour of americium and curium in the body have grown as these two elements will be produced in increasing quantities in fast-breeder nuclear reactors which use plutonium-239 as the fissionable-fuel element. Plutonium, americium and curium are regarded as major hazards to health as they emit energetic α-particles. This hazard to health has resulted in these elements becoming the subject of much research [1—4].

B. BASIC CHEMISTRY OF THE ACTINIDES

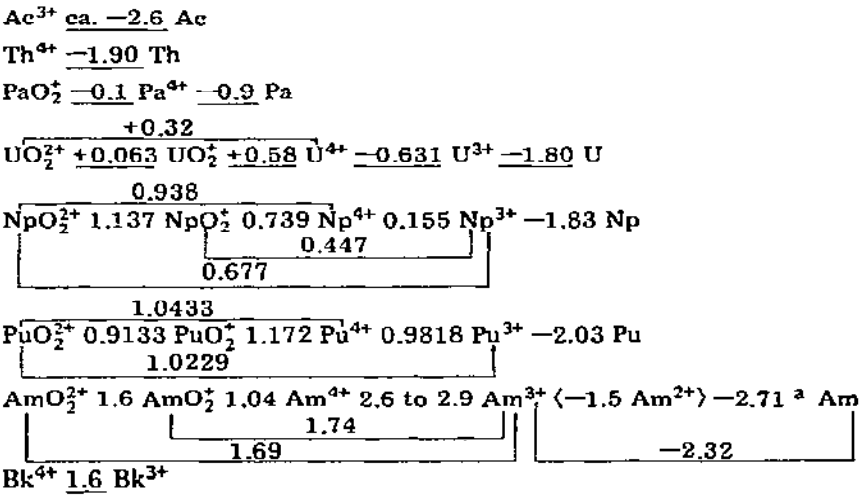
The chemistry of actinium and the following 14 elements, which are collectively identified as the actinides, is in many ways an uncharted area. Even though the chemistry of plutonium (element 94 in the periodic table) has been the subject of extensive research, it still remains an element surrounded by much chemical controversy.

With the discovery of the first few transuranium elements, neptunium, plutonium, americium and curium, it was realized that these elements contained electrons in the 5 *f* shell. The elements 57—71 (lanthanum and the following 14 elements in which there is a completion of the 4 *f* electron shell) possess chemical properties which might well be echoed by the actinides. However, this is an oversimplification. In the lanthanides the binding energies of the 4 *f* electrons are much greater than the binding energies of the 5 *f* electrons in the actinides. As the binding energies of the electrons in the 5 *f* shells are lower, they are more readily removed and thus the actinides possess several oxidation states (Tables 2 and 3). It is only towards the end of the actinide series that the elements start to exhibit chemical properties which resemble the corresponding lanthanides. Elements 57—71 exhibit the well-known "lanthanide contraction", typified by a 25% decrease in crystal radii from La^{3+} to Lu^{3+} which is somewhat greater than that observed in the actinide series and considerably greater than the corresponding contraction which takes place as the *d* shell is filled.

In general there is, however, broad periodicity between the lanthanides and the actinides, as evidenced by the similarity in reactions of cations of the same charge with specific reagents. There are, however, few instances of well-defined periodicity between specific lanthanide and actinide cations. Perhaps the best example of periodicity is to be found in the chromatographic properties of the tripositive cations, a feature which will be discussed later. Like the lanthanide ions, the actinide ions are coloured in those oxidation states in which one or more single *f* electrons are present. The chemical properties of the actinide cations are due, as are those of the lanthanides, to the high polarizing power of the cations which arises from the poor screening of the nuclear charge by the *f* electrons.

TABLE 2

Formal reduction potentials (V) of uranium, neptunium, plutonium and americium for 1 M perchloric acid solutions at 25°C (F.A. Cotton and G. Wilkinson, Advanced Inorganic Chemistry, Interscience Publishers, 1972)



[a] Estimated.

The heaviest naturally occurring elements, thorium, protactinium and uranium, lie in corresponding positions just below the 6th period transition elements, hafnium, tantalum and tungsten. These three elements which are in the process of filling up the 5 *d* electron shell are similar in their chemical properties to the corresponding transition elements, zirconium, niobium and molybdenum, which are in the process of filling up the 4 *d* shell. To some extent thorium and proactinium show some resemblance in chemical proper-

TABLE 3

Ionic radii (nm) of some actinides and lanthanides

No. of 4*f* or 5*f* electrons	Ionic radius		
	Actinide series		Lanthanide series
0	Ac 0.111	Th 0.095	La 0.105
1	Th 0.108	Pa 0.091	Ce 0.103
2	Pa 0.106	U 0.089	Pr 0.101
3	U 0.104	Np 0.0880	Nd 0.099
4	Np 0.102	Pu 0.090	Pm 0.095
5	Pu 0.101	Am 0.0885	Sm 0.096
6	Am 0.989	Cm 0.088	Eu 0.095
7	Cm 0.982		Gd 0.094

ties to these 4 *d* and 5 *d* elements. However, the resemblance of uranium to tungsten and molybdenum is much weaker. The reduction potentials of actinides with multi-oxidation states are presented in Table 2. The ionic radii of some actinides and lanthanides are presented in Table 3.

(i) Actinium (element 89)

Actinium exists in nature as a constituent of uranium ores (one ton of pitchblende yields 0.15 mg of actinium) as it is an equilibrium decay product of ^{235}U. The chemistry of actinium resembles that of the lanthanides although the hydroxide is more basic than lanthanum hydroxide and is only partially precipitated by ammonium hydroxide. Actinium hydroxide readily dissolves in ammonium salts.

(ii) Thorium (element 90)

Thorium is widely distributed in nature. The principal ore is monazite, a complex phosphate which contains uranium, cerium and other lanthanides. The 4+ oxidation state is the principal state for thorium, unlike its lanthanide homologue cerium, which can exist in the 3+ and 4+ oxidation states. Thorium iodate, $Th(IO_3)_4$, does resemble ceric iodate in being sparingly soluble in water. In many respects the chemical properties of thorium resemble those of hafnium just as the chemical properties of protactinium resemble those of tantalum. However, unlike hafnium dioxide, thorium dioxide possesses no acidic properties.

The thorium ion, Th^{4+}, does not hydrolyze quite as readily as other 4+ ions. The hydrolysis of Th^{4+} proceeds rapidly in aqueous solution at pH > 3. The hydrolyzed species are complex and dependent upon the conditions of pH, concentration and the anions present. In perchlorate solutions the main ions appear to be $Th(OH)^{3+}$, $Th(OH)_2^{3+}$, $Th_2(OH)_2^{6+}$, $Th_4(OH)_8^{8+}$ and $Th_6(OH)_{15}^{9+}$. The metal atoms are linked by hydroxo or oxo bridges. In crystals the hydroxide chain-like structures have been identified as $Th(OH)_2^{2+}$ which is the repeating unit. In solution the polymers may possess a similar structure plus additional cross-linking. The high charge on the thorium cation makes it susceptible to complex formation.

(iii) Protactinium (element 91)

In equilibrium the content of protactinium-231 in pitchblende is about 3.4×10^{-5} weight percent of the uranium content. It arises as a decay product of uranium-235 in the decay sequence

$$^{235}U \xrightarrow[\alpha]{7 \times 10^8\,y} {}^{231}Th \xrightarrow[25.6\,h]{\beta^-} {}^{231}Pa \xrightarrow[\alpha]{3.24 \times 10^4\,y} {}^{227}Ac$$

Protactinium has been investigated quite extensively in the last few years as

interest in the development of the thorium-based nuclear reactor has continued to grow. In 1960 130 g of protactinium was recovered from an etheral sludge produced during uranium processing at Springfields and this has remained the principal source of the element [5].

Mendeleev predicted in 1872 that the missing element "eka-tantalum", atomic number 91, would have an atomic weight of around 235 and that it would resemble niobium and tantalum in chemical properties. In the 5+ oxidation state protactinium resembles tantalum in its general inert character. However, Pa_2O_5 is more basic than Ta_2O_5 and the freshly precipitated oxide will dissolve in sulphuric acid, probably with the formation of $Pa_2O_5^+$. Protactinium pentoxide dissolves readily in hydrofluoric acid but is insoluble in alkalis.

In addition to existing in the 5+ oxidation state protactinium can exist in the unstable 4+ oxidation state. In the 4+ state it is unstable and readily oxidized by oxygen in acid to the 5+ oxidation state. The tetrafluoride is insoluble in acid solutions and thus resembles the thorium and lanthanum fluorides.

The aqueous chemistry of protactinium is of major interest in any discussion of the biochemical properties of the element for as will become more evident later there are quite major differences in the behaviour in the body of protactinium and elements such as thorium and plutonium. Most authors maintain that the presence of Pa^{5+} in solution is very unlikely although Elson [6] has suggested that it may exist in concentrated perchlorate solutions. Mikhailov [7] has estimated that the first hydrolysis constants of the ion $Pa^5 \cdot aq$ to be $10^{3\pm1}$. It is unlikely, therefore, that the ion Pa^{5+} can be present in significant amounts. The studies of Guillaumont and co-workers [8–10] indicate that the species $Pa(OH)_4^+$, $PaO(OH)_2^+$ and PaO_2^+ will exist in perchloric acid solutions (ionic strength, $\mu = 3$) in the range 1×10^{-5} to 3.2×10^{-2} N whereas in the range 1–3 N the species will be the doubly charged cations $Pa(OH)^{2+}$ or $PaO(OH)^{2+}$. However, Suzuki and Inoue [11] believe that both singly and doubly charged species will exist in 10^{-7} M Pa in 0.30–0.2 N perchloric acid solutions, whereas Welch [12] has indicated that PaO_2^+ will exist in 0.1–3.0 N perchloric acid.

The polymerisation of protactinium in mineral acids depends on both the hydrogen ion concentration and the concentration of the element. In freshly prepared solutions of protactinium (10^{-12}–10^{-5} M) in 1 N perchloric acid the polymeric content is probably insignificant [8]. In dilute acid solutions the species which undergoes polymerisation is believed to be $Pa(OH)_4^+$. In mineral acid solutions other than perchloric acid protactinium is present in complex forms. In 0.35–0.5 N HF protactinium is present as PaF_7^{2-} or $PaOF_5^{2-}$ while in 10–12 N HF the singly charged PaF_6^- exists. In very dilute hydrofluoric acid solutions (10^{-8}–10^{-6} N) the species are believed to be $Pa(OH)_2F^{2+}$, $Pa(OH)_2F_2^+$ and $Pa(OH)_2F_3$ [9,13,14]. In hydrochloric acid solutions the hydrolysis and polymerisation are less than in nitric acid or perchloric acid solutions. Casey and Maddock [15] studied the extraction, ion

exchange and absorption spectra of protactinium in HCl solutions and concluded that the element existed as hydroxychloride and chloride complex ions which resembled the analogous niobium ions. In nitric acid solutions protactinium exists as similar nitrato hydroxo species. In dilute acid solutions protactinium is believed to be present as hydroxo ions such as $Pa(OH)_4^+$.

Protactinium(V) forms stable complexes with the following organic acids: lactic, tartaric, citric and oxalic. In all cases these are more stable than the corresponding complexes with U(V), Np(V) and Pu(V). Protactinium tartrates are amongst the most stable of protactinium complexes; the hydroxide is not precipitated from tartrate solutions even at high pH although it precipitates at pH 4—7 from oxalate solutions and at pH 12 from citrate solutions. The protactinium complexes can be arranged in the following order of stability to alkalis: tartrates > citrates > oxalates [16]. This is also the order of stability for niobium, tantalum, zirconium, thorium and titanium complexes.

(iv) Uranium (element 92)

While thorium and protactinium resemble hafnium and tantalum there is no continuation of such similarities between tungsten, a semi-noble element, and uranium, a highly electropositive element. The lower oxidation states of tungsten are stable only in the form of complex ions which tend to complete the 5*d*, 6*s*, 6*p* shells, such as $W(CN)_8^{4-}$; in contrast the 3+ and 4+ states of uranium exist in aqueous solution as the simple ions.

The 2+ state of uranium is highly unstable while the 3+ state which is stable as solids, such as UF_3, reduces water with the evolution of hydrogen. The 5+ oxidation state is similarly of no consequence in this review as it disproportionates to the 4+ and 6+ states. The ions UO_2^{2+} and U^{4+} are the important species in the aqueous chemistry of uranium. It should be noted, however, that very few of the compounds produced in the chemical processing of uranium for nuclear fuel are in the 4+ state. The chemistry of the 4+ state is similar to that of Pu(IV) and Th(IV); many of the 4+ compounds are insoluble.

The hexahalides UF_6 and UCl_6 react with water to form UO_2F_2 and HF and UO_2Cl_2 and HCl. The non-volatile solid tetrafluoride is insoluble in water but is readily soluble in solutions of oxidising agents. In comparison the tetrachloride is soluble in water and polar organic solvents. In aqueous solutions of UO_2^{2+} and U^{4+} complex ions of the form UCl^{3+}, $U(SO_4)_2$, UO_2Cl^+, $UO_2(SO_4)_2^{2-}$ and $[UNO_3(H_2O)_4]^{3+}$ are formed. In concentrated nitric acid it appears that $[U(NO_3)_6]^{2-}$ can be formed and isolated by precipitation of the caesium salt. Complex ions are also formed with citrate and the anions of other organic acids.

The hydrated oxide, $UO_2 \cdot 2\,H_2O$, is precipitated when alkali is added to a uranous solution. The main hydrolysed species of UO_2^{2+} at 25° C are UO_2OH^+, $(UO_2)_2OH_2^{2+}$ and $(UO_2)_3(OH)_5^+$; however the system is complex and the species present depend on the composition of the medium. These uranyl

species hydrolyse at high temperatures to UO_3 which is readily soluble in UO_2^{2+} solutions as a result of the formation of UO_2OH^+ and polymerised hydroxo-bridged species. In aqueous solutions uranium salts exhibit acidic properties as a result of hydrolysis which increases in the order $U^{3+} > UO_2^{2+} > U^{4+}$.

(v) Neptunium (element 93)

Neptunium does not occur in nature to any appreciable extent. However, just as plutonium is present in uranium ores neptunium, in the form of the isotope ^{237}Np, can be found in uranium ores. This isotope is formed by the action of stray neutrons on ^{238}U as a result of the nuclear reactions $^{238}U \xrightarrow{n,2n} {}^{237}U \xrightarrow{\beta^-} {}^{237}Np$. The only practical source of this element is through the production of the isotope ^{237}Np in nuclear power stations.

The chemistry of neptunium differs from that of uranium in that the 3+ and 5+ as well as the 4+ and 6+ states are stable in aqueous solutions. Neptunium is quite electropositive and is readily oxidised to the 3+ state which is rapidly oxidised by air to Np^{4+}. The Np^{3+}—Np^{4+} couple is, however, reversible. The neptunium 3+ state tends to be moderately stable in solution and gives a purple colour to solutions; it resembles La^{3+} salts in solubility properties. The 4+ state is similar to the 4+ states of cerium and thorium in most of the solubility relationships.

Np^{4+} does not undergo ready air oxidation to NpO_2^+ but is slowly oxidised by nitric acid. Unlike the Np^{3+}—Np^{4+} couple the Np^{4+}—NpO_2^+ couple is not readily reversed since it requires the breaking of the Np—O bonds whereas the NpO_2^+—NpO_2^{2+} couple which involves the transfer of a single electron is reversible. The oxidation of NpO_2^+ (neptunol) to NpO_2^{2+} (neptunyl) requires a strong oxidising agent. The neptunyl ion is readily reduced to neptunol. NpO_2^{2+} resembles UO_2^{2+} and PuO_2^{2+}. The properties of these unique dioxo cations are discussed in greater detail on page 231.

(vi) Plutonium (element 94)

Plutonium has been detected in nature at levels of 10^{-12} in pitchblende from Zaire. More recently it has been identified in uranium ores found at the site of the fossil nuclear reactor at Oklo in Gabon. The plutonium is produced by neutron capture by ^{238}U.

Plutonium may well be unique in that four oxidation states can coexist in solution. Pu^{3+}, which in aqueous solution has a purple/violet colour, is more stable in aqueous solution than Np^{3+} whereas solutions of Pu^{4+} which have a green colour resemble those of Th^{4+} in solubility properties. As Pu^{4+} is the most commonly encountered ion of plutonium it has been studied extensively. Pu^{4+} hydrolyses rapidly to give the monomeric species $Pu(OH)^{3+}$ which undergoes rapid aggregation to form polymers. At a Pu^{4+} concentration, ranging from 0.4×10^{-4}—1.2×10^{-2} M in 0.1 M HNO_3, 40% of the plu-

tonium will polymerise within the first 30 min and within 60 min 55% will have polymerised. The polymers formed may reach molecular weights of 10^{10} daltons. The hydrolytic sequence is

$$Pu^{4+} + H_2O \rightleftharpoons Pu(OH)_2^{2+} + H^+$$

$$Pu(OH)_2^{2+} + n - 1\ Pu(OH)_2^{2+} \rightleftharpoons [Pu(OH)_2^{2+}]_n$$

$$[Pu(OH)_2^{2+}]_n + 2n\ H_2O \rightleftharpoons n[Pu(OH)_4] + 2n\ H^+$$

Katz and Seaborg [17] have shown the solubility product of the Pu(IV) hydroxide to be 7×10^{-56} and the solubility product of the readily oxidisable Pu(III) hydroxide to be 2×10^{-20}. As all the plutonium ions have a high charge and relatively small ionic radius they all exhibit a strong tendency to hydrolyse quite rapidly. The tendency to hydrolyse follows the sequence Pu(IV) > Pu(VI) > Pu(III) > Pu(V). However, this tendency to undergo hydrolysis can be suppressed by the addition of complexing agents to the solutions. Lindenbaum and Westfall [18] have shown that 92% of the plutonium solution (1.96×10^{-5} M) could be ultrafiltered in the presence of 3.4×10^{-2} M citrate over a pH range of 4.0—10.0.

In addition to suppressing polymerisation of plutonium, citrate facilitates the break-up of plutonium polymers [19]. The break-up of Pu(IV) colloids is slow and is dependent upon the age of the polymer. At 25°C in 5 M HNO_3 freshly prepared Pu(IV) polymers depolymerised with a half-life of 20 h whereas a polymer prepared under identical conditions and allowed to age had a half-life of 320 h. Unlike Pu^{4+}, there have been few investigations into the hydrolysis of PuO_2^{2+}, PuO_2^+ and Pu^{3+}. The hydrolysis constants of PuO_2^{2+} are considerably higher than those typical of divalent cations and show some similarities to those which typify tetravalent species. The hydrolysis of Pu^{3+} proceeds in a manner similar to that of Pu^{4+} whereas PuO_2^{2+} undergoes no hydrolysis up to pH 5. As Pu^{4+} is a small highly charged ion it can be expected to form complexes readily. The ability to form complexes decreases in the order: Pu(IV) > Pu(III) > Pu(VI) > Pu(V).

(vii) Americium (element 95)

An examination of the chemistry of americium indicates that its chemistry represents a transition from the multi-oxidation state chemistry of neptunium, uranium and plutonium to the chemistry of curium, where there begins actinide chemistry which resembles lanthanide chemistry. The 3+ oxidation state is highly stable in aqueous solution and is, unlike Np^{3+}, U^{3+} and Pu^{3+}, extremely difficult to oxidise or reduce. As Am^{3+} has a smaller ionic potential than the ions of plutonium it hydrolyses to a much lesser extent than the various plutonium ions. Am(III) exists in the ionic form up to pH 4.5 when hydrolysis commences, whereas colloidal species are formed at pH 7.0. The solubility of Am^{3+} resembles that of its homologue Eu^{3+} with respect to the solubility of its salts in water. In addition, americium

resembles europium in that there is evidence for the 2+ state.

Attempts to produce Am(IV) in aqueous solution were unsuccessful for a long time. The action of oxidants on Am(III) solutions in acids or alkali carbonates produces Am(V) or Am(VI), while the action of acids on americium dioxide results in Am(III) or Am(VI). It is now believed that Am(IV) is formed transiently and that it rapidly disproportionates into the ions of the 3+ and 5+ oxidation states

$$2\ Am^{4+} + 2\ H_2O = Am^{3+} + AmO_2^+ + 4\ H^+$$

This is followed by a very rapid reduction of the 4+ state by the 5+ state

$$Am^{4+} + AmO_2^+ = Am^{3+} + AmO_2^{2+}$$

One of the few americium(IV) compounds which can be isolated is the hydroxide which is prepared by oxidation of Am(III) to Am(IV) in alkaline medium in the presence of sodium hypochlorite.

Americium is the only transplutonium element that is oxidised to the 5+ state in aqueous solution. The species produced is the dioxo cation AmO_2^+ and which is very similar to the dioxo cations of neptunium and plutonium and much more stable than its uranium counterpart. Am(V) is unstable in acid medium and disproportionates into Am(III) and Am(VI)

$$3\ AmO_2^+ + 4\ H^+ = 2\ AmO_2^{2+} + Am^{3+} + 2\ H_2O$$

Americium can also exist in the 6+ state as the dioxo cation AmO_2^{2+} which also resembles the other dioxo cations of the actinides. Am(VI) is normally produced by oxidation of Am(III) in either nitric acid or perchloric acid with either ammonium persulphate or a ceric compound. It can also be produced by action of ozone on the 3+ state in an alkaline medium. As it is a strong oxidising agent it is readily reduced. There is no evidence for the existence of Am(VII).

Further complications in the chemistry of americium arise when the isotope ^{241}Am is used, as radiolytic reductions of Am(VI) to Am(V), together with radiolytic reduction of Am(V) to Am(IV) and Am(III), occur. This phenomenon is observed in the reactions with most transplutonium isotopes as most of the readily available isotopes are characterised by an exceptionally high specific activity (Table 1). The α-particles emitted by these elements are almost completely absorbed in aqueous solutions; consequently the chemical behaviour of these elements is influenced by the radiolytic products.

It is with americium that there is the commencement of some of the better examples of the periodicity of the elements. A good example of such periodicity is the existence of extremely sharp absorption lines of the lanthanide compounds and solid americium(III) compounds which can be identified at low temperatures.

(viii) Transamericium actinides

Curium (element 96) is the only transamericium element to be produced in any significant quantity by neutron irradiation of ^{239}Pu. Only 8 ng of ^{253}Es can be recovered after irradiating 100 mg of ^{239}Pu with an integral neutron flux of 2×10^{22} neutrons cm^{-2}. As such insignificant quantities of the higher actinides are produced in nuclear reactors most of the following account will be restricted to curium and berkelium (element 97).

The most stable oxidation state of the transamericium actinides is the 3+ state. However, for element 104 the 4+ state may be the more stable oxidation state while elements 101 and 102 (mendelevium and nobelium) can exist in the 2+ oxidation state. Berkelium is the only transplutonium element with a 4+ oxidation state which is so stable that it can be used in analytical operations. The potential of the pair Bk(IV)/Bk(III) has been estimated to be 1.6 V. The stability of the 4+ state for berkelium might be predicted as terbium, the lanthanide homologue of berkelium, can exist in the 4+ oxidation state. It is possible that the $4f^7$ and $5f^7$ configurations contribute towards the "special stability" of terbium(IV) and berkelium(IV). The 4+ oxidation state of curium exists in the dioxide and the unstable tetrafluoride. Additional examples of the periodicity of the lanthanides and actinides have been observed. Street et al. [20] have observed a large break between berkelium and curium in elution from an ion exchange resin. A similar break in elution occurs for terbium and gadolinium. Further similarities between the 3+ oxidation states of curium and gadolinium can be found. Both elements have no absorption bands in the visible spectrum but have strong absorption bands in the UV region.

(ix) The dioxo cations

As mentioned above the dioxo cations of 5+ and 6+ oxidation states of uranium, neptunium, plutonium and americium are a unique species of cation. Both groups are linear molecules which can survive a variety of chemical manipulations without perturbation of their essential feature. Both UO_2^{2+} and PuO_2^{2+} exhibit considerable stability in aqueous solution: the half-life for exchange with $H_2^{18}O$ is very long, although the isotopic exchange can be catalysed by the presence of reduced states or by self-reduction due to radiation effects. The bond strengths of MO_2^{2+} and resistances to reduction decrease in the order U > Np > Pu > Am. The stability of MO_2^{2+} is due to the combination of the appropriate *d* and *f* orbitals which produce one σ-bond plus one π-bond; in the dioxo cation UO_2^{2+} the molecular orbitals are filled while succeeding electrons pass into the non-bonding orbitals which results in an instability of MO_2^{2+} in the sequence U—Am. The instability of UO_2^+ is presumably due to the sensitivity of the energy of the 5 *f* electrons to total charge which will result in an overlap of electrons between the U and O atoms.

C. BIOINORGANIC ASPECTS OF THE ACTINIDES

From an examination of Fig. 1 it is apparent that both the lanthanides and actinides exhibit a wide variation in the distribution in the liver and skeleton of the rat. The variation in distribution of the lanthanides is presumably due to the variations in polarisability of the lanthanide ions. Durbin [21] has shown that Ac^{3+} (0.111 nm) is cleared from plasma at the same rate as Ce^{3+} (0.103 nm), ca. 20 min., while Tm^{3+} (0.0865 nm) remained in plasma for up to 24 h. However, the uptake of the actinides into the skeleton and liver of the rat is not quite so clear cut on account of the variation in stability of the various oxidation states of the actinides. The distribution of the actinides, and other elements, in the body is in part determined by the stability of the complex formed with constituents of the blood.

(i) Toxicity

Occasionally statements have been made in the popular scientific press that plutonium is not only toxic due to its radioactive properties but due also to its chemical properties. Although there are no experimental data available on the chemical toxicity of plutonium-239 it is possible to draw some conclusions as to its chemical toxicity from experimental data on

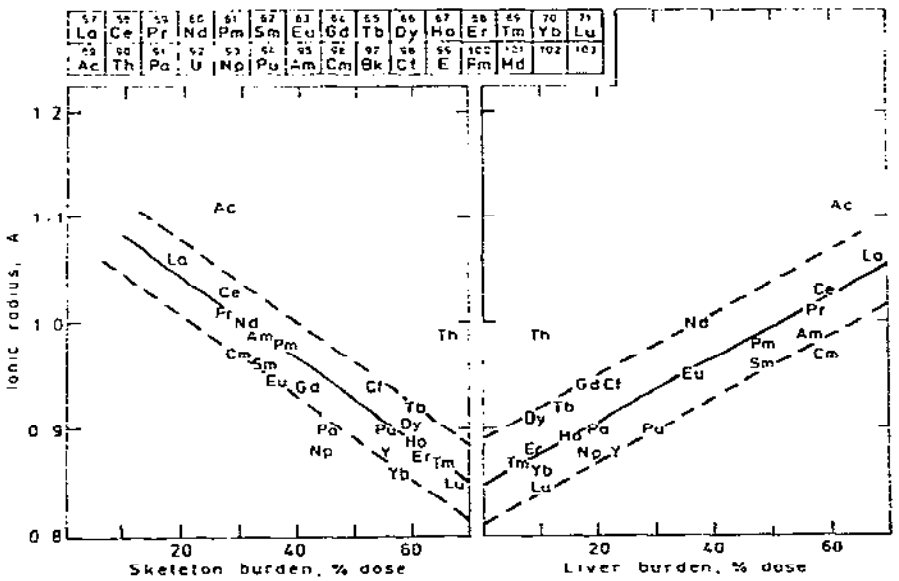


Fig. 1. Initial deposition of the lanthanide and actinide cations in the liver and skeleton of the rat and the influence of ionic radius on deposition. (Reproduced from P.W. Durbin, Health Phys., 8 (1962) 665 with the permission of the author and the Health Physics Society.)

related elements. It is a safe assumption that related elements with the same ionic radius and a similar charge will exhibit similar chemical behaviour in cells. Neptunium (ionic radius of 0.092 nm in the 4+ oxidation state) when injected intravenously into rats at 3 mg/kg has been shown to induce subacute changes in the liver [22]. As neptunium-237 has a half-life of 2.2×10^6 years it is possible to differentiate between the acute symptoms of chemical toxicity and the late effects of irradiation. It is presumed that the most stable oxidation state of plutonium in biological fluids is the 4+ state (ionic radius 0.09 nm) and it might be expected that plutonium would exhibit the same acute chemical toxicity in the liver. To achieve such a similar pathological change in man it would be necessary to administer intravenously around 200 mg of plutonium. This is approximately 330,000 times greater than the maximum permissible body burden for plutonium recommended by the International Commission on Radiological Protection in 1959 [23].

The acute toxicity of parenterally injected aqueous uranyl nitrate at 30 days ranges from 0.1 to 0.3 mg/kg in the rabbit and guinea pig to as much as 20 to 25 mg/kg in C_3H mice [24]. Most of the deaths occurred between day 14 and day 21. The variation in toxicity between the species has been attributed to differences of pH of the urine. As herbivores have a very acidic urine the clearance of the uranyl cation by dialysis from plasma, as its bicarbonate complex, is partially suppressed, thus favouring retention of the cation in the animal.

The mechanism of toxicity of uranium would appear, from Rothstein's work with yeasts [25], to be due to the suppression of glucose metabolism by interaction of UO_2^{2+} with the cell surface. The inhibition of glucose metabolism was found to be directly proportional to the amount of UO_2^{2+} present. The suppression of glucose metabolism could be lifted by either addition of excess phosphate to the system or by administration of some other complexing agent. This mechanism of cellular death by suppression of respiration of the cell is supported by the rate of onset and the nature of histological changes in the kidney. The only tissue damaged is the proximal kidney tubule [26].

(ii) Routes of entry into the body

As the actinides possess few or no chemical properties which are typical of elements which enter into biochemical processes it is not surprising that the gastrointestinal uptake of Pu^{4+}, Am^{3+} and Cm^{3+} is very insignificant (Table 4). However, gastrointestinal uptake of UO_2^{2+} and Np^{4+} is somewhat greater. Although uptake through the foodchain is perhaps one of the mechanisms by which the population might become exposed to the radiation hazard posed by these elements, it is of little concern in any consideration when computing the radiation dose received by the public. Such an assumption is substantiated by the findings of Bennett [27] who found that

TABLE 4

Actinide uptake from gastro-intestinal tract of rats [a]

Compound		% Absorption	
		Newborn	Adult
^{233}U(IV)	Nitrate	7	0.2
^{238}Pu(IV)	Nitrate	2	0.03
^{239}Pu(IV)	Nitrate	0.3	0.003
	Chloride		0.007
	Oxide		0.0001
^{241}Am(III)	Nitrate	9	0.07
	Chloride		0.03
	Oxide	0.5	0.01
^{244}Cm(III)	Nitrate	6	0.2
	Chloride		0.05
	Oxide (aged in H_2O)	2	0.1
	Oxide (fresh)	0.3	0.03

[a] After W.J. Bair, in Plutonium and other Transuranium Elements, WASH-1359, Washington D.C. USAEC, (1974).

most of the plutonium in the bodies of New York citizens was present in bronchio-thoracic lymph nodes. It should be noted, however, that iron-deficient subjects may exhibit increased uptake of plutonium from the gastro-intestinal tract. Ragan [28] has shown that iron-deficient mice take up more plutonium from the gastro-intestinal tract than control animals.

(iii) Transport of actinides in body fluids

Blood

Most of the research effort into the behaviour of the actinides in body fluids has been directed at identifying the chemical forms of plutonium, americium and curium in blood and urine. The major impetus in unravelling the mystery surrounding the fate of these three actinides in blood was a report by Boocock and Popplewell [29] who showed that plutonium injected intravenously into the rat was bound to serum transferrin. Similar procedures were subsequently used by Stover et al. [30] to demonstrate that plutonium was bound to transferrin in serum obtained from humans and from dogs. From the work of these two research groups it was established that plutonium was reversibly bound to transferrin and that it was bound to the same binding sites occupied by iron. The evidence that americium and curium are bound to transferrin is less conclusive. Bruenger et al. [31] and Chipperfield and Taylor [32] have shown that the binding of Am-(III) is very weak.

A knowledge of the binding site of transferrin might aid in understanding

the factors which contribute to cellular uptake of Pu^{4+}. Turner and Taylor [33] demonstrated the binding in vitro of Pu^{4+} with horse serum transferrin required the presence of bicarbonate. This anion is known to contribute to the binding of Fe^{3+} to transferrin.

Several spectroscopic investigations have demonstrated that transferrin—metal complexes possess at least one and perhaps even two protein—nitrogen ligands in the cation binding sites. The contribution of the various nitrogen-containing side-chains of the amino acids to the binding of cations has been investigated by using various chemicals as blocking groups. These studies have demonstrated that the amino groups of lysine and tryptophan are not components of the binding site. In human serum transferrin it would appear that two histidines may be located in each iron binding site although some studies indicate that there may be only 1.5 histidines while lactoferrin possesses only 0.5 histidines. Woodworth et al. [34] have used lanthanide shift reagents to demonstrate that the metal ion binding site consists of two tyrosyl residues and three histidyl residues. One residue is involved in binding the bicarbonate anion while the other binds the metal ion.

The investigations of Bruenger et al. [31] indicate that the sialic acid groups of transferrin are not involved in the binding of Pu^{4+} to transferrin. It is interesting that they demonstrated that destruction of the polysaccharide moiety inhibited the binding of Pu^{4+} by transferrin but did not inhibit the binding of Fe^{3+}. As Pu^{4+} interacts with transferrin and ferritin, the latter also appears to bind other 3+ transuranic species such as Cf^{3+} and Es^{3+}, an account of the interaction of these cations with the iron-transporting processes of the body is necessary. There is only limited interaction of these cations with the bioinorganic chemistry of iron. Presumably this failure of the actinide cations to enter into the biochemical reactions of iron is limited by the Fe^{3+}/Fe^{2+} cycle of oxidation and reduction. Further discrimination against the actinide cations in the bioinorganic chemistry of iron will arise with the ready reaction of sulphydryl groups with the ferrous and ferric ions. With the exception of dithiocarbamic acid the actinides do not form stable complexes with any sulphur-containing compounds. This absence of any interaction between the actinide cations and sulphydryl groups can be predicted from the "hard and soft acid and base" hypothesis which indicates that cations in a high oxidation state will not be complexed by weak bases such as sulphydryl groups.

As indicated above there have been very few investigations into the chemical form of the other actinides in blood. Neuman [35] and Dounce [24] reported that 50% of U(VI) in serum was associated with proteins and 50% with bicarbonate. The equilibrium of UO_2^{2+} between the protein and bicarbonate is established immediately. In the first few minutes after intravenous injection around 80—90% of the element remains ultrafilterable and flows out of the vascular compartment into extracellular fluid. As the level of the element in blood falls with its uptake by bone and its clearance through the kidney, the element diffuses out of the extracellular fluid. As the uranyl—

bicarbonate complex is filtered off by the glomeruli the equilibrium in the plasma is shifted from the protein to the bicarbonate until all the UO_2^{2+} not deposited in the bone has passed through the glomeruli. In marked contrast to UO_2^{2+}, U^{4+}, which is bound to proteins, is excreted very slowly [35].

Gel permeation chromatography studies indicate that protactinium(V) is associated with macroglobulins, high molecular weight lipoproteins and a low molecular weight component, possibly citrate, in rabbit serum [36].

Urine

Popplewell and his colleagues have reported that plutonium, americium and curium are excreted in urine as the citrate complexes [37,38]. It is reasonable to assume that these elements are dialysed through the kidneys as citrate complexes. There have been no other detailed investigations into the chemical form of the other actinides in urine. Presumably the other actinides in the 4+ and 3+ oxidation states will be excreted in urine as the citrate complexes and UO_2^{2+} as the bicarbonate complex.

Bile and other digestive fluids

Several investigations have demonstrated that plutonium, americium and curium are cleared from the liver through bile and that this is the principal source of these actinides in the faeces [39]. However, clearance of the actinides into faeces represents only a very small percentage of the activity in the animal. Durbin et al. [40] reported that bile 8 days after injection of plutonium contained about 0.021—0.048% of the injected activity. With the aid of gel permeation chromatography Popplewell and Smith demonstrated that ^{239}Pu was not present in bile in the citrate form but was present as the carbonate complex [41].

Ballou and Hess [42] have demonstrated that fluids secreted into the jejunum and duodenum contained around 40% of the ^{239}Pu in the gastrointestinal tract. It is known that other elements such as calcium and iron are present in digestive juices which are not of biliary origin [43,44].

Lymph fluid

The movement of plutonium from wound sites is known to involve transport via lymph. Gomez [45] has shown that plutonium movement occurs in both the acellular and cellular fractions of lymph. Schallberger et al. [46] have shown that the clearance of plutonium, applied to a simulated wound site in a dog, in the nitrate form was present in the acellular fraction as a transferrin complex, but was present in the cellular fraction when administered as the dioxide.

(iv) Uptake of actinides into liver

The variation in the distribution of some of the actinides in rat is presented in Table 5. The mechanism by which Pu, Am and Cm enter the liver is not understood and there have been very few attempts to understand it. Tay-

lor [47] has indicated that the evidence for pinocytotic uptake is tenuous as no significant amounts of transferrin-bound Pu(IV) can be demonstrated in liver cytoplasm 1 h after injection. The pinocytotic uptake of transferrin by the liver followed by regurgitation of the intact transferrin would be wasteful in terms of energy consumption and, similarly, the hydrolysis of the transferrin molecule in the cell would also be energetically expensive and must not be considered a possible reason for the absence of transferrin in liver cells. Indeed the evidence indicates that transferrin has a half-life of 150 days in serum [48].

As the actinide cations are hard acids it might be expected that these cations would complex with species such as phosphates. Barton [49], for instance, has demonstrated that Th^{4+} forms strong complexes with phospholipids. As La^{3+} [50] and Th^{4+} form strong complexes with phospholipids it must be expected that Pu^{4+}, Am^{3+} and Cm^{3+} will form complexes with phospholipids. If the cations of these three transuranics do form complexes with phospholipids it is possible that phospholipids could act as ionophores in the concentration of these elements in the liver.

Hemmaplardh et al. [51] have presented evidence that Fe^{3+} which is bound to transferrin is taken up into reticulocytes at receptor sites which comprise phospholipids. When the phospholipids are converted into lysophospholipids the transferrin is still taken up by the reticulocytes but Fe^{3+} does not enter the reticulocytes. It is possible, however, that the phospholipids are involved in more than merely providing a receptor site for transferrin, for it is possible that the phospholipids are acting as ionophores. Tyson et al. [52] have shown that phospholipids can act as ionophores, while Agate and Vishniac [53] have demonstrated that phospholipids complex Fe^{3+}. It is possible, however, that in the cell membrane there are other complexing agents present in cell membranes which could bind Fe^{3+} but which would discriminate against uptake of Pu^{4+}: it is quite conceivable that thiol-containing compounds regulate the transport of either Fe^{3+} or Fe^{2+}.

There is some indirect in vivo evidence that phospholipids may be involved in the concentration of Pu^{4+} by the liver. Bulman et al. [54] have found that thioacetamide intoxication, which is characterised by accumulation of acidic phospholipids in the liver, induces a 2.5-fold increase in Pu^{4+} uptake into the liver with a concomitant fall in uptake into bone. Bulman and Griffin [55] have shown that Pu^{4+}, Am^{3+} and Cm^{3+} can be extracted into heptane and butan-1-ol mixtures by phosphatidic acid, phosphatidylserine and cardiolipin. In further studies these authors demonstrated that protactinium uptake into the liver of the rat in the absence of thioacetamide intoxication did not exceed 2% but in thioacetamide-intoxicated animals the uptake was 35% [56]. As neither phosphatidylserine nor cardiolipin extracted Pa(V) (presumed to be present as PaO_2^+) into heptane and butan-1-ol, although phosphatidic acid did, these authors concluded that as phosphatidylserine, a component of normal liver cell membranes, cannot extract Pa(V) into organic solvents then this could be the reason why Pa(V) is not con-

TABLE 5

Distribution of intravenously administered uranium and some transuranics in rats (% of injected activity)

	^{233}U [b] monomeric	^{239}Pu [c]				^{241}Am [d]	
		monomeric		polymeric		monomeric	
time	4d	3d	2d	3d	0.12d	6d	43d
Liver	0.8	31	12	74	58	32	1.7
Kidneys	9.4					1.8	0.7
Spleen		0.3		1.7		0.08	0.09
Carcass [a]	32	53	61	12	14	26	26
Faeces	17	4.6	22.3	1.2	5.4		
Urine	32	1.5	2.1	0.6	0.8		

[a] Carcass is principally skeleton; all monomeric forms as citrates, except $^{252}CfCl_3$.
[b] J.E. Ballou and R.A. Gies, Pacific Northwest Laboratory, Ann. Rep. 1978, Pt.I, PNL-2850, 1979, p3.67.
[c] J.F. Markley, M.W. Rosenthal and A. Lindenbaum, Int. J. Radiat. Biol., 8 (1964) 271.
[d] M.W. Rosenthal and A. Lindenbaum, unpublished research cited in International Commission on Radiological Protection, ICRP 19, Pergamon, Oxford, 1972, p.18.

centrated in the liver. As phosphatidylserine can extract plutonium, americium and curium into the organic solvents it is possible that phosphatidylserine is acting as an ionophore in the transport of these three cations into the liver.

Several research groups have presented evidence that plutonium, americium and curium are taken up by lysosomes in the liver and that the activity ultimately becomes associated with the lysosome, One or two investigations, however, have shown that these actinides may become associated with other subcellular organelles. In studies with the rabbit, Taylor [57] showed that plutonium, administered as its nitrate, became associated with the mitochondria. Investigations by Popplewell and Taylor and co-workers [58] have shown that at 1 h after injection into the rat 40% of total liver ^{59}Fe and 64% of the plutonium were present in the soluble fraction (105,000 g supernatant). At 10 days the percentage recovery of these elements in this fraction had decreased to 12% and 5%. By means of differential centrifugation, as well as centrifugation through sucrose density gradients, it was shown that both isotopes became associated with lysosomal ferritin within 3 days. Further investigations by this group showed a similar pattern of uptake into the liver for ^{241}Am and ^{244}Cm when these isotopes were injected as their monomeric citrates [59]. After 1 h 52% of the total liver americium was associated with the 105,000 g supernatant and at 8 days only 4% of the activity was in the supernatant.

In studies with americium, injected as its monomeric citrate into the dog, Stover et al. [60] also demonstrated that americium complexed with ferritin.

		^{244}Cm [e]		Bk [f]		^{252}Cf [g]		Es [f]	
polymeric		monomeric		monomeric		monomeric		monomeric	
6d	44d	7d	63d	4h	21d	1d	32d	4h	21d
55	33	20.8	2.5	23	3	9.9	1.1	18	1.6
	0.6	1.5	0.5		0.7	2.4	0.8		1.0
3.8	2.8	1.5	0.5		1.5				0.8
8	10	32	38	30	38	49.1	45.8	30	30
		11	38		20	1.8	13.5		8
					12	9	16.3		42

[e] D.M. Taylor, unpublished results, cited in ICRP 19, p.19.
[f] F.P. Hungate, J.E. Ballou, D.D. Mahlum, M. Kashima, V.H. Smith, C.L. Sanders, D.W. Baxter, M.R. Sikov and R.C. Thompson, Health Phys., 22 (1972) 653.
[g] B.M. Graham, P.L. Ziemer, R.L. Landolt and S.M. Shaw, Health Phys., 34 (1978) 635.

In addition to binding to ferritin the authors also demonstrated that 7% of the injected activity was bound to a component which eluted from Sephadex G-50 in a low molecular weight fraction. In addition to demonstrating that americium was associated with ferritin and a low molecular weight component these authors also found that about 25% of the americium in the liver was associated with lipofucsin. This observation that americium was bound to lipofucsin would substantiate the hypotheses advanced above that phospholipids may bind actinides as it is known that lipofucsin, which binds metals, contains phospholipids [61]. Bruenger et al. [62] have reported evidence which would support such conclusions.

The more rapid clearance of plutonium from the livers of rats, in comparison to the clearance from the livers of hamsters, has been attributed to the higher rate of turnover of lysosomes in the rat liver [62a].

There is no reason to believe that the other actinides when in the 4+ and 3+ oxidation states are not taken up by the liver by the same mechanism. As indicated above, very little Pa(V) is accumulated by the normal liver and it is not surprising therefore, that little or no UO_2^{2+} is taken up by the liver of normal animals [63]. However, recent studies in this laboratory have shown that UO_2^{2+} is taken up into the livers of thioacetamide-intoxicated animals. In addition, it has also been shown that only UO_2^{2+} can be extracted into heptane by phosphatidic acid [63a].

(v) Uptake of actinides into bone

The uptake of these cations into mineralised tissue is not restricted to bone for these cations will bind readily to any mineralising tissue whether it

is phosphate based or carbonate based [64]. In cartilagenous fishes the plutonium concentration in the skeleton is about 20 times that in other parts of the body, whereas in bony fishes the skeletal concentration is about 150 times that in the remainder of the body. Plutonium has been found associated with mineral deposits such as kidney stones and the site of ectopic calcification in the aorta and tracheal cartilages of older animals. The rate of uptake into bone of these three actinides from the low molecular weight components of plasma is essentially the same [40]. However, the rate of uptake of plutonium from high molecular weight components in plasma is 5.2 times less than the rate of uptake from low molecular weight components. This slow rate of uptake by bone of plutonium may be because the radioelement is bound to transferrin. Such a slow clearance rate from plasma could account for the quite striking variations in distribution on the bone surface observed for plutonium in comparison to americium and curium. Variations in the pH of the bone surface together with variations in the concentration of citrate on the bone surface could influence the pattern of actinide deposition. Autoradiographic studies of the sites of deposition of ^{239}Pu, ^{241}Am and ^{45}Ca on bone surface show different deposition patterns. Plutonium deposits more extensively over the endosteal surface of bone than americium which exhibits a tendency to distribute through the cortex in small discrete concentrated zones [65].

Any theory of bone accumulation of plutonium must present a mechanism for the removal of plutonium from transferrin as well as present an explanation of the variations in deposition of the actinides over bone surfaces. Durbin et al. [40] have suggested that the plutonium—transferrin complex is dissociated in erythropoietic marrow where iron is normally liberated. The observations of Humphreys and Stones [66], however, do not support such an hypothesis. These authors demonstrated that the uptake of ^{59}Fe into the X-ray irradiated marrow of the femur was depressed three days after irradiation whereas there was not a noticeable decrease of ^{239}Pu uptake into the same femur.

Several research groups have examined the uptake of plutonium by various preparations in an attempt to reach some understanding of the mechanism by which the bone takes up plutonium and the other actinides. From their in vitro studies of the interactions of the actinides with glycoprotein, isolated from bone, Chipperfield and Taylor [32] concluded that these macromolecules were more likely to be important in the fixation of plutonium than of americium or curium. While it should be noted that such in vitro interactions do not necessarily imply in vivo interactions of these cations with bone glycoproteins, Bruenger et al. [67] have isolated from bone by a noncomplexing extraction process, glycoproteins which bind about 7% of the actinide concentrated in bone. These glycoproteins were characterised by a high acidic amino acid content. Investigations into the components of bone which bind the actinides go back over many years. In 1962 Foreman [68] reported on his examinations of a series of bone prepa-

rations and found that bone decalcified with EDTA for 48 h took up only 10% of plutonium from plutonium lactate solution in 24 h, whereas a fat-free preparation took up 70% of the plutonium in 8 h. A preparation, termed "organic free", prepared by boiling the bone with 5% KOH for 24 h, took up 70% of the plutonium in 2 h while a bone sample which had been heated for 6 h at 700°C took up 92% of the plutonium in 2 h. While it is difficult to relate some of these bone preparations to the mechanism and components which might be regulating actinide uptake onto bone they do serve to give some insight into the process of actinide absorption onto bone in view of some of the recent theories of calcification. From the poor uptake of plutonium by the decalcified bone it might be inferred that nucleation sites based upon Ca^{2+} are required to facilitate uptake of Pu^{4+}. Some support for such an hypothesis can be drawn from some more results obtained by Foreman who showed that rachitic rat bone took up 30% plutonium over 7 h but that this went up to 60% if the rachitic bone preparation was pre-treated with calcium nitrate solution. As indicated above these observations are valuable in view of the theories of calcification advanced by both Irving [69] and Wuthier [70] who have suggested that phospholipids are involved in the process of calcification. The ready uptake of plutonium by the fat-free bone preparation does not preclude a role for phospholipids in the uptake of plutonium by bone as the phospholipids will not be extracted by an ethanol—acetone mixture as phospholipids are insoluble in acetone. Studies in these laboratories have demonstrated that a lysozyme—inositol triphosphatide complex, which has been established as a model of calcification by Vogel et al. [71], strips Pu^{4+}, Am^{3+} and Cm^{3+} from citrate solutions and from plasma [71a].

Prior to the work of Neuman [35] it was not realised that uranium concentrated on bone. The in vitro studies of Neuman demonstrated that UO_2^{2+} was taken up onto bone surface by ion exchange such that two ions of calcium were replaced by one uranyl ion on the bone crystal surfaces. The uptake of UO_2^{2+} onto bone is in competition with renal filtration. If uranium is administered to the mouse as uranyl bicarbonate there is less uranium in the skeleton than when it is administered as the nitrate. In the more vascular immature skeleton where there is a larger surface area of mineralising tissue the uptake of UO_2^{2+} and Pu^{4+} is at a maximum. Further evidence that the uptake onto bone is dependent upon blood supply and mineral surface can be drawn from the observations of Tannenbaum et al. [72] who showed that the uptake of uranium into trabecular bones (ribs and vertebrae) was 4 to 20 times higher than into compact bone (long bone shafts).

Autoradiographic studies have demonstrated that the uranyl ion is associated with the bone surfaces which are in close proximity to the circulation system [72]. As expected the highest uptake of UO_2^{2+} was found associated with areas of active calcification, alveolar crests of the mandible and the primary spongiosa of the long bones. Although the overall uptake of UO_2^{2+} and Ca^{2+} onto bone was found to be similar, two important differences in

the uptake were obvious. Firstly, $^{45}Ca^{2+}$ was found to penetrate the microcirculation of bone and exchange with non-active Ca^{2+}, which was in deeply buried crystals remote from circulation. Secondly, $^{45}Ca^{2+}$ was found to be associated with bone formed after the radioactive isotope had been injected whereas very little uranium was to be found in new deposits of bone. This difference in behaviour comes about because calcium ions are resorbed very efficiently by the kidney whereas the non-physiological uranyl ions released from bone are cleared through the kidney.

(vi) Biochemical behaviour of oxides of plutonium, americium and curium

An understanding of the behaviour of the oxides of plutonium, americium and curium in biological fluids is of major importance in predicting the clearance of these elements from the lungs of individuals, who may be accidentally exposed to these elements during fuel reprocessing or in the event of a release from a plutonium fuelled fast breeder reactor. In the lung clearance model proposed by the Task Group on Lung Dynamics [73] which was subsequently modified and published by the International Commission on Radiological Protection [74] it was assumed that the rate of clearance of inhaled particulates into blood from the lung was determined by the chemical nature of the particles. Although particle size was recognised as a factor which might determine the clearance rate no account of this factor was incorporated into the model. Contrary to expectation the dioxides of plutonium, americium and curium do exhibit different biochemical fates in the body. A series of studies conducted in these laboratories by Stradling and coworkers [75—77,79,82] have demonstrated that not all these particles can be considered insoluble as indicated in the lung clearance model published by the International Commission on Radiological Protection [74]. This research group has demonstrated that 64% of the activity originating from mixed oxides of plutonium and sodium particles, 1 nm diameter, prepared by burning plutonium and sodium wire, was cleared from the lungs of rats within 18 h and this increased to 80% in 17 days [76]. In comparison only 8% of the activity originating from particles with a diameter of 0.025—0.22 μm had been cleared from the lung after 17 days. These authors demonstrated, with the aid of gel permeation chromatography, that mixed oxide particles with a diameter of 1 nm were degraded via an "intermediate" form to Pu^{4+} by citrate ions. This "intermediate" form which was present in serum after intravenous injection of 1 nm particles was also present in urine and was believed to be partially degraded particles, perhaps associated with citrate.

It is possible that particles with a diameter of 1 nm undergo rapid dissolution in the presence of citrate because of the high percentage (89%) of plutonium atoms on the surface of the particle. Presumably this surface location of the plutonium atoms facilitates the complexation of cations by citrate. It was calculated that particles with a diameter of 0.01 μm had only 15% of the plutonium atoms on the surface of the particle while those with a diam-

eter of 0.1 μm possessed only 2% of the plutonium on the surface [75].

Investigations into the clearance of americium dioxide [77], produced by calcining the oxalate at 650°C for 6 h, from the lung again revealed that the material should be considered moderately soluble in water and not as a Class Y (insoluble) compound as suggested by the Task Group on Lung Dynamics [73]. Unlike the larger plutonium dioxide particles (0.025—0.22 μm) the larger americium dioxide particles (0.025—1.2 μm) were cleared from the lung more quickly than the smaller particles (<0.025 μm) when the oxide suspension was freshly prepared; however, this order was reversed when the suspension was an aged one. Analysis of the skeleton-to-liver ratios for both the freshly prepared and the aged oxide suspensions 24 h after pulmonary intubation revealed quite striking differences in the uptake of americium into the liver and onto the skeleton. The skeleton/liver ratio for particles of diameter <0.025 μm was 0.72 for freshly prepared oxide suspensions and 0.92 for the aged oxide suspensions while for particles of diameter 0.025—1.2 μm the respective ratios were 2.9 and 0.89. The factors which favoured the high level of uptake of americium into the skeleton of those animals receiving the larger particles of the freshly prepared oxide suspension are obscure. The similarities in the skeleton/liver ratios at one day for both oxide suspensions would indicate that the factor which influences the clearance of americium from the lung is the reaction of the americium dioxide with the aqueous environment.

Examination of the aged americium dioxide by electron microscopy showed the material to be amorphous. It is possible that this amorphous form was an americium hydroxide polymer, a material which may cross the alveolar and glomerular membranes, as gel permeation chromatography of urine on Sephadex G-15 identified a form of americium which was not associated with either proteins or citrate in urine. It should be noted that when monomeric americium is administered to animals it is present in urine as the citrate [38]. It is possible that the mobile americium form originating from the fresh suspension of the oxide particles (0.025—1.3 μm) complexed with serum proteins once it had crossed the alveolar membrane for at one day only 11.6% of the initial lung burden was taken up into the liver, whereas 33.7% had been taken up by the skeleton. It is unlikely that this americium was present as Am^{3+} for when americium citrate was administered to the lung, 42.6% of the initial lung deposit concentrated in the liver within one day while 32.9% was taken up by the skeleton. As bone is rich in citrate [78] it is possible that the citrate in the bone aided the depolymerisation of americium hydroxide bound to serum proteins and that the resulting Am^{3+} was taken up by the bone surface.

The factors which controlled the rate of clearance from rat lung of plutonium-238 dioxide were found to be similar to those reported for plutonium-239 dioxide [79], even though the plutonium-238 dioxide was prepared by calcining the oxide at 750°C. This similarity in behaviour of plutonium-238 dioxide, which might be expected to be more inert because of the method of

preparation, and plutonium-239 dioxide is not unexpected. Several research groups have reported an anomalous "isotope effect" for plutonium-238. Hakonson and Johnson [80] have observed $^{238}Pu/^{239}Pu$ ratios of 0.5, 0.1 and 1.0 for soils, plants and animals respectively, at the Trinity Test site. This isotope effect bears no resemblance to the protium-deuterium isotope effect. Initially, it was believed that multi-atom particles were ejected from the $^{238}PuO_2$ particle as a ^{238}Pu atom ejected an α-particle. However, Fleischer and Rabbe [81] have disproved this hypothesis and they have suggested that ejection of the α-particle produces a damaged region in the particle which eventually sloughs off by a mechanical motion.

In an examination of the fate of curium dioxide in the rat lung Stradling et al. [82] showed that the dioxide particles (diameter 25 nm and 220—1,200 nm) underwent rapid breakdown in biological fluids. When urine samples obtained up to 20 min after the pulmonary intubation of fresh suspensions of $^{244}CmO_2$ (diameter of particles <25 nm and 220—1,200 nm) were examined by chromatography on Sephadex G-50, the activity was recovered in 80% yield immediately after the void volume whereas ^{244}Cm citrate was eluted at significantly greater volumes. However, ^{244}Cm in urine collected after 24 h appeared to be present as the citrate form. Similar chromatographic procedures demonstrated that $^{244}CmO_2$ in serum was bound to the serum proteins as particles with a diameter of ca. 1 nm. These results obtained in this study demonstrated that the serum proteins acted as a carrier for the particles as distinct from complexing ionic ^{244}Cm. These authors concluded that the larger particles were breaking down, possibly to smaller oxide or hydroxide particles, in the lung and on passing through the alveolar epithelium pores (1.2—2 nm) into blood the particles were bound to the serum proteins. The conversion of this protein-bound curium to curium citrate was believed to occur either in the renal tubule or in the urine. Essentially the behaviour of the curium dioxide particles mimicked that of the corresponding americium dioxide particles with one important exception; the americium dioxide particles (or americium hydroxide polymers) did not bind to the serum proteins. Electron diffraction studies confirmed that $^{244}CmO_2$ in freshly prepared aqueous suspensions underwent rapid transformation to an amorphous material which may have been the hydroxide or an hydrated oxide. These observations of Stradling et al. [82] do not support the assumptions that the chemical form of the actinide in urine is independent of the physiochemical form of the actinide at intake. Consequently it is wrong to assume that there is a constant relationship between the amount translocated to extrapulmonary tissue and cumulative excretion [83].

Cooper et al. [84] have shown that the mechanism of clearance of 1 nm diameter particles from the lung involves an electrostatic interaction of the particles with pulmonary surfactant. The particles were also shown to interact with the acidic phospholipids, phosphatidic acid and phosphatidylserine but not with phosphatidylcholine. It was subsequently shown that this

mechanism of clearance did not act in the clearance of negatively charged curium dioxide particles [85].

D. DECORPORATION PROCEDURES

The cell fractionation and liver perfusion investigations of Grube et al. [86] could act as a major impetus in the re-thinking of techniques for removing the actinides from the liver. These studies have substantiated suggestions that there is an association of plutonium with an extracellular compartment. At one day post-injection 18.8% of the injected activity could be cleared from the rat liver in the perfusate and 10.3% at 3 days, whereas at 7 days it had fallen to 2.5%. The demonstration of such a high level of extracellular plutonium is of interest as it could be taken to demonstrate the complexation of plutonium at binding sites on the outside surfaces of liver cells. As it is possible that some of this plutonium could be associated with binding sites of a partially lipophilic character the early administration of a lipophilic chelating agent together with DTPA could reduce the liver burden dramatically. These studies have confirmed that the hepatocytes take up most of the liver burden of plutonium and consequently the development of techniques to clear plutonium from the liver must be directed at the development of chelating agents which can penetrate the membrane of the hepatocytes. Grube et al. noted that there was a rapid loss of plutonium from the hepatocytes of the rat liver and that this was paralleled by a rapid loss of plutonium from sub-cellular organelles of these hepatocytes. In contrast, these authors noted that there was no rapid loss of plutonium from the hepatocytes of the canine liver but that there was a redistribution of the plutonium among the subcellular organelles of the hepatocytes. An understanding of these control mechanisms in the canine and rat livers could aid in the development of therapeutic aids for removing plutonium from the liver of man.

The development of techniques for the removal of plutonium from the liver must also be accompanied by the development of techniques for clearing plutonium from bone. In fact the uptake of the radioelements onto the surface of bone poses a major threat to health because of their carcinogenic potential through irradiation of the sensitive osteogenic cells lying close to the endosteal surface. As yet there has been no conclusive evidence that plutonium has precipitated cancer in man. However, the problems faced in designing chelating agents to remove plutonium, as well as americium and curium, from man are very daunting. To remove plutonium from soft tissue and from the skeleton could well require the use of two different types of chelating agent. As plutonium could have a biological half-life in man of 65 to 130 years [74] the problems in removing the element from the calcified tissue are obvious.

In fact it is quite possible that plutonium bound up in the calcified matrix of bone, far removed from the osteoprogenitor cells, is unlikely to be a

hazard to the health of man as the path-length of the α particle does not exceed 10 μ. This short path-length of the α particle will effectively put it outside the area where it could irradiate the osteoprogenitor cells. It is possible that the plutonium associated with the macrophages in the bone marrow [74] will be amenable to chelation therapy based upon lipophilic chelating agents.

Unfortunately advances in the development of decorporation procedures for clearing the actinides from the body have been disappointing. In 1958 Smith [87] reported that diethylenetriaminepentaacetic acid (DTPA) was superior to ethylenediaminetetraacetic acid (EDTA) in mobilising plutonium in experimental animals. Normally DTPA, as $CaNa_3DTPA$, is administered to man at 14 mg kg^{-1} and at this level there is no evidence of toxicity provided it is given as a single intravenous injection at intervals of 24 h or more. There is some evidence of toxicity in animals when DTPA is given in fractionated doses over a period of 24 h even though the total amount of injected DTPA does not exceed 14 mg kg^{-1} [88]. It is possible that this toxicity is due to depletion of zinc ions and it has been suggested that DTPA should be administered as the zinc salt [89]. The principal disadvantage with DTPA is its inability to cross, in significant levels, the membranes of cells. As it is insoluble in organic solvents, such as acetone and methanol, this inability to penetrate membranes is not unexpected. However, DTPA is effective in removing Pu^{4+}, Am^{3+} and Cm^{3+} from serum but it must be administered soon after uptake of the elements. In man about 50% of monomeric plutonium entering the blood is cleared with a half-time of 20 min and a further 27% with a half-time of about 7 h. As the chelate complex formed between any available plutonium and DTPA is rapidly and almost quantitatively excreted from the body [90] early administration of DTPA is recommended. Over the years many chemicals have been examined for ability to clear plutonium and the other actinides from the body. Some of these procedures have been reviewed by Volf [91]. As the liver accumulates significant levels of plutonium, there have been several attempts to enhance the uptake of chelatint agents into liver cells. Rahman et al. [92] demonstrated that liposomally entrapped DTPA was superior to DTPA in clearing plutonium (administered in the polymeric form) from mice. However, this procedure would appear to be species specific, as Stather et al. [93] observed no difference between the two forms of DTPA in clearing plutonium from either rats or hamsters. Other chemicals which have been examined, and found ineffective in clearing plutonium from experimental animals, include the lipophilic compounds N-stearoyldesferrioxamine, pyridine-2,6-dihydroxamic acid and a phosphatidylethanolamido-EDTA derivative, as well as the partially lipophilic ferric-complexing agents, rhodotorulic acid and 2,3-dihydroxybenzoyl-N-glycine [94]. Two new developments, one in the U.S.A. at the University of California, Berkeley [95], and the other in these laboratories [96,97], offer some promise in mobilising intracellularly deposited plutonium. The American approach has been to produce a biomimetic chemical while the British

approach has been to produce dialkylamido derivatives of DTPA. The studies in these laboratories have shown that Puchel, a dialkylamido derivative of DTPA, administered as an aerosol to hamsters, seven days after they had inhaled mixed oxides of plutonium and sodium, reduced the level of the plutonium contamination to 40% of that of control animals at 30 days [97]. It has been conjectured that the plutonium dioxide is first taken up by macrophages in the lungs and that the particles undergo hydrolysis in the environment of the lysosome to release Pu^{4+} inside the cells. As Puchel is partially lipophilic it might penetrate the membranes of the macrophages and complex Pu^{4+} which may be bound to phospholipids and transferrin associated with cell membranes. The veracity of a recent report [98] of an effective decorporation procedure based upon the simultaneous administration of DTPA and salicylic acid must be doubted, as investigations in several laboratories in the U.K. and the U.S.A. have failed to demonstrate the superiority claimed for this procedure [99,100].

Although DTPA is effective in removing plutonium, americium and curium from animals, it appears to be of little value in clearing uranium from the body, although there was an increase in the amount of thorium-288 cleared from the animals [63]. The authors assumed that the lack of effectiveness of DTPA in clearing the uranium from the animal was related to the relatively low stability of the chelate. The authors observed that 40% of U-233 was taken up by the kidney when injected as its DTPA complex whereas only 9.4% of the uranium was taken up by the kidney when administered in the citrate form.

The investigations now being conducted in various laboratories around the world into the mechanism of uptake of the actinide cations into cells, as well as into methods of removing these toxic elements, could throw new light upon the treatment of iron storage diseases and Wilson's disease. It is possible that such research might also give some insight into the possible influence of intracellular calcium concentrations upon the onset of cancer.

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