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UCRL-3607

UNIVERSITY OF CALIFORNIA
Radiation Laboratory
Berkeley, California

Contract No. W-7405-eng-48

THE DISTRIBUTION OF RADIOISOTOPES OF SOME HEAVY METALS IN THE RAT

Patricia W. Durbin, Kenneth G. Scott, and Joseph G. Hamilton

November 1956

Printed for the U.S. Atomic Energy Commission

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Division of Medical Physics, the Crocker Radiation Laboratory, and the Departments of Medicine and Radiology of the University of California, Berkeley and San Francisco

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ABSTRACT

Tracer studies have been performed to investigate the fate of carrier-free or high-specific-activity radioisotopes of cadmium, mercury, indium, thallium, tin, lead, niobium, tantalum, molybdenum, tungsten, technetium, rhenium, ruthenium, osmium, rhodium, iridium, palladium, and platinum. Radioisotopes were administered intravenously, intramuscularly, or by stomach tube in neutral isotonic saline or sodium citrate. A brief survey of the toxicological literature is presented for each element. Biological half times were calculated for total retention and retention in the so-called target organs (those organs in which concentration is highest).

On the basis of absorption, distribution, and excretion these 18 heavy metals can be divided roughly into four groups: (a) cadmium and mercury (valence state +2), characterized by relative ease of gastrointestinal absorption and by high accumulation and prolonged retention in liver and kidney; (b) indium, tin, lead, niobium, and tantalum (valence states +2 to +4), characterized by relatively slow absorption from an intramuscular injection site unless given with a complexing agent, by transient retention in liver and kidney, and by prolonged retention in the skeleton (thallium was exceptional probably because of the +1 oxidation state, and more closely resembled silver in its metabolic behavior); (c) molybdenum, tungsten, technetium, rhenium, osmium, and ruthenium (administered as complex anions), characterized by prompt and nearly complete urinary excretion; and (d) the platinum group, rhodium, iridium, palladium, and platinum (valence states +2 to +4), characterized by fairly rapid and nearly complete excretion--both fecal and urinary--with some transient retention in kidney, liver, and spleen. Although palladium and platinum were given as complex anions, they exhibited a metabolic behavior more nearly like that of rhodium and iridium.

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INTRODUCTION

Certain of the heavy metals have long been recognized as highly toxic and have been studied extensively from this viewpoint. The available information on the toxicology of many of the heavy metals has been compiled by Sollmann(1949), Goodman and Gilman (1955), Fairhall (1945), Monier-Williams (1949), and Rothstein (1953).

Recent advances in metallurgy and in the industrial technologies have brought into widespread use a number of metals that were in the past neglected by toxicologists because of their rarity or lack of industrial application. It was therefore of interest to learn something of the fate of small quantities of the lesser-known heavy metals when introduced into the mammalian organism.

Radioisotopes provide a unique tool for the investigation of the fate of minute amounts of various elements or compounds in the animal body under very nearly physiological conditions. In terms of mass, and either chemical toxicity or radiotoxicity, the amounts necessary for quantitative radioactive measurement are negligible, and are often well below the levels of detectability by even the most sensitive methods of chemical analysis. For example, 1 μC of Pb^{203} weighs 3.4×10^{-6} μg, and 1 μC of Cd^{109} weighs 3.9×10^{-4} μg. Naturally occurring radioisotopes were used quite early in the study of lead poisoning by Lomholt (1930), and more recently by Ginsberg and Weatherall (1948) and McDonald et al. (1953), among others. The behavior in animals of some radioactive compounds of thallium has been investigated by Thyresson (1951) and by Barclay et al. (1953); of molybdenum by Neilands et al. (1948) and Comar (1948); of rhenium by Shellabarger (1955); of mercury by Ray et al. (1949) and Lippman et al. (1951), among others; of ruthenium by Hamilton (1947) and Thompson et al. (1956); and of niobium by Hamilton (1947) and by Kawin et al. (1950). Our data on these particular elements are reproduced here in order to gather together the available data, and to facilitate comparison of the distributional patterns of carrier-free radioisotopes** of heavy metals on the basis of their chemical properties.

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** A carrier-free preparation is one in which all the atoms of a particular element are radioactive.

Within the last few years an extensive radiochemical and analytical program at the Crocker Laboratory made available for study small quantities of chemically and radioactively pure carrier-free isotopes of many of the heavy metals. These isotopes were routinely administered parenterally or orally to rats. Their deposition in the tissues and their excretion were followed in a series of tracer experiments; the length of each study was limited only by the half life of the isotope under investigation.

Preliminary presentations of the data from these experiments have appeared, scattered through University of California Radiation Laboratory Medical Physics Quarterly Progress Reports. With the exception of the material on Hg^{197}, In^{114}, and Os^{185}, the data for the various isotopes have been used by the International Commission on Radiological Protection (ICRP) (1955) in the determination of maximum permissible concentrations in air and water, and of tolerance levels in the body. The compilation presented here was prepared to make these data readily available in compact and usable form.

METHODS

Except for Nb^{95} and Ta^{182}--which were obtained from Oak Ridge National Laboratory, Oak Ridge, Tennessee--radioisotopes were prepared on the 60-inch cyclotron at the Crocker Laboratory. Details of target construction, bombardment, yield, chemical procedures, and establishment of radioactive purity can be found by referring to the sources tabulated below:

Isotope	Target element	Reference
Mo^{99}	zirconium	Garrison and Hamilton (1951)
W^{181}	tantalum	Gile et al. (1952)
$Tc^{95,96}$	molybdenum	Garrison and Hamilton (1951)
$Re^{183,184}$	tantalum	Gile et al. (1950a)
$Ru^{97,103}$	molybdenum	Gile et al. (1951c)
Os^{185}	tungsten	Gile et al. (1950b)
Rh^{105}	ruthenium	Gile et al. (1951d)
Ir^{190}	osmium	Haymond et al. (1952)
Pd^{103}	rhodium	Gile et al. (1951)
$Pt^{191,193}$	osmium	Gile et al. (1951b)
In^{114}	cadmium	Garrison and Hamilton (1951)
$Tl^{200,201,202}$	mercury	Gile et al. (1951e)
Sn^{113}	cadmium	Garrison and Hamilton (1951)
Pb^{203}	thallium	Haymond et al. (1951)
Cd^{109}	silver	Garrison and Hamilton (1951)
Hg^{197}	gold	Gile et al. (1951a)

The animals employed were rats--both males and females--of the Sprague-Dawley, Curtis-Dinning, and Slonaker strains, and were mature (more than 100 days of age) when used. A small-animal diet similar to Purina Lab Chow and tap water were given ad lib. throughout the experiments. Radioisotopes in neutral saline or sodium citrate were administered orally, intramuscularly in the right hind leg, or intravenously in the surgically exposed external jugular vein. The probable valence state and dosage in microcuries per rat are shown in Table I.

After injection the animals were placed in metabolism cages in groups of three; urine and feces were collected separately. Groups of three animals were sacrificed at time intervals ranging from 2 hours to 8 months, depending upon the half life of the radioisotope and the quantity available. Details of biological procedures, preparation of samples for radioactive assay, and beta-particle and gamma-ray counting techniques and calculation methods have been presented by Durbin et al. (1956).

RESULTS AND DISCUSSION

A summary of the biological half times in the rat, and the principal deposition sites of 18 heavy metals, are shown in Table II.* Because of their great bulk, the tabular data are not shown;** only major trends are indicated in the bar graphs in the figures. The results for each element are given individually below.

Cadmium

Prodan (1932) and Boudene and Truhaut (1954) found that cadmium accumulated in kidney, liver, and bone whether administered parenterally, orally, or by inhalation. Similar findings for radiocadmium have been reported by the University of Tennessee Agricultural Research Group (1956), who also showed that high-protein diets favored cadmium retention in liver and spleen, and that administration of Cd^{115} as a complex with EDTA (ethylenediamine tetracetic acid) markedly enhanced urinary excretion (40% in 24 hours). At high levels of administration (135 ppm in the diet), Sutton (1939) and Fitzhugh and Meiller (1941) demonstrated that cadmium induced a severe anemia. Wilson and De Eds (1939) indicated that this anemia occurred without significant alteration of the bone marrow. Pathological changes induced by cadmium in the liver and kidney were reported by Prodan (1932), and testicular necrosis has been observed by Parizek and Zahor (1956). Hepatic degeneration might account for the anemia observed by other investigators.

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* Biological half time is definied as the time necessary to eliminate one-half the material initially depositied in the whole animal or tissue, and should not be confused with radioactive half life, which is a physical property of the radioisotope.

** These are available from the authors upon request.

Table I

The probable valence state when injected, and the dosage administered in microcuries of carrier-free radioisotopes[a] of 18 heavy metals

Subgroup, Element	Probable valence state when injected	Dosage μC/ rat
II		
Cd^{109}	+2 as $CdCl_2$	~2
Hg^{197}	+2 as $HgCl_2$	6-160
III		
In^{114}	+3 as $InCl_3$	0.5
$Tl^{200,201,202}$	+1 as TlCl	15-40
IV		
Sn^{113}	+4 as $SnCl_4$[b]	2
Pb^{203}	+2 as $PbCl_2$	3-7
V		
Nb^{95}	+3 as $NbCl_3$[b]	~10
Ta^{182}	+5 as Ta_2O_5[b]	10
VI		
Mo^{99}	+6 as Na_2MoO_4	3
W^{181}	+6 as Na_2WO_4	1-2
VII		
$Tc^{95,96,98}$	+4 or +6	100
$Re^{183,184}$	+7 as $NaReO_4$	2-4
Transition Group		
$Ru^{97,103}$	+4 as Na_2RuCl_5OH	10-50
Os^{185}	+8 as Na_2OsO_5	~20
Rh^{105}	+3 as $RhCl_3$	2-7
Ir^{190}	+3 as $IrCl_3$	7-14
Pd^{103}	+2 as Na_2PdCl_4	0.5-2
$Pt^{191,193}$	+2 as Na_2PtCl_4	2-14

[a] Half lives and radiation characteristics have been published by Hollander, Perlman, and Seaborg (1953).

[b] Administered with sodium citrate.

Figure 1 shows the distribution of Cd^{109} 1, 8, and 60 days after intramuscular administration. During the 2 months following administration of Cd^{109}, 95% of the dose was absorbed from the site of injection. After oral administration 0.25% of the dose could be detected in the animal at 4 days. Cd^{109} was excreted slowly by way of the digestive tract; only 18% was eliminated in 60 days. That which was eliminated could be accounted for by the loss from the liver and the gastrointestinal tract. The liver and kidney contained the greater part of the retained Cd^{109} (70% of the administered dose at 2 months). In contrast to liver and bone, which gradually eliminated the isotope, the kidney continued to accumulate some of the Cd^{109} that had been returned to the circulation from these tissues. Cd^{109} was not eliminated to a significant degree from the soft tissues (designated as balance), for these contained as much at 2 months as they had at 1 day.

The tracer data agree quite well with chemical analyses of cadmium-poisoned animals and with the spectrographic analyses by Tipton et al. (1956) of normal human tissues, indicating that traces of cadmium are handled in much the same manner as macroscopic amounts.

Mercury

Extensive data on the occurrence of mercury in foods and the tissues of normal unexposed animals and man have been compiled by Stock (1940), Butt et al. (1950), and Griffiths et al. (1954). These investigators found traces of mercury in nearly all human and animal tissues, in excreta, and in most foods. In normal animals mercury is deposited primarily in kidney and bone, and excreted by the kidney and gastrointestinal tract.

Lippman and co-workers (1951) demonstrated autoradiographically that radiomercury administered with stable $HgCl_2$ was deposited to a great extent in the renal cortex. Mercury has long been recognized as a serious industrial hazard. Inhalation of its vapor or introduction of mercury compounds orally or parenterally is followed by progressive renal-tubular damage (reviewed by Sollmann, 1949), and hepatic degeneration, which was described by MacNider (1919). The severity of acute symptoms is a function of the solubility of the compound as well as of the dose. Chronic mercury poisoning (reviewed by Fairhall, 1945) often involves one or more of the following: stomatitis, renal irritation, malnutrition, anemia (probably of hepatic origin), bone decalcification, and nervous symptoms.

Using Hg^{203} as a tracer for a mercurial diuretic, chloromerodrin, Borghgraef and Pitts (1956) found that BAL (British Anti-Lewisite) enhanced urinary excretion and reduced renal binding of mercury.

Figure 1 shows the distribution of carrier-free Hg^{197}, 1 and 8 days after intravenous administration. Nearly one-half the administered radioisotope was excreted, mainly in the feces. The initial phase of urinary excretion following the administration of soluble mercurials to man described by Sollmann (1949) was not observed, however, This has been attributed to a

Table II

Physical and biological half lives and half times for removal from the principal sites of deposition of 18 heavy metals. Where more than one half-time value is shown, retention curve is complex and consists of at least two components.

Subgroup, Element	Half life	Biological half life	Half time for removal from principal organs of deposition
II			
Cd^{109}	470d	200d	Liver: 200d, kidney: no elimination
Hg^{197}	65h	8.5d	Kidney,[a] liver: 2.5d
III			
$In^{114,114m}$	49d	17.5d	Spleen: no elimination, kidney: 20d, skeleton: 32d, liver: 18d
$Tl^{201,202}$	72h, 12.5d	5.2d	Kidney: 7d, muscle: 6d
IV			
Sn^{113}	112d	0.4d, 84d	Skeleton: 100d
Pb^{203}	52h	<5d[b]	Skeleton,[b] kidney,[b] liver[b]
V			
Nb^{95}	35d	2d, 56d	Skeleton: 2.8d, 125d, kidney: 44d, liver: 45d
Ta^{182}	111d	0.5d, 70d	Skeleton: 260d, liver: 125d spleen: no elimination
VI			
Mo^{99}	67h	<0.5d[b]	Liver,[b] kidney[b]
W^{181}	140d	1.5h, 7h	None: Excretion 95% complete in 24 hours
VII			
$Tc^{95,96}$	60d, 4.2d	0.4d[b]	Kidney[b]
$Re^{183,184}$	155d, 50d	<0.5d[b]	None: Excretion 90% complete in 24 hours
Transition Group			
$Ru^{97,103}$	2.8d, 39.8d	11d	Kidney,[a] liver: 19.5d, skeleton: 11d, GI: 12d
Os^{185}	97d	<1d[b]	Kidney,[b] liver[b]
Rh^{105}	36.5h	16.5d	Kidney: 25d, liver: 9.5d, spleen: no elimination
Ir^{190}	12.6d	11d	Liver: 10d, 300d, kidney: 26d
Pd^{103}	17d	2 hr, 6d	Kidney: 9d, liver: 6d
$Pt^{191,193}$	3d, 4.3d	1d, 10d	Kidney: 3d, 47d, spleen[a]

[a] Isotope content of organ increased during time interval investigated.

[b] Biological half times in doubt; less than three points available.

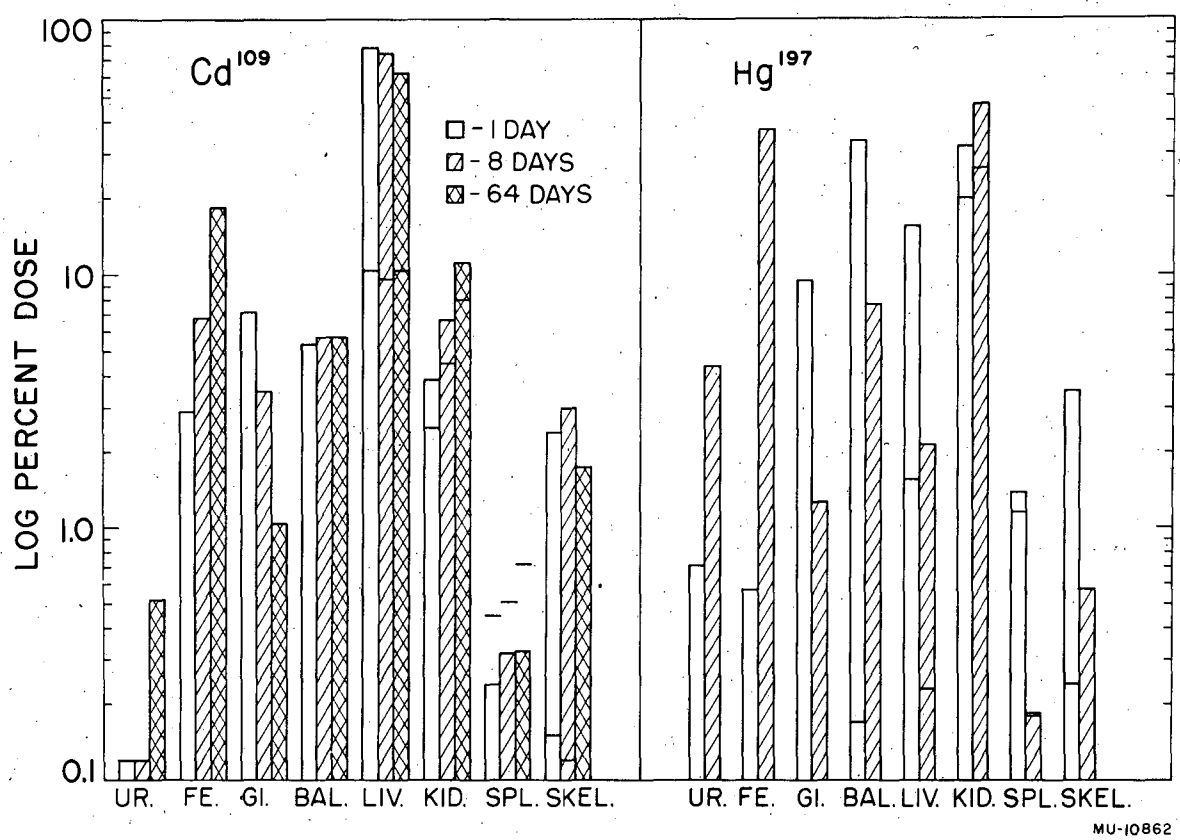

Fig. 1. The distribution of Cd^{109} and Hg^{197} in the rat. The data are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100%. The horizontal cross bars show the concentrations in percent per gram of wet tissue.

species difference by Borghgraef and Pitts (1956). The Hg^{197} content of the skeleton and of all the soft tissues except kidney decreased notably from the first to the eighth day, on the average by a factor of 5 to 7. Although the longest time interval investigated was only 8 days, the enhancement of the Hg^{197} concentration in the kidney indicated that even minute amounts of mercury would be held tenaciously for long periods of time. These data on the excretion and distribution of tracer doses of Hg^{197} are in accord with the findings by Stock (1936) and by Sollmann and Schreiber (1936), which were obtained from acutely poisoned animals and from man.

An attempt by Scott et al. (1951) in this laboratory to increase the excretion of Hg^{197} by the oral administration of a chelating agent, the calcium salt of ethylene diaminetetracetic acid (CaEDTA), was unsuccessful.

The distributions of carrier-free Cd^{109} and Hg^{197} were similar, as might be expected on the basis of their chemical similarity; however, Hg^{197} seemed to be more readily released from soft tissues (excluding kidney) and excreted to a greater extend than was Cd^{109}. Localization of Hg^{197} in the kidney was more selective.

Indium

Orally administered indium is relatively nontoxic. This has been ascribed, by Steidle (1933) and by Harrold et al. (1943), among others, to its slow absorption from the digestive tract. McCord et al. (1942) showed that indium is much more toxic when administered parenterally. Vignoli et al. (1946) described lesions in liver, kidney, and skeletal muscle after toxic doses.

Results of the tracer studies with $In^{114, 114m}$ are shown in Fig. 2. Radioindium was slowly absorbed; 46% remained at the intramuscular injection site at 1 day, and 17.4% remained at 16 days. Less than 0.1% of the dose was absorbed when In^{114} was given orally. Excretion was fecal for the most part, but some radioindium was also eliminated in the urine. Liver, kidney, spleen, and bone were the principal sites of deposition, and elimination from these tissues was small. The In^{114} excreted was apparently derived from muscle and skin, although after 16 days both these tissues retained a large fraction of that originally deposited--11.8 and 16.4%, respectively.

The results of these tracer studies are in complete agreement with previous toxicological studies as regards absorption, excretion, and sites of damage, which are probably a reflection of the quantity deposited and retained.

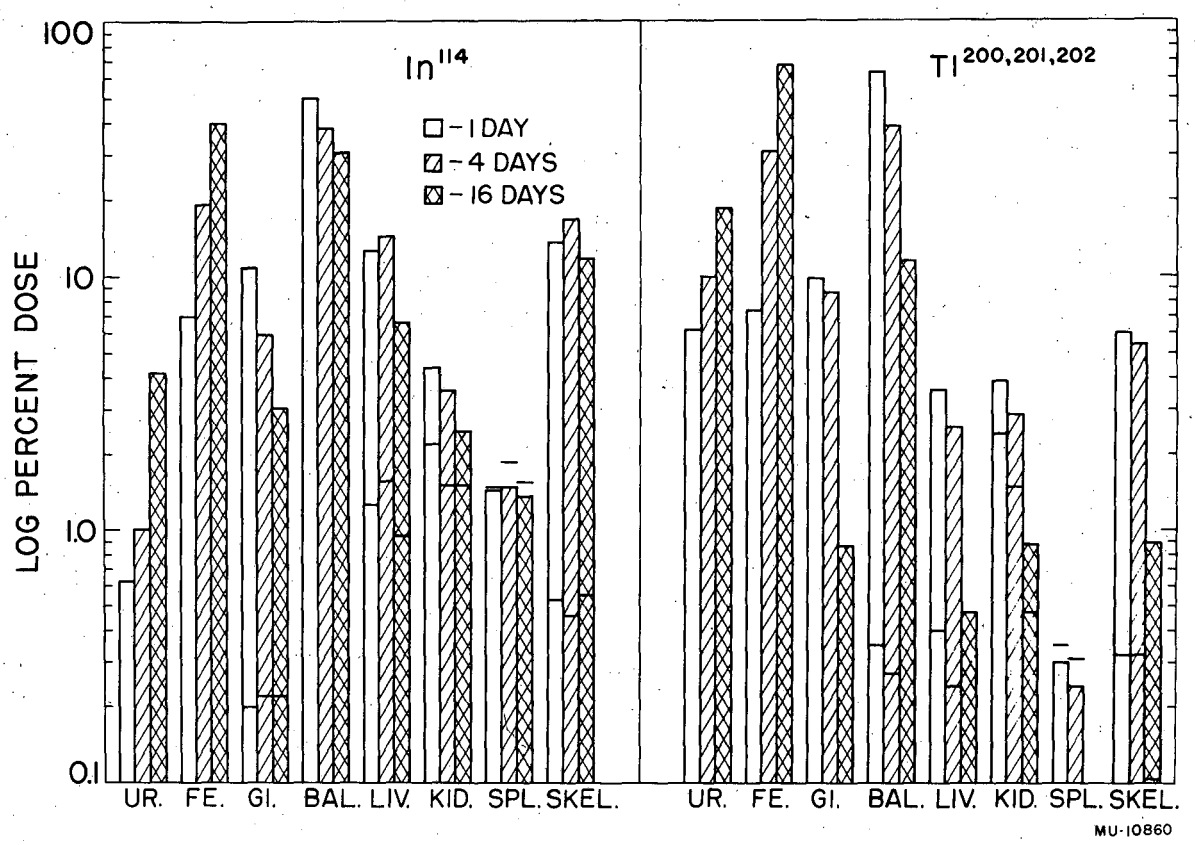

Fig. 2. The distribution of In^{114} and $Tl^{200, 201, 202}$ in the rat. The data are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100%. The horizontal cross bars show concentrations in percent per gram of wet tissue.

Thallium

According to Monier-Williams (1949) and Tipton et al. (1956), thallium does not occur in either plants or animals even in traces, but it is of considerable interest because of its chemical toxicity--very nearly that of arsenic--and because of its use in depilatories and vermicides. Truhaut (1952) reported that after parenteral administration thallium was present in all tissues and organs, but mainly in liver, brain, and skeletal muscle. Shaw (1933) and Testoni (1933) found that orally administered thallium was excreted, to a large extent, in the urine. Pathological changes in many tissues have been described by various workers (reviewed by Sollmann, 1949) following chronic thallium intoxication; the most noteworthy are the degeneration of the endocrine glands, epilation, central necrosis of the liver, and renal tubular and glomerular damage.

Figure 2 shows the change of distribution of $Tl^{201,202}$ with time after intravenous injection. Radiothallium was readily absorbed from the gastrointestinal tract; 8 days after oral administration 25% of the dose was retained in the animal, and another 17.7% had been excreted in the urine. Thus, a lower limit of 50% absorption may be set. This value is somewhat lower than has been reported by Sollmann (1949) for other species. Excretion of intravenous radiothallium was both fecal and urinary, the former predominating. Initially, the principal deposition sites were kidney and muscle, and to a lesser extent, skin and skeleton. Although the longest time interval studied was only 15 days, it does not appear likely that any of these tissues retain carrier-free radiothallium for long periods of time. Auxiliary experiments indicated that this distribution was not significantly altered when as much as 1 mg of stable thallium was given with the tracer, although there was a tendency towards greater deposition in muscle and towards reduced fecal excretion.

The results of our tracer studies with radiothallium are in accord with those conducted by Thyresson (1951) and by Barclay et al. (1953). Carrier-free $Tl^{201,202}$ appears to be more readily excreted than macroscopic amounts.

Although indium and thallium belong to the same chamical subgroup, their metabolic behavior cannot be compared because of the difference in the oxidation state stable at the pH of the animal body; thallium exists as Tl^{+} and indium as In^{+++}. Indeed, the metabolism of radiothallium more closely resembles that of radiosilver (administered as Ag^{+}), which has been described by Scott and Hamilton (1950); the retention of $Tl^{201,202}$ was more prolonged. The distribution of In^{114}, on the other hand, was reminiscent of that of Ga^{72} (Ga^{+++}), reported by Bruner et al. (1953).

Tin

Tin is found in traces in most soils, and very small amounts occur in plant and animal tissues, but as far as is known, it has no biological function. The presence of larger quantities in food and in the human body is due, for the most part, to its use as a protective coating for food containers. Kent and McCance (1941) found that 50% of a 1-mg dose of a soluble tin salt was absorbed and subsequently excreted in the urine. The proportion absorbed appeared to decrease with increasing dosage. The retention of tin in the normal human body was demonstrated by Salent et al. (1914, 1918) and by Misk (1923). Seifter and Rambousek (1943) detected tin in all organs and tissues, with greater amounts in liver, kidney, skeleton, and muscle after the administration of stannous and stannic citrates or tartrates. According to findings reviewed by Monier-Williams (1949), soluble tin salts are relatively nontoxic when given orally; however, 1 g per week to rabbits for several weeks causes death, with inflammation of the stomach, degeneration of liver and kidneys, and paralysis of the hind legs.

Our tracer results, except those for the 2-month interval, are summarized in Fig. 3. Orally administered carrier-free Sn^{113} was absorbed to some extent. Skeleton and muscle contained 0.36% at 16 days; the reminder had passed in the feces 48 hours after administration. Absorption of an intramuscular injection was likewise poor; 85% of the administered dose was unabsorbed 25 hours after injection. When the radiotin was complexed with sodium citrate, absorption was greatly enhanced, and the amount remaining at the injection site was 11% at 1 day and 3% at 2 months.

Urinary excretion of radiotin occurred only during the first 24 hours after administration, and amounted to 50% of the injected dose. In the ensuing 30 days another 20% of the dose was eliminated by the digestive tract; no further excretion occurred after this time. The Sn^{114} initially distributed in the soft tissues was rapidly lost, and accounted for most of the fecal excretion. The most important deposition site of radiotin was the skeleton, which had accumulated 30% of the administered dose by the end of the first day. Two-thirds of that originally laid down in bone was still present 2 months later, indicating prolonged skeletal retention.

Lead

Lead constitutes one of the most important industrial hazards, not because of its acute toxicity, which is rather low, but because of its tendency towards cumulative effects. Most lead compounds are absorbed readily from mucous membranes and exposed surfaces. Kehoe et al. (1940) reported a daily excretion of lead by normal adults that was very nearly equal to intake. In chronic lead poisoning excretion is intermittent and prolonged, traces appearing in both urine and feces long after absorption has ceased. The tissue distribution of lead compounds has been studied exhaustively--chemically and with radioactive isotopes by Behrens et al. (1928, 1933), Lomholt (1930), Butt and Simonsen (1950), and Tipton et al. (1956), among others--and has been found to be generally similar for various compounds,

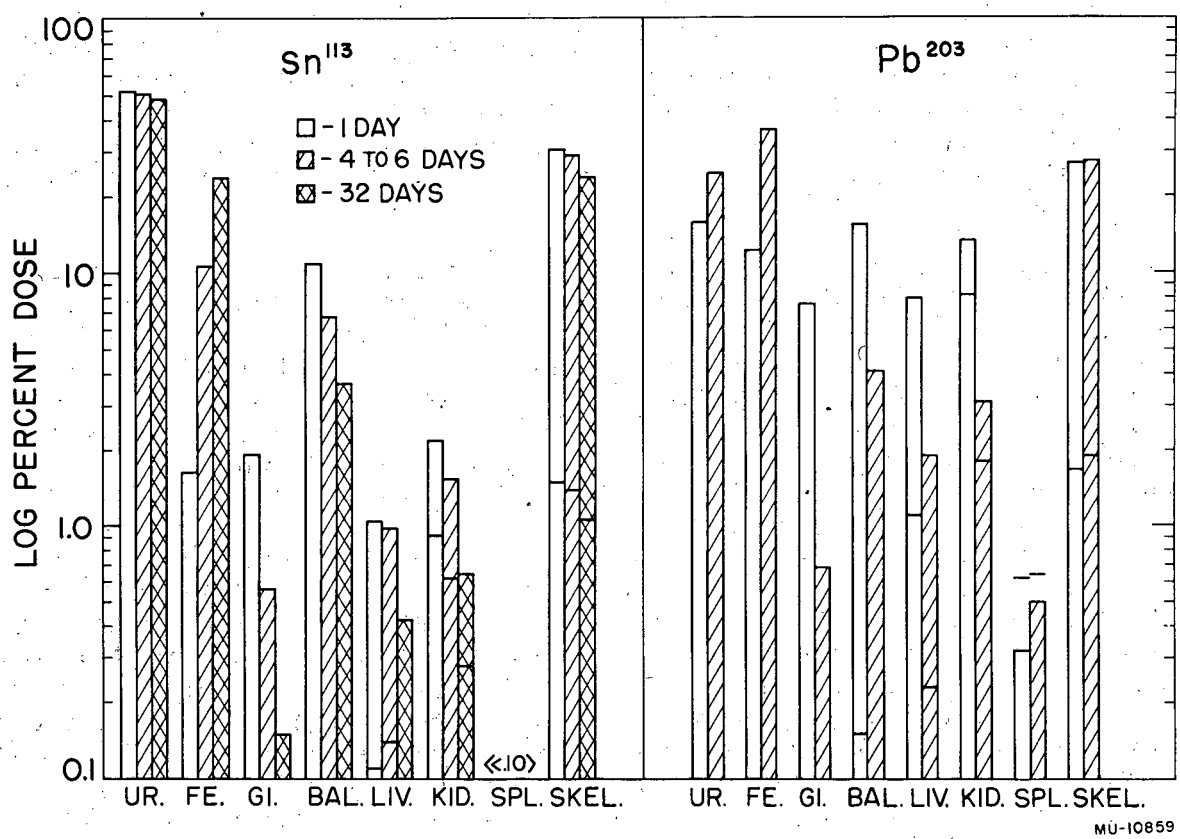

Fig. 3. The distribution of Sn^{113} and Pb^{203} in the rat. The data are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100%. The horizontal cross bars show the concentrations in percent per gram of wet tissue.

species, and amounts of lead administered. Early after absorption the greater part is in kidney and liver, but later a shift to the bones occurs, so that in chronic lead poisoning nearly one-third of the total body lead is found in the skeleton. The ultimate association of skeletally fixed lead with calcified bone was noted quite early (see Sollmann (1949) for early work), and has recently been studied by MacDonald et al. (1951) using x-ray diffraction techniques. These workers found that skeletally deposited lead was incorporated into the crystal structure of the bone salt, and that its subsequent elimination was therefore dependent upon the extent of bone resorption and reformation.

The effects of zirconium citrate and of the tetrasodium salt of EDTA on the tissue distribution and excretion of lead have been studied by Ginsburg and Weatherall (1948), Schubert and White (1952), and MacDonald et al. (1953). These two chemicals enhanced urinary excretion and diminished soft-tissue binding to some extent, but did not significantly alter skeletal retention. Skeletal lead was decreased by sodium-EDTA, but only when it was given immediately after the lead injection, and then at the expense of skeletal calcium, which is also strongly chelated by this agent. Neither of the above-mentioned compounds has been successfully applied in the treatment of lead poisoning.

Sollmann (1949) lists kidney damage, anemia, and various muscular, nervous, and skeletal disorders among the symptoms of chronic lead poisoning.

The tracer data for the distribution of Pb^{203} 1 and 6 days after intravenous administration are shown in Fig. 3. On the first day liver, kidney, blood, and bone contained 55% of the administered dose; 28% had been excreted in the urine and feces. By the sixth day most of the lead in the soft tissues had been eliminated (in the feces), whereas the skeletal lead remained the same as on the first day.

The dicalcium salt of EDTA was administered to another group of rats treated with radiolead. EDTA was given at a level of 3% in the food daily on the fourth, fifth, and sixth days after the lead injection, and the animals were sacrificed on the sixth day. Given orally, in this form (Ca_2EDTA), the chelating agent had no effect on the distribution of radiolead in either soft tissue or skeleton, and failed to augment its excretion significantly.

The tracer data for both radiotin and radiolead are in line with previous findings on the sites of deposition and channels of elimination, both qualitatively and quantitatively. The distribution of these two radioelements was quite similar in most respects; however, comparative data on absorption are lacking. Both are accumulated and retained by the skeleton to the extent of 25 to 30% of the administered dose. Both are eliminated initially by the kidney and later by the gastrointestinal tract, and to about the same extent. The pattern of distribution in the soft tissues is similar; more radiolead is found in kidney, blood, and liver at the earlier times.

Niobium

Ores containing niobium (columbium) are usually associated with those of tantalum, zirconium, and the rare earths. Little work has been done on the toxicology of niobium because of the rarity of its minerals, their insolubility, and its relatively limited industrial uses. No detectable quantities of niobium have been found by Tipton et al. (1956) in their extensive spectrographic analysis for trace elements in human tissues. The acute oral toxicity of $KNbO_3$ in rats is quite low, 3 g/kilo as determined by Cochran et al. (1950). These same workers reported an MLD (mean lethal dose) of 14 mg/kilo of niobium when injected intraperitoneally as $NbCl_3$. Shubert (1949) reported, without elaboration, that toxic symptoms of a chronic nature developed after the intravenous administration of $NbCl_3$. Deposition of radioisotopes of soluble niobium compounds has been studied by Hamilton et al. (1948) and Kawin et al. (1950).

The tracer data for Nb^{95} are shown in Fig. 4. When administered intramuscularly in isotonic saline, $Nb^{95}Cl_3$ was slowly absorbed, 35% at 1 day and 60% at 16 days. Absorption was increased to 70% at 1 day and 92% at 16 days when Nb^{95} was complexed with either sodium citrate or oxalate. Niobium was eliminated by both major channels; urinary excretion predominated during the first 2 weeks, and fecal excretion thereafter.

As might be expected for a tripositive ion, the main deposition sites of Nb^{95} were liver and skeleton; however, the soft tissues and blood contained a large proportion of the administered dose--38% at 1 day. Elimination from muscle, blood, skin, and liver was fairly rapid, whereas Nb^{95} deposited in kidney, bone, and lymphatic tissue (e.g., spleen) was removed quite slowly.

Tantalum

Metallic tantalum is so insoluble that it is used widely in surgery for sutures, plates, and internal splints, and when embedded in tissue produces no detectable physiological or toxicological effects. To date tantalum has not been found, even in minute amounts, in either plant or animal tissues. Cochran et al. (1950) determined the acute toxicity of suspensions of several compounds of tantalum in rats: orally the mean lethal dose of Ta_2O_5 was 6.5 g/kilo and of $TaCl_5$, 0.96 mg/kilo; intraperitoneally the toxic doses of TaK_2F_7 and $TaCl_5$ were 173 and 38 mg/kilo respectively. According to Machlin et al. (1952), $Ta(OH)_5$ is about as toxic to the developing chick embryo as is $ThCl_4$. Doull et al. (1950) studied the intraperitoneal absorption of suspensions of radioactively tagged Ta_2O_5 in rats. Approximately 95% of the Ta^{182} activity remained in the peritoneal cavity 6 days after injection; less than 0.1% appeared in the urine during this time.

In our experiments radiotantalum was administered with 0.1 mg of stable tantalum carrier, both intravenously and intramuscularly. After 1 month only 15% of the radiotantalum was absorbed from an intramuscular injection site when no complexing agent was used. Reducing the amount of carrier and complexing with sodium citrate increased absorption to 70% of the dose at 30 days; no further absorption occurred thereafter.

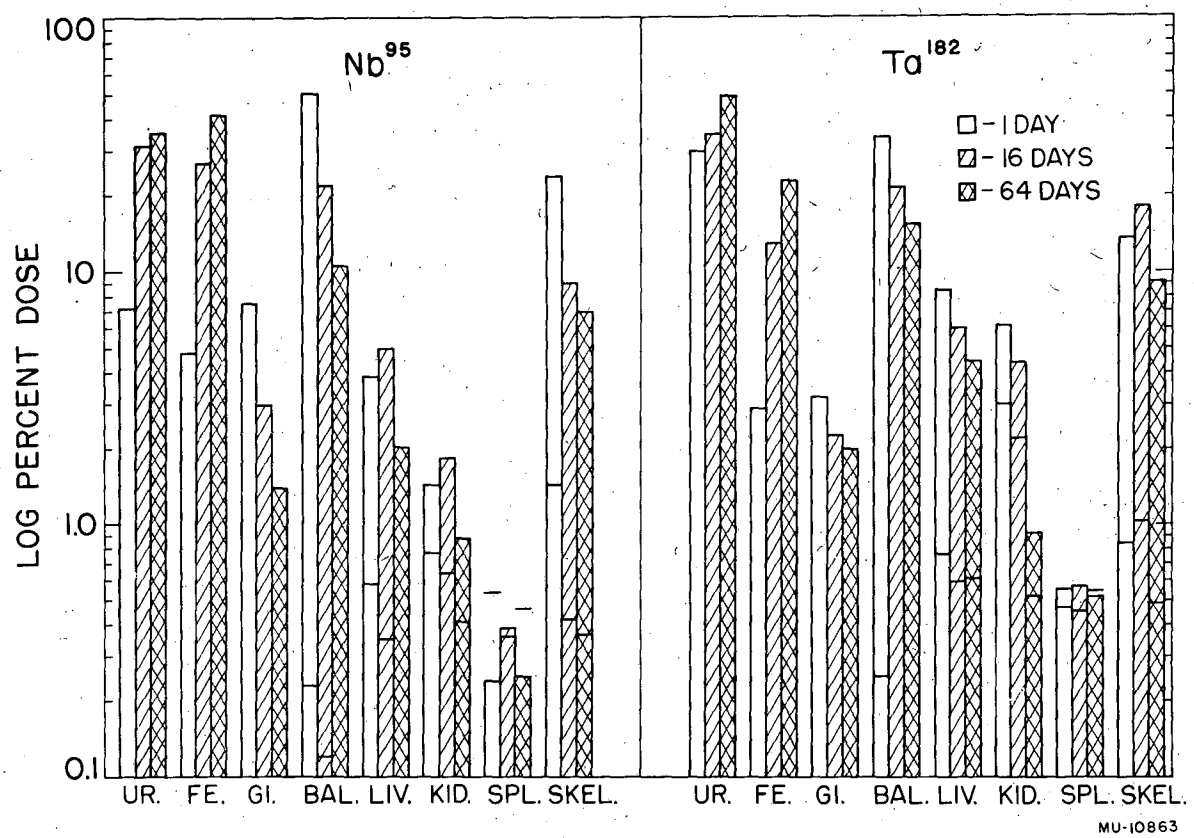

Fig. 4. The distribution of Nb^{95} and Ta^{182} in the rat. The data are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100%. The horizontal cross bars show the concentrations in percent per gram of wet tissue.

Intravenously administered radiotantalum (data not shown) with or without sodium citrate behaved in a colloidlike fashion, that is, high concentrations were found in spleen and lymphatic tissues, liver, and bone marrow. Less than half the radiotantalum colloid was broken down and excreted during the ensuing 8 months.

After absorption from an intramuscular injection site, radiotantalum behaved presumably as an ion. The results of such studies are shown in Fig. 4. The early distribution was much like that of niobium; the highest concentrations were found in liver, kidney, and skeleton, but with significant quantities in blood, muscle, and skin. With the exception of blood, tantalum was eliminated from these tissues very slowly; the half times for these tissues were greater than 6 months. Half the eliminated tantalum was passed in the urine in the first 24 hours, apparently as the unchanged complex. After this time fecal and urinary excretion were similar in both rate and amount.

The distributions of Nb^{95} and Ta^{182} (despite the difference in valence state of the compounds administered) were surprisingly similar; however, Ta was more difficultly absorbed and was generally eliminated much more slowly.

Molybdenum

Molybdenum occurs in variable amounts in almost all soils and plant and animal tissues (Underwood, 1956). Burk and Horner (1936), among others, have pointed out that traces of molybdenum in the soil were necessary to nitrogen fixation and thus to plant growth.

Orally administered molybdenum is poorly absorbed by rats (Teresi, 1942), but is fairly well absorbed by ruminants (Comar, 1948). Excretion of molybdenum takes place mainly via the kidneys (50 to 80%) in most species (Comar, 1948, and Nielands et al., 1948). Fecal excretion takes place to a lesser degree; molybdenum has also been found in bile by Canjolle (1937). Elimination is rapid even when large amounts are given, according to Nielands et al. (1948). Most of the tissues of normal animals contain traces of molybdenum, particularly liver and kidney (Tipton et al., 1956); some is also found in bone and lymphatic tissues (Comar, 1948). In poisoned animals the tissue distribution is similar to the trace distribution (Nielands et al., 1948).

Large amounts of molybdenum in pasture cover and cattle fodder have been shown to produce in ruminants pathological changes similar to those induced by selenium (Ferguson et al., 1938). This condition, reviewed by Monier-Williams (1949), can be overcome by adding copper sulfate to the ration; there is no adequate explanation for this interaction at the present time. The oral toxicity of molybdenum has been reported for rats by Franke and Maxon (1937) as equivalent to that of arsenic. The acutely toxic oral dose for rats has been established by Nielands et al., (1948) at about 0.5% in the diet. Gray and Ellis (1950) and Williams and Van Reen (1956) found that 0.8% of molybdenum in the diet of rats retarded growth, reduced food consumption, and altered the alkaline phosphatase content of liver and kidney. Comar et al. (1937) reported that rats on a diet containing 80 ppm of molybdenum showed retarded skeletal growth, with poor calcification, diarrhea, rough coat, and in severe cases excessive lacrimation.

The tracer data for the short-term tracer study with Mo^{99} are shown in Fig. 5. After intravenous injection, urinary excretion accounted for nearly one-third of the administered dose and liver for an additional third. The remainder was distributed in the gastrointestinal tract, blood, and soft tissues. Liver, kidney, and pancreas contained the highest concentration of Mo^{99}--3.8%, 1.5%, and 0.8% per gram, respectively.

Tungsten

Chemically, tungsten resembles molybdenum in many respects and is toxic to animals, but has not been reported as occurring in vegetation or in unexposed animals (Monier-Williams, 1949). Kinard and Aull (1945) fed Na_2WO_4 to rats and found that bone and spleen and--to a lesser degree--skin, kidneys, and liver accumulated tungsten. Tungsten was not detected, however, in any tussues taken from the control animals. These findings substantiated earlier work with guinea pigs by Karantassis (1925). Selle (1942) reported that subcutaneously injected tungstate was almost quantitatively excreted in the urine in 12 hours, and that when it was administered orally, elimination was complete in 24 hours.

Kinard and his co-workers (1940, 1941) determined that 2% tungsten as Na_2WO_4 in the diet of rats was fatal in from 3 days to a few weeks. They also found that for rats the MLD of intravenously administered tungstate was 240 mg/kilo and that toxicity was greater in older rats. Prolonged daily subcutaneous administration to rats of 0.5 cc/100 g body weight of a 0.1 M solution of sodium tungstate retarded growth (body weights 25% less than controls) and caused a 45% increase in the weights of the kidneys and adrenal glands (Selle, 1942).

The results of a 4-hour tracer study of intravenously injected W^{181} are shown in Fig. 5. Absorption of intramuscularly administered W^{181} was quite rapid--55% at 4 hours and 99% at 24 hours. Orally administered radiotungsten was absorbed more slowly; only 10% was found in the urine and tissues other than the gastrointestinal tract at 4 hours.

Parenterally administered W^{181} was excreted almost quantitatively in 24 hours; 86 to 90% in the urine and 5 to 9% in the feces. Four days after injection excretion was 98% complete.

The route of injection did not appear to influence organ distribution. Four hours postinjection kidney, skeleton, and lung had the highest concentration of W^{181}. At 4 days only liver, skeleton, and skin contained measurable amounts of W^{181}, totaling 2% of the administered dose.

Distribution and excretion of radioactive isotopes of molybdenum and tungsten in the +6 state were generally similar. The lack of data for Mo^{99} makes comparison difficult, but it would seem that W^{181} was more rapidly absorbed and more rapidly and completely eliminated.

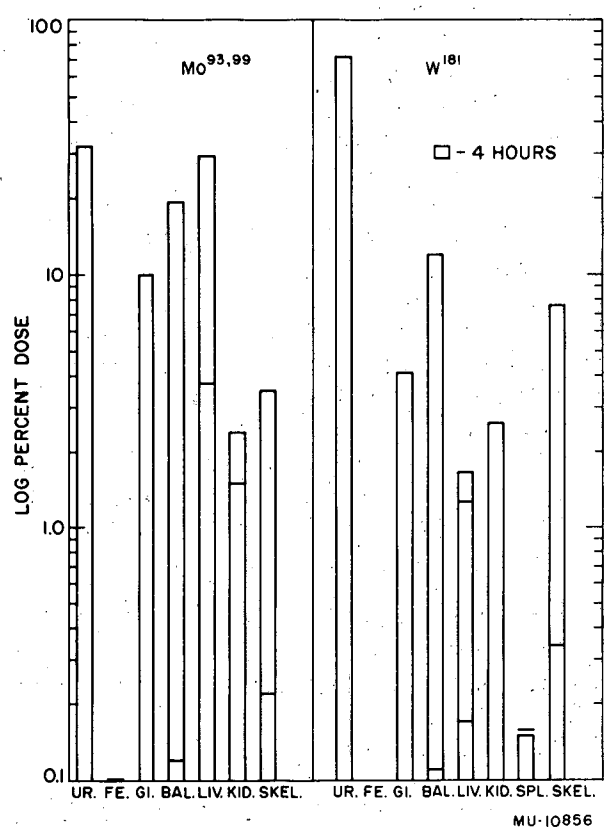

Fig. 5. The distribution of $Mo^{93,99}$ and W^{181} in the rat. The data are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100%. The horizontal cross bars show the concentrations in percent per gram of wet tissue.

Technetium

This element (atomic number 43) does not occur in nature, but can be produced by cyclotron bombardment, and its isotopes are found in relatively large quantities in the products of nuclear fission (Hollander et al., 1953). It is of interest for two reasons, (a) as a potential radiation hazard, and (b) for comparison with chemically similar elements, manganese and rhenium.

Results of 1-day tracer study with $Tc^{95,96}$ are shown in Fig. 6. Intramuscularly administered technetium was almost completely absorbed within 24 hours--97.3%. Elimination was rapid; urinary and fecal excretion accounted for 73% and 15% of the dose at 1 day, and 80.4% and 18.4% of the dose at 8 days, respectively. At 8 days kidney and skin were the only tissues containing measurable amounts of $Tc^{95,96}$. Tracer studies of only a few hours' duration were performed in an attempt to repeat the observation of Baumann et al. (1953) that $Tc^{95,96}$ was selectively accumulated by the thyroid gland; our experiments were inconclusive.

Rhenium

Rhenium is a rare element and occurs in association with platinum and molybdenum ores. To date it has not been detected in living systems, even in traces. Hurd et al. (1933) administered potassium perrhenate intravenously to rabbits. Large amounts were found in the urine and smaller amounts in liver, kidney, and spleen 60 to 90 minutes after injection. Baumann et al. (1949) and Shellabarger (1955) investigated the thyroidal uptake of radioactively tagged perrhenate and found that the thyroid glands from animals poisoned with thiouracil or maintained on a low-iodine diet rapidly accumulated and released rhenium. The peak rhenium concentration (10% / g of thyroid) occurred 1 to 2 hours after injection.

The acutely lethal dose of parenterally administered perrhenates was found by Maresh et al. (1940) to be in the neighborhood of 900 mg rhenium per kilo. Solutions of K_2ReCl_6 were much more toxic (exact figures were not given), and at the autopsy of animals intraperitoneally injected with this compound a black residue of mixed rhenium oxides coated the organs of the peritoneal cavity. The same investigators subjected rats to periodic injections to 40 to 230 mg/kilo of rhenium for long periods of time, and concluded that there were no significant effects.

Distribution of $Re^{183,184}$ 1 day after intravenous administration is shown in Fig. 6. Even as early as 4 hours postinjection, excretion was 50% complete. At this time skin, stomach, and thyroid had the highest concentrations of rhenium--0.58%, 3.03%, and 6.4% of the dose respectively. The gastric contents contained 8%. By the end of 24 hours only the skin and gastrointestinal contents retained significant amounts of $Re^{183,184}$. At 16 days the skin still contained 1% of the administered dose (possibly owing to contamination by urine). Urinary excretion accounted for 92% of the injected $Re^{183,184}$ in 24 hours. By 16 days excretion was essentially complete--urine 94% and feces 5%. Administration of 50 μg of stable rhenium depressed thyroid uptake to less than 1% / g at 4 hours and accelerated the urinary excretion rate.

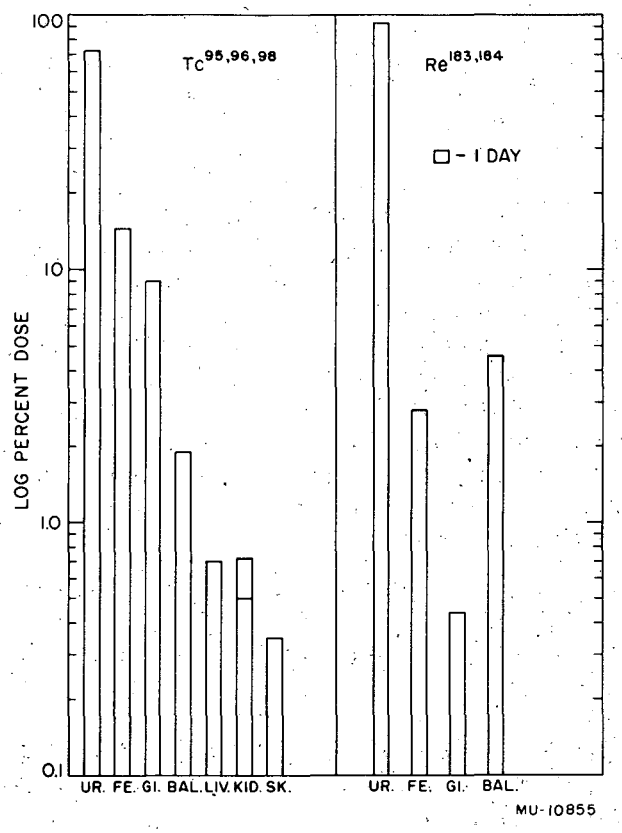

Fig. 6. The distribution of $Tc^{95, 96, 98}$ and $Re^{183, 184}$ in the rat. The data are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100%. The horizontal cross bars show the concentrations in percent per gram of wet tissue.

The excretion and distribution of $Tc^{95, 96}$ and $Re^{183, 184}$ were almost identical, and at early postinjection intervals, 1 to 4 hours, were quite reminiscent of carrier-free radioiodine (Hamilton et al., 1953). The data on tissue distribution agree well with the observations by Shellabarger (1955). The reports of selective accumulation of rhenium by the thyroid gland, mentioned above, are well documented. Thus it is likely that our failure to demonstrate thyroidal accumulation of $Tc^{95, 96}$ was the result of inadequately controlled experimental conditions--in particular, the valence state of the administered $Tc^{95, 96}$ and the high iodine content of the stock diet in use at the time.

Ruthenium

A search of the literature revealed no previous work on the toxicity or biological effects of ruthenium. Tipton's (1956) group looked for ruthenium in human tissues, but not even traces were found. Recently Thompson et al. (1955) have completed a comprehensive study of the absorption, distribution, and elimination of radioactively tagged ruthenium in rats. Gastrointestinal absorption of radioruthenium in the +3 or +4 valence state as soluble compounds or colloidal suspensions ranged from 0.9 to 1.7% of the administered dose in 24 hours. Addition of as little as 0.05 mg of stable ruthenium reduced absorp absorption by a factor of nearly two; larger amounts of carrier had little further effect. A group of rats was fed Ru^{106} for time intervals ranging from 1 to 200 days. Tissues that experienced a build-up of Ru^{106} concentration during the feeding period were kidney, liver, testes, spleen, and bone. Equilibrium was apparently established in these tissues by the seventieth day. Muscle, however, continued to accumulate Ru^{106} during the remainder of the feeding period. After a single intravenous or intraperitoneal injection, tissue concentrations of Ru^{106} were very similar to those found in the chronically fed animals. Excretion of parenterally administered radioruthenium was both fecal and urinary, 20% and 50% of the dose respectively in 60 days. Half times for retention were given for a number of tissues.

The data for the short-term intravenous tracer studies with Ru^{97} are shown in Fig. 7. On the whole these data agree well with those of the Hanford group. The kidney appeared to be the chief excretory organ and the main deposition site. At 7 days the greatest concentrations of radioruthenium were found in kidney, liver, bone, skin, and the lymphatic tissues. At this time, the abdominal organs of our animals contained less Ru^{97}, and skin and muscle contained more, than was reported by Thompson et al. (1955). These discrepancies may be due to (a) the different route of injection, (b) the chemical compound of ruthenium employed, and (c) the presence of small amounts of stable ruthenium in the preparations used by the Hanford group.

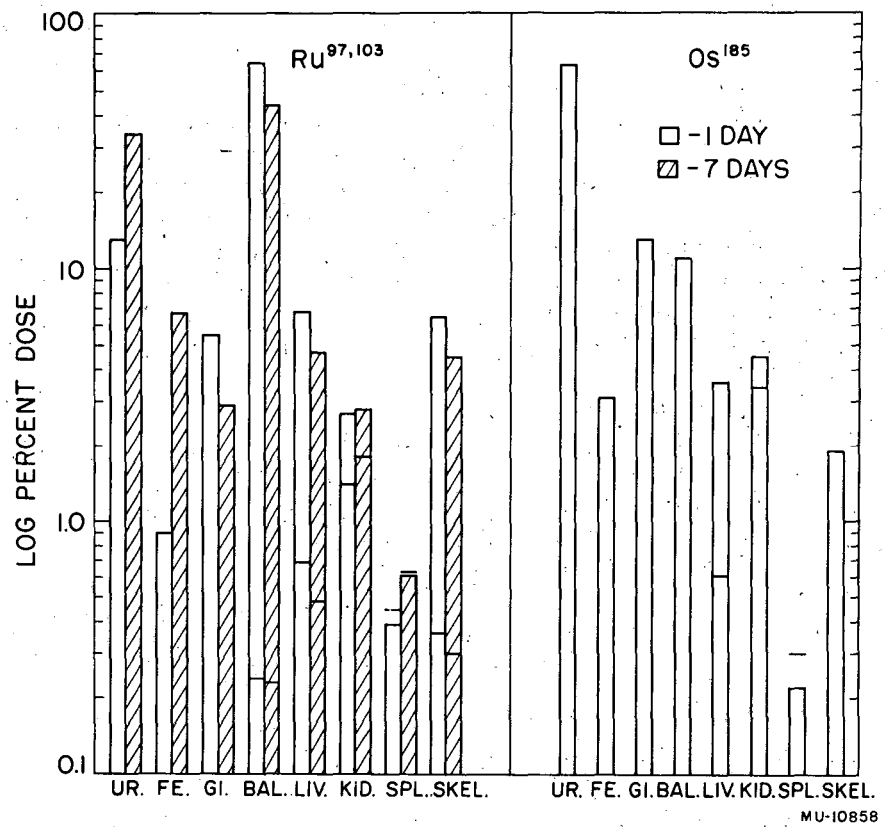

Fig. 7. The distribution of $Ru^{97, 103}$ and Os^{185} in the rat. The data are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100%. The horizontal cross bars show concentrations in percent per gram of wet tissue.

Osmium

Metallic osmium is relatively nontoxic (Fairhall, 1949), but osmic acid, OsO_4, is highly corrosive strong acid often employed as a fixing agent for fat and myelin. At one time osmic acid was used to produce nerve degeneration for the relief of persistent neuralgia (Sollmann, 1949). Cases of industrial poisoning following inhalation of osmic acid vapors have been reported (reviewed by Fairhall, 1949), and symptoms include irritation of the conjunctivae and the mucous membranes of the nose, throat, and bronchi. No chronic toxic effects were noted in workmen exposed to 640 μg of OsO_4 per m^3 of air according to McLaughlin et al. (1946). Brunot (1933) reported that osmic acid was readily absorbed through the skin and exposed mucous membranes. Masturzo (1950, 1951) described degenerative changes in the lungs and kidneys of rabbits and guinea pigs, and a chronic anemia with hyperactivity of the bone marrow in the latter animal after inhalation of OsO_4 vapor.

The fate of carrier-free Os^{185} 24 hours after intramuscular injection as OsO_4 is shown in Fig. 7. Absorption from the injection site was 75% complete in 24 hours. Excretion of Os^{185} was rapid; 62.7% of the absorbed dose had been eliminated in the urine and 3.1% in the feces during the experimental period. An additional 10.5% was found in the contents of the large bowel and would probably have been eliminated within a few hours. The kidney contained the greatest amount of Os^{185}, 3.4% of the absorbed dose per gram; smaller concentrations were found in liver, blood, and lymphatic tissues.

Although both ruthenium and osmium are usually classed as platinum metals, when osmium was administered as a complex anion the distribution was almost the same as the complex anions of the metals discussed immediately above, molybdenum, tungsten, technetium, and rhenium. On the basis of excretion and distribution pattern, ruthenium should probably be included with the platinum metals, despite the chemical form in which it was administered.

Rhodium

The toxicological literature on rhodium is scanty. The only report of the presence of rhodium in animal tissues is that of Voinar (1949), who claimed to have detected traces in human liver specimens. Rhodium metal and its salts are apparently relatively nontoxic. Neither Plant (1936) nor Van Arsdell (1947) obtained any indication of a systemic reaction of any sort following the intravenous administration of 60 mg/kilo or more of $RhCl_3$ to laboratory animals. There was, however, a marked local irritation at the site of the injection. Inhibition of growth and production of abnormalities in chick embryos have been described by Ridgway and Karnofsky (1952) and Taylor and Carmichael (1953).

The deposition of carrier-free Rh^{105} in rats up to 7 days after administration is shown in Fig. 8. Orally administered Rh^{105} was poorly absorbed; 4 days after administration by stomach tube the only tissue with a measurable

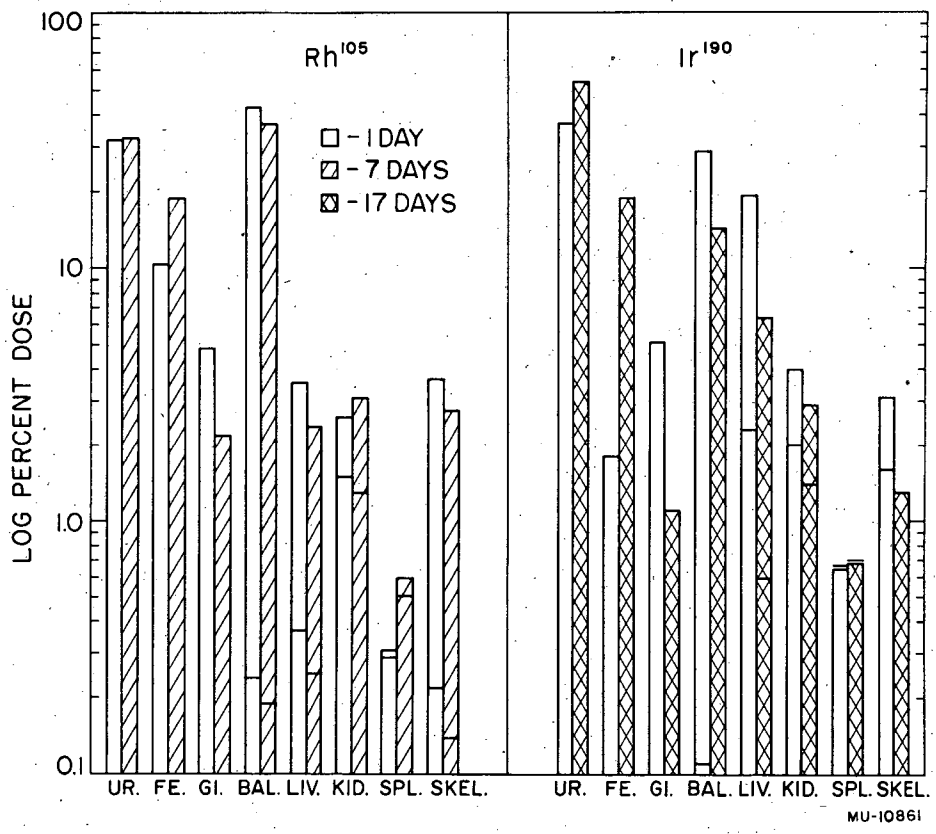

Fig. 8. The distribution of Rh^{105} and Ir^{190} in the rat. The data are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100%. The horizontal cross bars show the concentration percent per gram of wet tissue.

amount of Rh^{105} was the kidney, which contained 0.04% of the dose. Eighteen hours after intramuscular injection only 10% of the administered Rh^{105} remained unabsorbed. Excretion of Rh^{105} given either intramuscularly or intravenously was chiefly urinary during the first few hours. By 18 days, 46% had been eliminated by the kidneys and 27.6% by the gastrointestinal tract. Throughout the studies the highest concentrations of Rh^{105} were found in kidney, spleen, pymph glands, and skin. Eighteen days post-injection these tissues contained 1.07%, 0.50%, 0.35%, and 0.33%, respectively.

Iridium

Iridium is one of the rarest of the platinum group of metals. It is the common alloy in platinum for the production of corrosion-resistant standard weights, jewelry, and fine tools. Some iridium salts are employed in ceramics and photography, but do not seem to represent an industrial hazard (Fairhall, 1945).

The results of tracer studies with carrier-free Ir^{190} are shown in Fig. 8. Absorption from the gastrointestinal tract was negligible; 7 days after intragastric administration 0.05% was found in the tissues. After intravenous injection 36% was promptly excreted in the urine (4 hours after injection), and by 33 days, 45% had been eliminated by this route. Fecal excretion, which was negligible for the first few days, accounted for 35% after 33 days. Removal of Ir^{190} from the blood was relatively slow, and 2.7% still remained in the circulation 4 days after injection. Initially, liver and skin contained the largest amounts of Ir^{190}--19% and 10% of the dose respectively. Retention in most of the soft tissues was somewhat prolonged; by 33 days 12.1% still remained in liver, skin, and muscle. During all the time intervals investigated, kidney, liver, and spleen concentrated Ir^{190} to the greatest extent.

Palladium

Meek et al. (1943) studied the metabolism and toxic effects of palladium salts and stated that palladium salts were not dangerous to industrial workers. Subcutaneously injected solutions were apparently rendered insoluble and remained unabsorbed, producing local irritation. When introduced by vein into rabbits, palladium was eliminated chiefly by the kidneys; 40% was recovered in the first 4 days' urine and only traces in the feces. Tissues containing detectable amounts of palladium were kidney, liver, lung, bone marrow, spleen, and muscle. Animals that received 0.0186 g/kilo of $PdCl_2$ intravenously had a mean survival time of 10 days, and 0.05 g/kilo was immediately lethal. The most severely damaged tissues were liver, bone marrow, and kidney. Albuminuria started soon after the injections, and persisted until death.

Fields and Charles (1950) demonstrated the presence of palladium in teeth with metallic palladium fillings, indicating that small amounts of this metal can be rendered soluble by the body fluids. Voinar (1949) found

traces of palladium in human liver. Bodine and Takmisian (1943) showed a definite toxic action of the complex salt, chloropalladate, towards the enzyme tyrosinase. Palladium salts were also toxic towards growing yeast (White and Munns, 1951).

The distribution of Pd^{103} in the tissues of the rat 1 and 7 days after intravenous injection is shown in Fig. 9. Excretion was quite rapid; as early as 4 hours postinjection 60% of the administered Pd^{103} had been eliminated in the urine. At 7 days the urine contained 76% of the administered Pd^{103}, and the feces contained 13%. Kidney, liver, and spleen were the only tissues that retained Pd^{103} to a significant degree. Sixteen days after injection both liver and kidney still contained detectable amounts of Pd^{103}--1.3% and 0.3%, per g, respectively.

Platinum

Of all the platinum metals, platinum itself appears to represent the greatest potential industrial hazard. Inhalation of air-borne mists of complex salts of platinum, chiefly the sodium chloroplatinates, produces a condition known as platinosis. Generally, the symptoms are bronchial asthma, and allergic manifestations of the skin and respiratory systems (Hunter et al., 1945, and Roberts, 1951).

The distribution of carrier-free$Pt^{191, 193}$ in the rat 1 and 7 days after intravenous administration is shown in Fig. 9. Absorption from the gastrointestinal tract was poor; 4 days after administration by stomach tube, 0.15% was found in the tissues. Intramuscularly injected $Pt^{191, 193}$ was absorbed with relative ease; after 4 days only 11.5% remained at the injection site.

$Pt^{191, 193}$ was excreted approximately equally in urine and feces, and excretion was 92% complete in 32 days. Kidney, liver, and spleen had the highest initial concentrations of $Pt^{191, 193}$. Shortly after injections most of the retained platinum was evenly distributed in the other soft tissues and skeleton, and elimination from these soft tissues and skeleton was uniform. At 32 days only kidney and spleen contained significant amounts of $Pt^{191, 193}$--0.93% and 0.27% of the dose respectively.

From the standpoint of their metabolic behavior, there was a general similarity among the platinum-group metals, ruthenium, rhodium, iridium, palladium, and platinum. Although palladium and platinum, both administered as the complexes, chloropalladite and chloroplatinite, exhibited a fairly high degree of prompt urinary excretion characteristic of the complex anion group, they were more nearly like the cations Rh^{+3} and Ir^{+3} in their distribution and total rate of elimination.

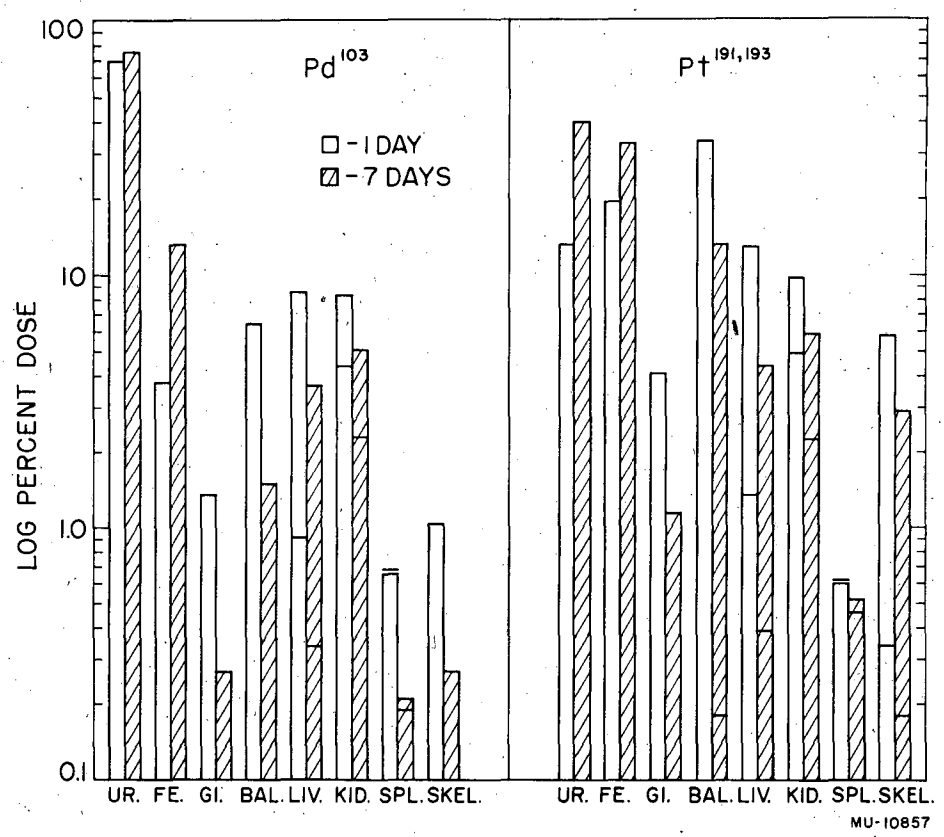

Fig. 9. The distribution of Pd^{103} and $Pt^{191, 193}$ in the rat. The data are expressed in percent of absorbed dose and are corrected for deviation of recovery from 100%. The horizontal cross bars show concentrations in percent per gram of wet tissue.

ACKNOWLEDGMENTS

The authors wish to express their indebtedness to Dr. Henry Lanz, Jr., and Dr. Harry Foreman for their continued interest in this work; Dr. Warren M. Garrison and the Radiation Chemistry group at the Crocker Laboratory for the production and isolation of the radioisotopes; Josephine C. Ellis, Helen G. Hayden, Alberta M. Stoddard, Margaret Gee, Marilyn H. Williams, Gretchen T. Bettler, Edith S. Bryan, Gudrun C. Brown, Barbara Bonstin, Helen I. Johnson, Dr. John C. Alley and Dr. Baldwin Lamson for technical assistance; Grace Walpole and Jean C. Burg for the preparation of the manuscript.

This work was performed under the auspices of the U.S. Atomic Energy Commission.

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