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METABOLIC CHARACTERISTICS WITHIN A CHEMICAL FAMILY

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ABSTRACT

The available data has been revewed for the biological behavior in rats of high-specific-activity radioisotopes of 70 elements. Tracer quantities were administered in single intramuscular injections. Groups of rats were autopsied at various intervals, and tissues and excreta were assayed for radioactivity.

Distribution data were arranged according to the grouping of the periodic table of the elements. The anions, (including the halogens), the oxygenated or halogenated ions of Groups IV, V, and VI, and the transition metals were rapidly eliminated by the kidney. The monovalent alkali metals were distributed almost uniformly in soft tissue with subsequent excretion by the kidney. The bivalent cations, except Hg^{++}, Cd^{++}, and UO_2^{++}, were deposited primarily in bone mineral and were eliminated slowly in both urine and feces. The tripositive elements of Group III, the lanthanides, and the actinides were deposited in liver and bone. The liver fraction was excreted via the bile without recirculation, while that deposited in bone was turned over at a rate slower than that of normal bone remodelling. The quadrivalent cations such as Zr^{+4}, Th^{+4}, and PuO_2^{+2} were deposited almost exclusively in bone and were bound more strongly than the Group III elements.

The properties that determine biological behavior are (a) the oxidation state stable at body pH, (b) the solubility of the stable state, (c) the tendency to be incorporated into organic compounds, and (d) the tendency to associate with specific proteins.

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METABOLIC CHARACTERISTICS WITHIN A CHEMICAL FAMILY[a]

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INTRODUCTION

The great potential hazard of the radioactive products of nuclear fission and of the fissionable elements was recognized almost as soon as the nuclear chain reaction was successfully demonstrated. The necessity for strict control measures was apparent. To provide a sound basis for such control measures an intensive investigation was begun of the metabolic behavior and biological effects of these radioactive substances. By 1946, a wealth of information had been gathered from these radiobiological researches which provided a logical framework for the establishment of minimum precautions to be taken by users of radioactive materials and for the protection of the general public.(1-5) A great deal of ground remained to be covered. With the increasing use of radioactive substances, many radionuclides, in addition to the fission products and the heaviest elements, would soon be produced in reactors and cyclotrons in hazardous quantities. Under the direction of the late Dr. Joseph G. Hamilton, a systematic investigation was made of the biological behavior in laboratory rodents of tracer amounts of some 70 radioelements. Most of the radioisotopes were prepared on the Crocker Laboratory 60-inch cyclotron by Dr. Thomas M. Putnam and, Mr. G. Bernard Rossi and their staff. Dr. Warren M. Garrison and his co-workers isolated and purified the radioactive products and prepared them for biological use. Dr. Kenneth G. Scott directed the animal work. This report is derived largely from the data collected by this group during the years 1943 to 1952. Data for

([a] This work was performed under the auspices of the U. S. ATOMIC ENERGY COMMISSION.)

several elements that were not investigated in this laboratory have been drawn from the literature.

Some of the data contained in this summary report have been published elsewhere in various forms.[1, 5-16] They have been reanalyzed for this presentation and information is included that was previously available only in University of California Radiation Laboratory Project Reports. The distribution and elimination data have been arranged to compare the biological behavior of the elements of the various periodic groups.

Since Mendeleef's presentation of the periodic table, the chemical properties of elements have been successfully predicted from knowledge of the behavior of other members of the same periodic group. The properties of the other halogens, for example, suggested the basic analytical methods first used to isolate and identify element 85, astatine.[17] In many instances the biological behavior of an untested element has also been predicted (at least qualitatively) from knowledge of its near chemical neighbors. It was logical to look for and not surprising to find halogens other than iodine concentrating in the thyroid gland,[18] and to find alkaline earths other than calcium being incorporated into bone mineral.[19]

Meaningful comparisons of the behavior of the elements of each periodic group and sub-group were possible because the tracer experiments were performed by the same group of experimenters, using the same analytical techniques and equipment, and the same animal species in the test system.

METHODS

Detailed descriptions of the preparation of the radioisotopes and of the biological procedures appear elsewhere[6,7,19a], and only a brief outline of the experimental methods is presented here. The radioisotope of each element investigated was selected on the basis of ease of preparation in carrier-free form or at very high-specific activity, length of half-life, and desirable radiation

characteristics. The specific radioisotopes used are shown in the Tables of data.

The animals used were mostly female adult albino rats. Radioisotopes of the elements presumed to be anions or monovalent cations were injected intramuscularly or intravenously in isotonic saline. Radioisotopes of cations in the di-, tri-, or quadrivalent state were injected intramuscularly, usually in isotonic or hypertonic sodium citrate. The complexing agent was used to prevent radiocolloid formation either in the injection solution or in the animal's circulation, and to facilitate absorption from the site of injection. A minimal amount of each radionuclide was administered to avoid radiation effects, but enough was given to ensure accurate radioactive assay of tissues and excreta at the longest time-interval studied. After injection, groups of three rats were placed in metabolism cages for the separate collection of urine and feces. Cages of three rats were autopsied at intervals varying from 1 hour to 8 months, the length of each experiment depending upon the half-life of the isotope and the quantity available.

Tissues and excreta were usually oven dried at 100°C, ashed in a muffle furnace at 500°C, and dissolved in dilute nitric acid. Aliquot samples were evaporated in small porcilain capsules and assayed for beta-particle activity with a thin window G-M counter. A known portion of the injection solution served as a counting standard, and self absorption curves were prepared for each radioisotope by the dilution method. In some cases gamma rays were sufficiently intense to permit accurate assay with a lead-shielded G-M tube. After 1951 a NaI-TlI crystal scintillator was used for gamma ray counting. Arsenic, Tc, Se, Te, I, and Ge were found to be partially volatile at muffle furnace temperatures. These radioelements and those with very short half-lives (At, Sc, and La) were either dried at temperatures less than 100°C, and the beta particle activity measured; or fresh tissues were assayed for gamma activity when these were present at sufficiently high intensity. In all cases samples were counted for a long enough time to keep

counting errors within the range of ±5%. A balance sheet of radioactivity was prepared for each animal in every experiment, samples were rechecked, or the experiment was repeated until the total recovery varied by no more than ± 10% from the amount injected.

The method of calculating the radioisotope distribution in terms of percent of administered dose (percent of absorbed dose in oral or intramuscular experiments) has already been described.(6)

Several of the lightest elements appear as blanks in the Tables. Some---oxygen, silicon, boron, aluminum, nitrogen, lithium, magnesium, and chlorine---either could not be prepared carrier-free or have only very short-lived radioisotopes. Comparable tracer data in the rat were not available for several other elements: sulfur, carbon, titanium, and nickel.

The chemical states of the elements as they appear in the Tables were not determined experimentally, but rather are best estimates based on the chemistry of separation from the target material and a study of their oxidation-reduction potentials.(20)

The tracer data are collected in Tables I through X. In most cases the 4-day postinjection interval is shown because data were available for the majority of the elements at this time period. Results of shorter-term tracer studies are shown for those elements that were very rapidly eliminated or for those with half-lives shorter than a few hours. Several biological criteria suggested the selection of the 4-day interval as most informative: (a) intramuscularly injected material had been largely absorbed--less than 10% remained at the site of injection when a complexing agent was added; (b) the blood stream had very nearly been cleared: (c) tissues whose initial radioisotope concentrations represented blood-borne isotope or simple mixing with extra-cellular fluid had been cleared; (d) prompt excretion, reflecting initial clearance of the blood

had very nearly ceased; (e) the excretion resulting from slower processes of turnover had not yet become important.

In the Tables radioisotope content is shown for those tissues which are important sites of deposition for at least one member of the particular periodic group. The symbol U or F to the right of the value for total excretion indicates that the greater proportion of a particular radioisotope was eliminated by the kidney (U) or by the digestive tract (F). Where the symbol UF appears, about equal amounts were eliminated by the two routes.

GROUP I: THE ALKALI METALS

As shown in Table I, skeletal muscle was the important deposition site of most of the Group I elements. The kidney was the chief route of elimination. A few days after injection the concentration of these metals in muscle was three to four times that of the blood and one and one-half times greater than the concentrations in other soft tissues. The behavior of the group was not completely uniform; Na tended to be eliminated almost twice as fast as the other members of the group, and Na and Rb concentrated in bone to a significantly greater extent than K or Cs.

The metabolic behavior of the Sub-Group I elements--Cu, Ag, and Au---differed from the elements of the main group. Incomplete data of Ashikawa et al.[21] indicate that in adult rats Cu^{++} concentrated in the liver, kidney, and spleen. Tracer data were not available for bone; however, the values of Tipton et al.[22] for trace elements in human tissues show bone concentration of Cu to be about 10% of the concentration in the soft tissues.

Silver in the +1 state has a unique fate. Scott and Hamilton[9] found that injected carrier-free radiosilver combined almost quantitatively with plasma protein, was rapidly removed from the circulation by the liver, and was eliminated by the gastrointestinal tract via the bile. In an attempt to study the fate of a presumably soluble Au compound, radioactive auric thiosulfate was prepared. After intravenous injection of this compound colloidal aggregates were apparently formed; the distribution pattern was typical of colloids of small particle size; that is, high concentrations of radiogold were found in liver, spleen, and bone marrow.[23,24] The behavior of non-colloidal Au remainsto be demonstrated.

GROUP II: THE ALKALINE EARTHS

A summary of the tracer experiments with the alkaline earth elements is shown in Table II. The metabolic behavior of these elements was nearly uniform in the

rat. After the first few days more than 95% of retained Ca, Sr, Ba, or Ra was found in bone. Tracer data are not available for Mg, but Tipton's spectrographic analysis of human tissue shows that bone contains 10 times more Mg per unit weight than does any other tissue--a value that agrees well with analyses for the other alkaline earths.[22] With the possible exception of Be, the alkaline earth elements in bone are associated with the mineral phase. Calcium receives preferential treatment by the kidney[29] and by the gastrointestinal tract,[30] so that after oral administration or parenteral injection a greater percentage of a single dose of radiocalcium is deposited in the skeleton than any other element of the group.

Recent evidence indicates that the alkaline earth in mineral bone is distributed in at least three grossly observable compartments--one with a rapid turnover, one of intermediate half-time, and a third that is turning over very slowly. It has been postulated that these three compartments represent (a) rapid physico-chemical exchange, (b) gross bone turnover due to growth and (or) remodeling,[31] and (c) very slow exchange processes resembling solid state diffusion.[32] The amount of administered alkaline earth tracer that appears in the various turnover compartments depends largely on the age of the animal; the older the animal, the smaller the percentage that will be associated with the slower turnover compartments.[33] In rats the half-times of the various skeletal turnover compartments have been found to be similar for Ca and Sr.[34] Beryllium concentrated to a significient degree in liver and kidney as well as in bone but was removed from bone at an apparently slower rate than the other members of the main group. Beryllium thus resembles Zn in exhibiting certain of the characteristics of both the alkaline earths and the elements of Sub-Group II.

Although apparently in the +2 state in neutral aqueous solutions, the Sub-Group II elements (Zn, Cd, and Hg) were not deposited in bone to the great extent noted for the elements of the main group. Immediately after injection, tracer Zn was most highly concentrated in the liver.[35] Tipton's study of trace elements in human tissues indicates, however, that concentrations of stable Zn in the

prostate gland and in bone, are more than twice those in liver, kidney, or other soft tissues.[22]

Tracers of Cd and Hg were deposited preferentially in the liver and kidney. Retention of tracer Cd in both organs was quite prolonged.[7] The short half-lives of the $Hg^{196,197}$ isotopes precluded long-term study, but during an 8-day observation period the renal concentration actually increased, while that in the other tissues declined which indicates a high degree of retention.[7] The prolonged retention of Cd and Hg strongly suggests some stable combination of these two elements with protein in the liver and kidney.

GROUP III: THE LANTHANIDES AND ACTINIDES

The distribution of the lanthanides, actinides, and elements of Group III is summarized in Tables III, IV, and V respectively. Two of these elements (Tl and U) resembled other periodic groups in their biological behavior. The stable state of Tl in neutral aqueous solutions is Tl^{+}, and its behavior, i.e., nearly uniform distribution in the soft tissues and rapid elimination, was reminiscent of the Group I elements.[7,38] Uranyl ion, UO_2^{++}, resembled Hg^{++} and Cd^{++} in its tendency to concentrate in the kidney,[7,39] and should probably be classified with the elements of Sub-Group II.

The behavior of the trivalent cations was remarkably uniform. Liver and bone are the major deposition sites. For those elements deposited primarily in the liver, the gastrointestinal tract was eventually the main route of elimination. For those concentrating primarily in bone, the kidney was the major excretory organ. Skeletal muscle accumulated significant amounts of Ga, In, and Sc, the lightest members of the group.

There is some evidence pointing to combination of these highly charged ions with protein in the liver. That fraction of a trivalent ion initially deposited in the liver was eliminated with a half-time ranging from 10 to 20 days. Comparison of the amount originally accumulated in the liver, and the total fecal

excretion during the first 60 days postinjection indicated that the elimination pathway was directly from the liver into the small bowel via the bile with little gastrointestinal reabsorption. Retention of trivalent cations in the skeleton was prolonged. The half time for removal of these elements was 2.5 years on the average for the rat. While gross autoradiographs indicate that these elements concentrate on bony surfaces and at sites of resorption and growth,[5,11-13,16,47-49] the question of the ultimate skeletal deposition site--the surface of the organic matrix or the bone salt--is yet to be completely resolved.

The more basic light lanthanons with their large ionic radii tended to be deposited largely in the liver. The heavier lanthanons, more acidic and of smaller ionic size, were laid down exclusively in bone. Yttrium, and the actinides whose stable oxidation state is greater than +3,--Pu, Np, Pa, and Th--resembled the heavy lanthanons, while the tripositive actinides--Ac, Am, and Cm--behaved like light lanthanons.

GROUP IV

The important deposition sites of tracers of the Group IV elements are shown in Table VI. These elements constitute the third major group of bone seekers. There was one demonstrated exception--Ge--which under physiological conditions exists in hydrated anionic form. Tracer Ge was readily absorbed from an intramuscular injection site and was rapidly and almost uniformly distributed in the soft tissues. It was almost quantitatively excreted by the kidney in the first 24 hours after injection. After a few hours the concentration in bone was somewhat greater than that in most of the other tissues, but this deposit was quickly eliminated, and within 4 days after injection constituted only 0.5% of the administered dose.

Lead has long been recognized as a hazardous bone seeker. The association of Pb^{++} with the mineral phase of bone, is well documented.[50] Tracer Pb was eliminated by the kidney and gastrointestinal tract in nearly equal proportions, also reminiscent of the Group II elements.

Tin and Zr tracers were deposited in the skeleton to the same extent--30% to 35% of the absorbed dose. Timed studies were not sufficiently long to establish skeletal removal rates; however, from 2 to 4 months after administration nearly two-thirds of the initial deposit remained, indicating skeletal turnover times in excess of 400 days. There is some difference in the manner in which radioactive Sn and Zr were eliminated. A large fraction of the tracer Sn was excreted by the kidney in the first 24 hours. After the first day, urinary excretion became almost negligible, and the intestinal tract took over as the chief excretory organ. Very little carrier-free Zr^{95} was excreted during the first day. In the ensuing months 80% of the eliminated Zr was found in the feces. The early urinary excretion of Zr can be greatly enhanced by the simultaneous administration of milligram amounts of stable zirconium citrate.[51]

Presumably colloidal aggregates are formed that are readily filterable by the renal glomeruli, yet are small enough to escape filtration from the circulation by the reticuloendothelial system.

The data shown for Hf are drawn from Kittle et al.[52] Most Hf compounds are relatively insoluble in neutral solutions at moderate temperatures. The high concentration of radiohafnium in the liver does not fit with the deposition patterns of the other members of the group, and suggests that a portion of the sodium-hafnium-mandelate-complex was in an aggregated form. The presence of 15% of the administered Hf in bone does indicate a behavior similar to Sn, Zr, and Pb.

GROUP V

The distribution of the Group V elements is shown in Table VII. With the exception of Bi and perhaps Nb, the prinicipal oxidation state for this periodic group is +5. Radioarsenate and, to a small degree, radioantimonate were incorporated into the circulating erythrocytes. During in vitro incubation, radiophosphate is believed to exchange with the stable phosphate of the cells, whereas tracer As and Sb apparently form stable compounds with the protein, globin. The cells thus tagged retain the radioactive label until their destruction. The circulating blood was the only important deposition site for both of these radioelements, and much of the apparent tissue deposition of both could be accounted for by blood contained in the tissues at autopsy. That fraction of both isotopes not initially associated with the red cells was excreted in the first few days, chiefly by the kidney. The mean life of As^{74} in the body was roughly equivalent to the red cell life span which indicates that there was little tendency for recirculation of radioarsenic after the destruction of the original host cell.

The tracer data for Bi^{206} agree with pharmacological observations of the distribution of stable Bi compounds. The metabolism of radiobismuth in the +3 state was not like the majority of the trivalent elements but more closely resembled UO_2^{++}, suggesting that Bi (III) was in an oxygenated or "basic" form.

Lake UO_2^{++}, retention of Bi in the kidney was not prolonged, and by the 17th day after injection only 0.6% remained in the kidney, and 95% had been excreted.

The Sub-Group V elements tended to combine with the serum proteins rather than with the red cells, and their plasma concentrations were still appreciable as long as two weeks after injection. Shortly after injection all three elements--V, Nb and Ta--were distributed throughout the body, with the highest concentrations in the liver, kidney, and bone. Initial excretion was chiefly urinary, but after the first few days some was eliminated by the gastrointestinal tract as well. Retention was generally more prolonged in the skeleton than in the soft tissues, and by the second month bone was the critical organ for V and Nb. Skeletal turnover of these elements seemed to be more rapid than the turnover found for the alkaline earths or for the lanthanides.

Vanadium, the lightest of the group, forms the most soluble compounds. It was rapidly and almost completely absorbed and was eliminated nearly quantitatively in the first two months. By the 64th day muscle, skin, and liver contained 4.3% of the injected dose, and 4.6% remained in the skeleton.

Niobium belongs to a group of elements with high positive charge--Pu, Tm and Y--that combine in a stable fashion with the serum proteins and remain in the circulation for many hours after injection.[51] Compounds of Nb are less soluble and more basic than those of V, and a complexing agent was required to facilitate absorption. Retention of Nb^{95} was more prolonged than that of V. As long as two months after injection, 28% of the administered dose was retained, with significant quantities in the muscle and skin as well as in liver, kidney, and bone.

Compounds of Ta are generally inert and exceedingly insoluble. Only 15% of intramuscularly administered radioactive Ta_2O_5 was absorbed when no complexing agent was added, and intravenously administered Ta_2O_5 was almost entirely colloidal. Like Nb and V, Ta was found in nearly all the tissues, and most highly concentrated in liver, kidney, and bone. Tantalum was retained more strongly than the other

members of the sub-group, and eight months after an intramuscular injection the skeleton and soft tissues still contained 27% of the administered dose.

GROUP VI

Most of the Group VI elements (Table VIII) showed some tendency towards association with the circulating red cells (as was noted for the Group V elements.) The metal-protein combination becomes more stable with increasing atomic weight of the Group VI metal. Sixteen days after injection only 0.1% of the Se remained in the blood stream, while 10% of the Te was still circulating. After oral administration of Po, the same amount was present in the red cells at 70 days as at 8 to 10 days. The urine was the important route of elimination for Se and Te, and kidney was the only tissue that consistently contained either isotope at higher concentration than the blood. Excretion of Po following absorption from the gastrointestinal tract; i.e., noncollodial Po, was predominantly fecal, although urinary excretion was higher than was found for intravenously injected colloidal Po. There is some evidence for a greater concentration of Po in tissues such as liver and kidney than can be accounted for by tissue blood content.

The Sub-Group VI elements apparently did not combine with the circulating red cells to any significant degree, although radiochromate is frequently the method of choice for in vitro red cell labeling. Urinary elimination of these elements occurred chiefly during the first few hours after injection when the blood level was high. Subsequently, most of the excretion took place via the liver and the gastrointestinal tract. The heaviest member of the group, W, was the most rapidly excreted; 22% of the administered Cr was retained after 16 days, whereas only 2% of the tungstate was still present at 4 days. These elements were initially present in nearly all the tissues. Several days after injection bone, liver, and kidney were the only tissues that contained appreciable amounts of Cr and W. No critical organ was determined for Mo.

GROUP VII: THE HALOGENS

The metabolic characteristics of the halogens, Group VII, are shown in Table IX. Excretion tended to be almost exclusively urinary, and soft tissue concentrations were generally low. The skeletal deposition of F was unique among the members of this group. After an intravenous injection, all of the main group halogens were secreted by the gastric mucosa to some extent and were reabsorbed almost completely in the small bowel. This phenomenon shows a definite trend of increasing gastric secretion with increasing atomic number.[60] Fluorine was not concentrated by the thyroid gland, and thus far At is the only halogen other than iodine that has been shown to be accumulated by the thyroid to a significant degree under normal conditions[14,18]. Astatine homologues of the iodinated organic compounds synthesized by the thyroid gland have not been identified.

The metabolic characteristics of Mn, the first member of the seventh sub-group, were quite unlike those of the main halogen group elements and the other sub-group VII elements. Manganese injected intravenously in the +2 state was accumulated largely by the liver and rapidly appeared in the gastrointestinal tract. One day after injection the liver still contained 11% of the injected dose, another 11% was found in the gastrointestinal contents, and 41% had been eliminated in the feces. Significant amounts of Mn were found in spleen, pancreas, kidney and skeleton. It was not determined whether the skeletal Mn was deposited in the marrow as colloidal particles or was present in the bone tissue itself in a manner similar to other divalent elements.

There is some evidence for at least transient thyroidal accumulation of the highly hydrated positive valence states of Re and Tc, particularly in rats that have been maintained on a low-iodine diet or in rats made goiterous with thiouracil[62]. These elements were eliminated almost quantitatively by the kidney and exhibited the gastric secretion and subsequent intestinal re-

absorption seen with the elements of the main group.

THE PLATINUM METALS

The distribution of the platinum metals is shown in Table X. The oxidation states of these elements as they were prepared for injection ranged from +2 for Pd and Pt to +8 for Os. Although the trichloride is shown as the injected form of Rh and Ir, it is possible that they existed to some extent as complex chlorides, i.e., $Rh(Cl_6)$. Ruthenium, Os, Pd, and Pt were administered as complex anions. The subsequent behavior in the circulation and in the tissues would depend on whether they remained in the injected form, or were rendered less soluble (as by hydroxide formation), or were reduced to the metallic state. There seemed to be little tendency for these elements to form radiocolloids following intravenous injection as judged by (a) the low liver uptakes and spleen concentrations (less than 0.7%/g in all cases), and (b) the similar distribution of Pt after intravenous or intramuscular injection.

While the transition and platinum metals form relatively homogeneous chemical groups, each element possesses a certain degree of individuality, and the biological behavior of carrier-free radioisotopes of these metals agreed with this general picture. Kidney, liver, and spleen were the chief deposition sites of the platinum metals, and were the only tissues that consistently showed higher concentrations than the blood. Bone was not a major site of accumulation of any of the platinum metals during the longest period of observation which was 33 days. It has been shown, however, that after prolonged feeding of radioruthenium the bone concentration is built up to potentially hazardous levels, and that skeletally deposited Ru is held more strongly than that in the soft tissues.[66] Except for Pd, the blood levels of these elements were still high 24 hours after injection (compared with many other elements studied), and Ir and Pt were easily measurable

in the blood as long as 32 days after injection. Loss of the lighter members of the Group (Ru, Rh, and Pd) from the tissues was less rapid than the decline in their blood concentrations, while the decrease in tissue content of Ir and Pt roughly paralleled the decline of the blood concentrations. Retention of Ru and Rh is probably more prolonged than that of the other members of the group. Excretion of Ru was comparatively low, for only 43.3% had been excreted by the 7th day. Initial excretion of Rh was somewhat higher--47% in the first 24 hours--and only an additional 7% was eliminated in the ensuing 5 days. The other members of the group were eliminated much more efficiently: 80% of the Ir in 33 days, 92% of the Pt in 32 days, 89% in the Pd in 7 days, and 79% of the Os in the first 24 hours.

DISCUSSION

The behavior of the elements of a main chemical group is usually more predictable than the behavior of a sub-group element. For example, the alkaline earths are deposited predominantly in bone mineral, while the sub-group elements (Cd and Hg) which are also stable in the +2 state are retained tenaciously in the liver and kidney. Less than 2% of either can be found in the skeleton. Relatively uniform behavior was seen in the main groups of the alkali metals, the alkaline earths, the lanthanides and actinides in the +3 state, the halogens, and the platinum metals. There were some exceptions, particularly among those elements essential to tissue function and survival. In the adult rat skeletal deposition of Ca was nearly twice that of any other element in the +2 state, and urinary elimination was one-fifteenth that of the other alkaline earths. Although most of the halogens can be demonstrated to concentrate at least transiently in the thyroid gland, this gland has been found to utilize only iodine. In mammals the ferric-ferrous redox couple is overwhelmingly preferred in metallo-enzyme systems, and the distribution of tracer Fe bore no resemblance to the other transition and platinum metals studied.

Four properties appeared to be the chief determinants of the behavior of a tracer element in the mammalian organism: (a) the oxidation state stable at the pH of the body fluids, (b) the solubility of the stable state, (c) the tendency towards incorporation into organic compounds, and (d) the tendency to be chelated by or to form complexes with proteins in the circulation or in a particular tissue.

Oxidation state was by far the most important factor. Although Tl is a Group III element, the +1 state is more stable than the +3 state characteristic of the other members of the group. It was not surprising to find that Tl deposited primarily in the soft tissues and that its distribution closely resembled the heavy alkali metals.

Almost as important as oxidation state in determing biological behavior was

the tendency of many highly positively charged metal ions to assume complex hydrated, oxygenated or halogenated forms. Such complex anions were readily eliminated, particularly by the kidney. For example, radiogermanium (Group IV) was prepared in its most oxidized form and was probably given as the germanate ($NaHGeO_3$) rather than as the tetrachloride. In four days 98.5% of the Ge had been eliminated. Tin and Zr which were most likely given as +4 cations were retained to a high degree and exhibited the distribution typical of bone seekers.

Solubility in the tissue fluids also influenced distribution to a high degree, even in the case of carrier-free radioelements where mass effect need not be considered. Polonium, radiotantalum as Ta_2O_5, and radiogold in any form thus far tested displayed a marked tendency towards radiocolloid formation. They were poorly absorped after intraperitoneal or intramuscular injection and accumulated rapidly in the reticulo endothelial tissues after intravenous administration.

Certain of the cations tend to be bound to proteins and present what seem at first to be anomalies. Radiosilver was associated with serum albumen which was then deposited almost quantitatively in the liver and excreted into the intestinal tract. Radioarsenate rapidly entered the circulating red blood cells as an apparently permanent part of the hemoglobin molecule to be eliminated only at the death of the original host cell. This affinity for the protein--globin--was scarcely detectable for the other members of Group V.

Many other radioelements combined with proteins but in a less spectacular fashion. The rare earths in carrier-free form--the actinides--and several other Group III and Group IV elements, formed complexes with the heavier serum proteins with liver proteins, and possibly with the mucoproteins on bony surfaces. In contrast to the majority of the bone-seeking bivalent cations--Hg^{++}, Cd^{++}, and UO_2^{++}--apparently combine with some as yet unidentified protein in the renal cortex.

It is possible to make some generalizations for the benefit of the industrial

physician and health physicist. With few exceptions, the anions--including most of the halogens and the oxygenated or halogenated oxidation states of the elements of Groups IV, V, VI, and the platinum metals--are eliminated quite rapidly, chiefly by the kidney. The monovalent cations are distributed almost uniformly in the soft tissues, and are subsequently excreted by the kidney but with longer turnover times than the anions. The bivalent cations (with previously indicated exceptions) constitute the first major group of bone seekers. They are associated almost exclusively with bone mineral and are eliminated very slowly as the structural elements of the skeleton matures with advancing age. The tri-positive ions tend to associate with protein in the circulating blood, in the liver, and quite possibly in bone, and the most important deposition site of each individual +3 element seems to depend upon the relative stability of the particular protein complex. The fraction laid down in the liver is eliminated quickly while that deposited in bone is turned over much more slowly than are the bivalent elements. The quadrivalent cations such as Zr, Th, and Pu are deposited almost exclusively in the skeleton, and are held there as tenaciously as are the +3 elements.

Table I

Distribution of radioisotopes of the elements of Group I, the alkali metals, in various tissues of the rat after intramuscular injection

Radioisotope	Chemical form administered	Time	Percent of absorbed dose				Ref.
			Bone	Liver	Muscle	Excreta	
Li	-	-	-	-	-	-	-
Na^{22}	NaCl	2 days	6.1	1.3	10.3	55.2 U	25
$K^{42,43}$	KCl	2 days	4.2	3.3	47.6	26.9 U	26
Rb^{86}	RbCl	4 days	14.4	4.8	43.6	20.8 U	27
$Cs^{134,135}$	CsCl	4 days	1.5	2.1	38.5	44.9 U	4
Sub-Group I							
Cu^{64} [a]	$CuCl_2$	6 hours	-	2.9	0.1	-	21
Ag^{110}	$AgNO_3$	1 day	4.2	2.8	2.2	60.9 F	9
Au^{196} [b]	$Au_2(S_2O_3)_3$	1 day	6.9	66.4	2.3	6.8 U	28

[a] Kidney 10%, spleen 6.2%.

[b] Injected intravenously.

Table II

Distribution of radioisotopes of the elements of Group II, the alkaline earths, in various tissues of the rat after intramuscular injection

Radioisotope	Chemical form administered	Time	Percent of absorbed dose				Ref.
			Bone	Liver	Kidney	Excreta	
Be^{7}	$BeCl_2$	4 days	32.2	9.6	2.0	49.0 U	10
Mg	-	-	-	-	-	-	-
Ca^{45}	$Ca_3(Cit)_2$	4 days	70.0	-	-	30.0 F	34
Sr^{90}	$Sr_3(Cit)_2$	4 days	44.0	-	-	56.0 UF	34
Ba^{140}	$BaCl_2$	4 days	37.3	-	-	55.0 UF	16
Ra^{223}	$Ra_3(Cit)_2$	4 days	40.4	-	-	59.6 UF	36
Sub-Group II							
Zn^{65}	$ZnCl_2$	1 day	-	38.5	2.4	-	35
Cd^{109}	$CdCl_2$	4 days	3.3	77.8	6.1	5.6 F	7,27
$Hg^{196,197}$	$HgCl_2$	5 days	1.2	7.9	25.5	49.0 F	7,37

[a] Tumor-bearing mice data.

Table III

Distribution of radioisotopes of the elements of Group III in various tissues of the rat after intramuscular injection

Radioisotope	Chemical form administered	Time	Percent of absorbed dose				Ref.
			Bone	Liver	Muscle	Excreta	
B	-	-	-	-	-	-	-
Al	-	-	-	-	-	-	-
Ga^{67}	Ga (citrate)	4 days	19.6	7.1	13.2	48.7 F	40
In^{114}	$InCl_3$	4 days	16.8	14.0	14.7	25.8 F	7, 41, 67
$Tl^{200,202}$	TlCl	4 days	5.4	2.6	28.5	50.1 F	7, 38
Sub-Group III							
Sc^{46}	Sc (citrate)	4 days	15.9	21.2	12.5	31.1 F	28
Y^{91}	YCl_3	4 days	55.6	12.1	2.6	26.3 U	42
La^{140}	La (citrate)	4 days	18.4	64.2	1.2	11.3 UF	6

Table IV

Distribution of radioisotopes of the rare earth elements, the lanthanons, in various tissues of the rat 4 days after intramuscular injection as complex citrates.[a]

Radioisotope	Percent of absorbed dose			
	Bone	Liver	Urine	Feces
Ce^{144}	27.7	51.0	6.0	8.0
Pr^{143}	26.6	48.4	6.6	8.6
Nd^{147}	31.2	27.1	22.1	10.0
Pm^{147}	36.4	41.4	9.6	6.5
Sm^{153}	33.2	34.8	12.7	13.1
$Eu^{152,154}$	35.6	25.0	16.6	11.1
Gd^{159}	41.4	12.1	26.9	10.1
Tb^{160}	60.5	6.8	15.6	6.9
Dy^{166}	59.9	2.8	24.1	6.2
Ho^{166}	55.6	2.4	21.2	13.2
Er^{169}	56.4	1.2	27.4	7.4
Tm^{170}	64.1	1.9	22.1	5.2
Yb^{175}	57.8	2.6	19.3	7.3
Lu^{177}	67.6	2.7	15.6	7.3

[a] See reference 6a for complete tabulation of data.

Table V

Distribution of radioisotopes of the actinide elements in various tissues of the rat after intramuscular injection

Radioisotope	Chemical form administered	Time	Percent of absorbed dose				Ref.
			Bone	Kidney	Liver	Excreta	
Ac^{227}	Ac (citrate)	4 days	26.8	0.6	56.4	10.6 UF	43
Th^{237}	Th (citrate)	8 days	66.3	3.3	4.1	14.8 UF	44
Pa^{230}	a	4 days	45.1	4.0	7.8	24.6 F	45
U^{230}	UO_2Cl_2	4 days	10.9	11.8	0.2	76.0 U	39
Np^{237}	b	1 day	44.4	2.6	8.5	36.9 U	46
Pu^{239}	PuO_2Cl_2	4 days	70.9	1.8	8.4	8.2 F	11
Am^{241}	$AmCl_3$	4 days	19.1	2.3	35.7	34.7 F	12
Cm^{242}	$CmCl_3$	4 days	29.0	1.6	40.2	20.0 F	13

a Chemical form unknown but oxidation state probably +4 or +5.

b Administered ion Conc. NH_4Cl and Na_3 citrate; oxidation state +4 or +5.

Table VI

Distribution of radioisotopes of the elements of Group IV in various tissues of the rat after intramuscular injection

Radioisotope	Chemical form administered	Time	Percent of absorbed dose				Ref.
			Bone	Liver	Kidney	Excreta	
C	-	-	-	-	-	-	-
Si	-	-	-	-	-	-	-
Ge^{71}	$NaHGeO_3$	4 days	0.4	0.5	1.1	98.5 U	27
Sn^{113}	Sn (citrate)	4 days	29.4	1.0	3.1	61.2 U	7,42
Pb^{203}	$PbCl_2$	4 days	27.7	1.9	3.1	62.0 UF	7,53
Sub-Group IV							
Ti	-	-	-	-	-	-	-
Zr^{95}	Zr (citrate)	4 days	34.9	6.6	4.3	17.8 [illegible]	27
Hf^{181}	NaHf Mandelate[a]	4 days	15.4	37.8	1.5	5.0 UF	52

[a] Intravenous injection

Table VII

Distribution of radioisotopes of the elements of Group V in various tissues of the rat after intramuscular injection

Radioisotopes	Chemical form administered	Time	Percent of absorbed dose						Ref.
			Muscle	Bone	Liver	Kidney	Blood	Excreta	
N	-	-	-	-	-	-	-	-	-
P^{32}	Na_2HPO_4	1 day	27.4	17.7	-	a	-	22.8 U	54
As^{74}	NaH_2AsO_4	4 days	1.4	2.3	2.4	0.8	44.1	45.7 U	8
$Sb^{122,124}$	$HSbO_3$	4 days	0.1	0.9	0.1	<.1	2.0	96.5 U	41
Bi^{206}	BiOCl or BiO(OH)	4 days	0.6	1.5	6.6	14.4	<.1	75.2 U	55
Sub-Group V									
V^{48}	$Na_2H_2V_6O_{17}$	4 days	5.0	9.9	6.2	4.4	1.5	63.9 UF	56
Nb^{95}	Nb (citrate)	4 days	8.0	16.2	8.4	2.9	7.7	39.4 UF	7, 45
Ta^{182}	Ta_2O_5 in Na_3(citrate)	4 days	12.2	11.9	7.4	5.4	1.2	48.6 U	7, 57

[a] Viscera contained 23.9% of the injected P^{32}

Table VIII

Distribution of radioisotopes of the elements of Group VI in various tissues of the rat after intramuscular injection

Radioisotopes	Chemical form administered	Time	Percent of absorbed dose					Ref.
			Bone	Liver	Kidney	Blood	Excreta	
O	-	-	-	-	-	-	-	-
S	-	-	-	-	-	-	-	-
Se^{75}	$NaHSeO_4$	1 day	8.1	7.3	3.8	6.1	49.8 U	46
$Te^{127,129}$	NaH_5TeO_6	1 day	9.5	5.4	5.4	12.7	61.9 U	4
Po^{210}	Unknown[a]	1 day	2.7	21.0	2.0	19.4	-	58
Sub-Group VI								
Cr^{51}	$NaHCrO_4$	1 day	10.6	3.3	1.4	6.6	57.5 U	59
$Mo^{93,99}$	$NaHMoO_4$	4 hours	3.6	30.3	2.5	2.5	33.0 U	7,55
W^{181}	$NaHWO_4$	1 day	1.2	0.1	0.4	0.2	96.6 U	7,28

[a] Administered orally, converted to whole tissue estimates from specific activity (%/g wet tissue).

Table IX

Distribution of radioisotopes of the elements of Group VII, the halogens, in various tissues of the rat after intravenous injection.

Radioisotopes	Chemical form administered	Time	Percent of absorbed dose					
			Bone	Liver	Thyroid	GI tract + contents	Excreta	Ref.
F^{18}	NaF	9 hours	56.1	.1	.1	0.8	33.2 U	15
Cl	-	-	-	-	-	-	-	
Br^{82}	KBr	8 hours	-	5.6	-	9.2	14.4 U	61
I^{131}	NaI	9 hours	1.2	1.0	23.6	8.4	34.4 U	14
At^{211}	NaAt	9 hours	3.7	6.1	1.6	21.8	16.6 U	14
Sub-Group VII								
Mn^{52}	$MnCl_2$	5 hours	7.1	26.2	.1	35.8	-	55
$Tc^{95,96,98}$	(+4 or +6 hydrated)	24 hours	0.4	0.7	.1	9.0	87.3 U	7
$Re^{183,184}$	$NaReO_4$	4 hours	1.0	1.1	.1	13.2	49.6 U	7,53

Table X

Distribution of radioisotopes of the transition and platinum metals in various tissues of the rat after intravenous injection

Radioisotopes	Chemical form administered	Time	Percent of absorbed dose						Ref.
			Bone	Liver	Kidney	Blood	Muscle	Excreta	
Fe^{59}	$FeCl_3$	3 days	8.4	20.0	2.1	52.5	7.7	6.3 F	44
Ru^{97}	Na_2RuCl_5OH	1 day	6.5	5.8	2.7	7.4	21.4	19.4 U	53
Os^{185} [a]	$NaHOsO_5$ or OsO_4	1 day	1.9	3.6	4.5	2.9	3.4	78.7 U	64
Co^{60}	$COCl_2$	1 day	-	6.3	0.8	0.6	-	67.9 U	65
Rh^{105}	$RhCl_3$ or $RhCl_6^{---}$	1 day	3.7	3.6	2.6	5.9	12.1	47.2 U	37
$Ir^{190,192}$	$IrCl_3$ or $IrCl_6^{---}$	1 day	3.1	19.3	4.0	6.4	5.6	43.5 U	53
Ni	-	-	-	-	-	-	-	-	-
Pd^{103}	Na_2PtCl_4	1 day	1.0	8.6	8.4	0.8	1.3	74.8 U	53
$Pt^{191,193}$	Na_2PtCl_4	1 day	5.8	12.9	9.9	6.6	11.6	36.6 UF	37

[a] Os injected intramuscularly

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