REPOSITORY DOE-OHRE

COLLECTION PLUTONIUM INJECTION

BOX NO. 3

FOLDER Reprints: Uranium - Radium

Chapter 4

HISTORICAL BACKGROUND

By H. E. Silberstein

Much has been written, especially in the last 25 years, on the subject of chronic radium poisoning, its physiological and pathological effects, and its mode and rate of elimination and deposition. However, relatively few clear-cut quantitative experimental studies in support of the accepted concept of the behavior of radium in human or other animal organisms have been made. The radium literature nevertheless yields almost the only data available concerning human reaction to long-continued internal irradiation. It was, accordingly, completely surveyed for the period from 1908 to 1944.[1] A somewhat abbreviated survey of the literature on radium metabolism is given below.

1. REVIEW OF ELIMINATION AND RETENTION STUDIES

From a very few experimental studies with human subjects it is apparent that the immediate rate of elimination of radium, which in all cases is relatively fast, depends upon the route of intake. If the radium is ingested, elimination is very rapid during the first few days, leaving 25 to 35 per cent of the ingested amount in the body after five days, according to the early work of Seil, Viol, and Gordon.[2] By the tenth day the daily excretion rate is less than 1 per cent of the amount remaining in the body. In two brief experiments Schlundt and Failla[3] found even more rapid elimination of radium bromide, with 91 per cent of the dose excreted in four days in one subject and 98 per cent excreted in five days in the other. Of the total excretion of radium, Seil found less than 1 per cent in the urine in the first two days and thereafter was apparently unable to detect any activity in the urine by the method employed. Meanwhile the concentration of radon eliminated through the lungs fell from 0.59 millimicrocurie per liter of exhaled air on the day after ingestion to 0.18 on the second day and

0.07 on the third day. During the first few days, according to Evans,[4] 70 to 90 per cent of the radon produced in the body at any one time may be exhaled, so that immediately after the ingestion of radium 1 micromicrocurie of breath radon corresponds to 0.05 to 0.07 μg of radium in the body.

Table 4.1—Elimination of Radium after Intravenous Administration to a Human Subject*

Days after injection	Ra in body, μg	Ra excreted, μg			Daily elimination, % of body content
		Urine	Feces	Total	
		Experiment 1			
1	100	1.75	17.9	19.65	19.65
2	80.35	0.22	16.6	16.82	20.9
3	63.53	0.065	7.12	7.185	11.3
4	56.34	0.040	1.6	1.640	2.9
5	54.70		1.6	1.6	2.9
6	53.10		0.98	0.98	1.8
7	52.12		0.58	0.58	1.1
8	51.54		0.44	0.44	0.85
9	51.10		0.42	0.42	0.82
10	50.68				
		Experiment 2			
1	100	1.4	18.4	19.8	19.8
2	80.2	0.16	12.58	12.74	15.9
3	67.4	0.065	3.34	3.40	5.0
4	64.0		1.68	1.68	2.6
5	62.3		0.54	0.54	
6	61.8		1.67	1.67	1.8†
7	60.1		0.45	0.45	0.75
8	59.7				
10	≈59.0		0.30	0.30	≈0.5
12	≈58.5		0.20	0.20	≈0.34
21	≈57.0		0.14	0.14	≈0.25

*From Seil, Viol, and Gordon.[3]
†Average for days 5 and 6.

After intravenous administration the initial rate of elimination is considerably slower than after ingestion, with 55 to 65 per cent of the dose reported to remain in the body four or five days after injection. Here again the early work of Seil et al.[2] is the only study of single intravenous injection in man. The first injection of 100 μg of radium

was followed by a 10-day observation period, the data from which are shown in Table 4.1. The same injection, indicated as experiment 2 in Table 4.1, was repeated two months later, when the residual excretion from the first injection was considered negligible. The values under the heading "Daily elimination, % of body content" are based, as Seil expressed them, on the portion of the last dose present in the body. The extremely high proportion of eliminated radium reported in the feces may be due to inadequate methods for determining small amounts in the urine samples.

Table 4.2—Elimination of Inhaled Radium by a Human Subject*

Weeks after exposure	Regime	Ra in body, μg	Ra excreted per day, mμg			% of Ra eliminated per day
			Urine	Feces	Total	
4	Normal	0.8		15.0		2.0
7	High Ca	0.6	0.09	6.0	6.1	1.01
7.5	High Ca		0.11	5.0	5.1	0.85
8	High Ca		0.09	3.8	3.9	~0.7
9–12	Low Ca, plus therapy		0.07	3.5	3.6	0.7†
24	High Ca	0.3	0.017	0.45	0.47	0.1‡

*From Aub, Evans, Gallagher, and Tibbetts;[5] Evans, Harris, and Bunker.[6]
†Average of seven determinations.
‡Average of two determinations.

Elimination occurring relatively soon after the inhalation of radium has been studied in a single case of Evans's group. The patient was a 54-year-old physicist, in good health, who had inhaled a very small quantity of radium dust in an explosion involving 100 mg of radium chloride. Nine weeks later he was placed on a low-calcium diet with mild de-leading therapy for three weeks, during which time he excreted about 1 per cent of this stored radium per day. Average daily values derived from the data of Evans et al.[5,6] for three-day periods are given in Table 4.2. Evans questions the accuracy of the determination of the small quantity of radium present in the last sample. The authors state that, since the radium had not yet been stored to a great extent in bone, the treatment was given not to mobilize it but to prevent its deposition. The treatment apparently had little effect on the rate of elimination.

In contrast to the early excretion picture, the later elimination of radium depends not so much upon the route of intake as upon the depth and manner of fixation in the skeleton. This fixation, in turn, depends

mainly upon the length of the retention period and upon the nutritional and metabolic state of the individual, especially with regard to bone metabolism. Other factors are the duration of exposure and the rate of absorption.

These relations are illustrated by Evans's findings[4] in radium-dial workers who were transferred to nonradioactive work or were given vacations as soon as their body content was found to have exceeded the tolerance amount, 0.1 μg of radium. Exhalation of 1 micromicrocurie of radon per liter of breath indicated 100 per cent of tolerance. Breath-radon measurements showed reductions to between one-half and one-eighth of the radium burden within one month after removal from exposure in about forty cases, but five others failed to show the satisfactory response. Evans's five sample cases indicated that those who accumulated radium more gradually tended to lose it less quickly than those whose uptake was rapid. In one worker, who had accumulated 300 per cent of the tolerance amount in less than five months, the value fell to about 120 per cent in his first 10 days away from work and then more slowly to 50 per cent during the next 36 days.

In a useful review article Hoecker[7] discusses the validity of the exponential equation, suggested by Schlundt and Failla,[3] to describe the elimination of so-called "fixed" radium:

$$Q = Q_0 e^{-\mu t}$$

where Q_0 is the amount present in the body at the beginning, Q is the amount present at the end of the time interval t, and μ is the coefficient of elimination. When t is expressed in days, the value for μ, if multiplied by 100, more accurately represents the daily percentage of body radium content eliminated than does the simple average derived from the percentage lost during the time t. In general, Hoecker points out, the shorter the period between determinations of Q_0 and Q and the longer the time since exposure, the more nearly will μ approach constancy. He shows the inverse relation of elimination rate to retention period by plotting his own and other workers' data,[3-5,8] scattered though they are, on a logarithmic graph in which the value for μ falls from the order of 0.1 at 8 months after beginning exposure to about 0.00005 at 150 months.

The elimination rate in long-standing chronic radium poisoning has been shown to be of the order of 0.005 per cent of the body content per day by actual determination of the urinary and fecal activity in a few cases in which breath-radon and gamma-ray tests were also made. Evans[4] has pointed out that at this rate about 45 years would be required for the elimination of one-half the radium burden. About

90 per cent of the radium eliminated was usually found in the feces, the rest in the urine. Table 4.3 includes not only these so-called "normal" elimination figures but also some data showing the influence of calcium metabolism on the level of radium excretion. Flinn[9,10] had reported deactivations amounting to 45 to 57 per cent of the radium burden and marked improvement in health after only two

Table 4.3—Elimination of Fixed Radium by Human Subjects

Subject	Retention period	Ra in body, μg	Ra excreted per day, mμg			% of Ra eliminated per day	Metabolic regime
			Urine	Feces	Total		
Subject A*	12 yr	24	0.103	1.058	1.161	0.0056	Normal (average values)
Subject B*	12 yr	14	0.055	0.308	0.363	0.0026	Normal (average values)
Patient A†	8 yr	20			1.115	0.0056	Normal
	9 yr 8 mo.	20			1.040	0.0052	Normal
	9 yr 9 mo.	20			1.639	0.0082	Low Ca; parathormone
	9 yr 10 mo.	20			0.895	0.0045	High Ca; viosterol
	9 yr 11 mo.	20			1.361	0.0069	Low Ca; parathormone
	10 yr	20			0.979	0.0049	High Ca; viosterol
Patient 1‡	10 yr	15	0.055	0.770	0.825	0.0055	Low Ca
	10 yr	15	0.570	5.480	6.050	0.0404 max.	1 mo. on low-Ca diet, with NH_4Cl and thyroid-parathyroid treatment
	10 yr	15	0.310	2.530	2.840	0.019 av.	
	10 yr 2 mo.	15	0.110	0.830	0.940	0.006	High Ca; control
Patient 2‡	14 yr	18	0.040	0.900	0.940	0.0052	Normal
	14 yr	18	0.180	4.800	4.980	0.027 max.	3 mo. on low-Ca diet, with NH_4Cl and thyroid-parathyroid treatment
	14 yr	18	0.150	2.800	2.950	0.016 av.	
	14 yr 3 mo.	18	0.056	1.670	1.726	0.0096	High Ca; control

*From Schlundt and Failla.[3]
†From Craver and Schlundt.[11]
‡From Aub, Evans, Gallagher, and Tibbetts.[5]

months of decalcification therapy. In contrast to this finding, Craver and Schlundt[11] and Aub et al.[5] were unable to produce enough increase in radium loss to lead to any significant decline in the total body content, even if the maximum rate under treatment could have been maintained. In Aub's cases the response in radium output lagged behind the calcium response.

In connection with patient 2, Aub et al.[5] calculated the relative efficiency of the kidneys and intestine in removing radium from the blood stream. During a period in which the blood activity averaged 0.95×10^{-12} g per milliliter, the urinary output was 0.04×10^{-9} g per day, about 1 per cent of the total circulatory content. If a blood supply

to the kidneys of 500 liters per day is assumed, 5×10^{-7} g of radium was carried through them, yet less than 0.01 per cent of that quantity appeared in the total 24-hr urine collection. The daily fecal elimination, on the other hand, amounted to slightly more than the total blood radium content at any one moment of the day. The finding of radium in the gallstones of another radium-poisoning case was mentioned as evidence that the bile plays a role in the elimination of fecal radium.

The permanent retention of radium in human subjects has been found to vary between 0.1 and 10 per cent of the intake, averaging about 2 per cent.[5] Rajewsky[12] has stated that it stabilizes at 0.5 to 1 per cent about a year after ingestion and at 2 to 5 per cent after inhalation. Schlundt's data[8,13] indicate retentions ranging from less than 1 per cent to nearly 4 per cent of the radium administered intravenously.

Retention figures are based mainly on the reports of Schlundt and coworkers in the early 1930's. Their first series of patients, data from which are summarized in Table 4.4, received varying doses of radium chloride orally or intravenously. The zero retentions listed in the table were in cases described as having no detectable activity; and the values for percentage retained are obviously only approximations in view of the wide range of errors in their activity measurements.[13] Table 4.4 also includes the post-mortem retention values found in two ingestion cases reported by Gettler and Norris[14] and by Neitzel.[15] These values, which have the advantage of being derived analytically, suggest that the early methods of in vivo determination gave erroneously low results.

Schlundt's second series,[8] with a group of 25 patients in a mental hospital, was carried out more consistently. Radium chloride injections, given intravenously in 10-μg doses at weekly intervals over periods of two to ten months, were followed by activity measurements six months apart. The amount of retained radium was estimated from gamma-ray measurements made at the patient's back and from radon determinations in the expired air. Their estimates of the amount of body radium giving exhaled radon were admittedly subject to error, inasmuch as studies of breathing rate and volume were not performed on each individual. Their retention data are given in Table 4.5, and the daily coefficients of elimination calculated by Hoecker[7] are also given wherever possible. Twelve of these cases showed a total elimination of 55 per cent of their body radium burden during the six months between examinations. Generally, as would be expected in all these intermittent-dose studies, the observed retention was lower whenever the total period of administration was more prolonged, even when the time interval between the last injection and the examination was the same.

The portion of the radon produced in the body at any one time that is eliminated through the lungs also depends chiefly on the depth of fixation of the radium. This fact can be seen from the values for the term Rn/Ra, which has been used to express the ratio of body radium detectable as exhaled breath radon to total-body radium. Values for this expression given in Table 4.5 range from 0.98 to 0.65 during the

Table 4.4—Radium Retention by Human Subjects after Prolonged Administration*

Time after initial dose, years	Reference	Time since last treatment	Route of administration	Radium, μg		% of dose retained	Rn/Ra†
				Total dose	Retained		
⅝	13	7 mo.	Intravenous	80	0	0	
2¼	13	1¾ yr	Intravenous and oral	250	Trace		
2½	13	3 hr	Oral	1,455	4–6	0.4	0.50
2½	15	At death	Oral	1,825	40	2.2	
3	13	2 wk	Intravenous	330	9–14	3.5	0.43
3	13	1⅔ yr	Intravenous	890	19–33	3	0.46
3	13	2 yr	Intravenous and oral	205	0	0	
3⅓	13	2½ yr	Intravenous and oral	380	0	0	
4⅓	13	1⅔ yr	Intravenous	1,130	10–18	1.2	0.50
5	13	5 wk	Intravenous	305	9–14	3.8	0.43
5⅓	13	5 yr	Intravenous and oral	290	0	0	
5⅓	13	5 yr	Intravenous and oral	240	0	0	
5½	14	At death	Oral	2,800	73.7	2.6	

* From Barker and Schlundt;[13] Gettler and Norris;[14] Neitzel.[15]
† Rn/Ra values estimated by reviewer from data on gamma-ray and breath-radon determinations given in reference 13.

first year or year and a half after the beginning of the injection. Although they vary considerably among individuals, the average Rn/Ra values remain at a fairly constant level of 0.45 when the retention period has been two or more years.[4] This fact is demonstrated by the Rn/Ra values ranging from 0.32 to 0.55 in subjects examined by Evans[16] after exposure 8 to 25 years previously and by the approximate values listed in Table 4.4, which were derived from the data of Barker and Schlundt.[13] It is also borne out by two other cases, in which the Rn/Ra values were 0.44 and 0.47 at 10 and 12 years, respectively, after beginning exposure.[3,5] In the light of this consistency among independent findings, there is some question as to the significance of the low values of 5 to 15 per cent radon elimination, calculated from data on some of Flinn's cases[9] and on one of Schlundt's cases,[3] and of 2 to 20 per cent mentioned by Rajewsky.[12,17] These values may be explained by the presence of mesothorium decay prod-

Table 4.5—Retention of Radium after Intravenous Administration to Human Subjects*

Radium injected, μg	Time since last injection, months	Radium retained, μg	% of dose retained	Elimination coefficient	Rn/Ra
70	2	0.5†			
90	1	0.5†			
	7	0.6†			
90	1	9.7	10.8		0.89
90	1	4.2	4.7		0.93
100	1	6.5	6.5		0.95
110	1	9.0	8.2		0.92
	7	5.3	4.9	0.003	0.91
150	6	8.2	5.5		0.88
	12	3.4	2.3	0.0049	0.73
150	6	6.0	4.0		0.90
	12	3.1	2.2	0.0036	0.90
150	6	3.7	2.5		0.92
	12	1.6	1.1	0.0047	0.87
150	6	13.9	9.3		0.90
160	6	13.8	8.6		0.91
	12	5.5	3.5	0.0051	0.75
160	6	4.6	2.9		0.80
160	6	3.6	2.3		0.80
	12	0.3	0.2		0‡
160	6	3.8	2.4		0.90
	12	1.9	1.2		0.95§
180	6	6.7	3.7		0.88
	12	1.9	1.1	0.007	0.95
200	6	6.2	3.1		0.95
	12	4.2	2.1	0.0021	0.98
200	6	0.5†			
250	1	6.9	2.8		0.84
	7	5.1	2.1	0.0016	0.82
260	0.75	7.6	2.9		0.84
	7	3.1	1.2	0.0051	0.77
260	4	14.3	5.5		0.84
	10	5.1	2.0	0.0059	0.65
360	6	2.9‡	0.8		
	12	6.6	1.8		0.86
380	4	1.0†			
	10	1.3†			
410	0.5	1.1†			
450	0.75	17.7			
	7	1.3†			

*From Hoecker;[7] Schlundt, Nerancy, and Morris.[8]
†Gamma-ray determinations only.
‡Authors questioned the radon determination.
§Gamma test less than 0.1 μg.

ucts in larger amounts than these workers indicated. It seems, then, that the percentage of radon exhaled tends to fall quite rapidly during the first year and a half after radium intake and is thereafter apparently independent of retention time.

Information on the metabolism of radium by experimental animals, such as the rat, rabbit, dog, or horse, is limited. The findings generally support the observations with respect to the early human excretion rates but are inconsistent with those made at later periods. For example, the late excretion rates in terms of percentage of the body content found in long-term animal experiments are at least 10 times higher than in comparable chronic human cases, yet their final retentions remain considerably greater than the retentions indicated by in vivo measurements on human subjects.

The only indication of the fate of ingested radium in rats was obtained from the reports of Evans's group.[6,18] Their results cannot be easily evaluated because the feeding was prolonged, analyses were made on mixed urine and feces, and in most instances the dosage control depended on the final recovery values. They consistently found, however, that within four days after the last administration 92 to 96 per cent of the total dose had been eliminated, thus indicating rapid initial excretion. About 120 days later, three of the animals had daily elimination rates corresponding to 0.6, 0.3, and 0.4 per cent of the body content. Three other animals, started at higher dose levels, excreted only about 0.15 per cent of their radium per day at 110 days and an average of 0.035 per cent per day during the period from 100 to 300 days after the beginning of radium ingestion. The Rn/Ra ratio during the chronic stages of the experiment ranged from 0.70 to 0.90, with an average value of 0.85. The authors suggest that this high rate of radon exhalation may be accounted for by the more rapid metabolic, circulatory, and respiratory rates of the rat.[6]

In studies on rats injected intradermally with radium, Evans[6] found a low initial excretion rate and a much slower diminution in excretion rate. These rats, in which a considerable portion of the dose remained entrapped in areas of relatively poor vascularity, exhaled only 62 to 74 per cent of the radon produced in the body about 190 days after injection. Their final retentions were much higher than in the animals given radium orally.

In the rat experiments of Thomas and Bruner[19] the analysis of early elimination was also somewhat complicated by the fact that intermittent doses were given. In general, analyses of combined urine and feces showed that an immediate rapid excretion of 35 per cent of the dose took place the first day and was followed by a decreasing rate, giving a total of 50 to 55 per cent elimination in the first week after

subcutaneous injection. After each subsequent injection the apparent value for the percentage of the last dose eliminated was slightly higher because of the slow excretion of the radium retained from previous injections. The later elimination values from pooled weekly collections for two animals during the terminal period of the experiment are listed in Table 4.6. The final retentions found in seven animals

Table 4.6 — Rate of Elimination of Radium Administered Subcutaneously to Rats*

Time	Radium eliminated: Amt., mμg	Radium eliminated: % of that in body
Rat 2		
4 weeks† before death	100.5	
3 weeks before death	112.1	
2 weeks before death	44.4	
1 week before death	29.2	
Total for 4 weeks	286.2	
Average per week	71.5	0.42§
Average per week for 3d and 4th weeks before death‡	106.3	0.61¶
Amount retained at death	17,116.0	
Rat 3		
2 weeks before death	82.6	
1 week before death	61.1	
Total for 2 weeks	143.7	
Average per week	71.8	0.62**
Amount retained at death	11,594.3	

*From Thomas and Bruner.[19]
†230 days after first injection.
‡Values for last two weeks before death discounted because of the animal's abnormal state.
§Equivalent to 0.06% per day.
¶Equivalent to 0.09% per day.
**Equivalent to 0.09% per day.

about 200 days after the beginning of the experiment ranged from 15 to 31 per cent of the total dose, with an average of 25 per cent.

The earliest study with rabbits was reported by Salant and Meyer[20] in a qualitative study of the routes of elimination of injected radium bromide. On the basis of sacrifice experiments, with ligation of various sections of the gastrointestinal tract and bile-duct cannulation, they reported that the kidney, liver, and small intestines, but not the stomach or colon, were active in the elimination of radium by dogs and rabbits.

Dominici and his coworkers[21,22] used rabbits to compare the behavior of soluble radium bromide and insoluble radium sulfate after single intravenous or intramuscular injections. They found a somewhat longer retention of the insoluble radium and also a longer retention after intramuscular than after intravenous injection. Ten animals, sacrificed after five or six days, retained 30 to 55 per cent of the dose, with no significant differences between the different types of intake. The recovery values from a few animals sacrificed later were inconsistent, but they at least indicated that the intramuscularly treated animals retained more radium at about 130 and 165 days than the intravenously treated animals did at 90 days.

The data on dog experiments are extremely meager and inconclusive. In 1912 Brill and Zehner gave single subcutaneous injections of radium chloride to two dogs, using doses of 18.4 and 47 μg of radium, equivalent, respectively, to about 2 and 5 μg per kilogram of body weight. Their elimination values, as cited by Seil et al.,[2] are only approximations, but they concluded that from 4 to 19 per cent of the dose was excreted during the first four days, and very little thereafter. In two of Hosokawa's animals[23] an appreciable urinary activity was found during the first week after the intravenous injection of about 9 μg of radium per kilogram. Two other dogs, which received by mouth the equivalent of 0.017 μg of radium per kilogram every day throughout the experimental period, apparently showed some lag in excretion. The relative activities of the feces determined at irregular intervals from the seventh day on rose gradually by the thirtieth or fortieth day to about 30 times the early activity. No detectable activity was found in the urine until 30 days after the feeding began. Although Hosokawa gave no quantitative equivalent for his arbitrary units, they indicated that over 97 per cent of the excretion was fecal.

Dominici[24] reported a few observations of urinary excretion in a horse after the intravenous injection of 1 mg of radium sulfate. The urine excreted during the first day contained about 20 per cent of the dose, as estimated from its relative activity per liter. The values fell gradually from approximately 15 per cent of the dose on the third day to 0.03 per cent of the dose per day at 50 days and to no detectable activity at 140 days.

2. REVIEW OF DISTRIBUTION STUDIES

Reports available at the time of writing on radium levels in the blood indicated that it is thrown out of the circulation too quickly to be accounted for by the immediate excretion. It must, therefore, go into the tissues rapidly. Dominici and his coworkers[25] found, in a horse injected with radium, a concentration in blood of only 0.8 per

cent of the dose per liter on the day of the injection. Assuming a total blood volume of 25 liters, about 20 per cent of the dose was in the circulation a few hours after injection. By the second day the value had fallen to 0.1 per cent of the dose per liter; then it apparently declined very gradually to 0.02 per cent at eight months and to 0.005 per cent at one year.

Some of Van Hove's[26] qualitative autoradiographic studies of human blood activity also showed a rapid fall in one day, or even during the first few hours after the intravenous injection of 100 and 350 μg of radium. One or two samples, however, did not seem to show this response until the second day. Distinct images from blood samples were still obtainable after two months, but they were of such intensity and required such exposure times as to indicate certainly more than a fivefold decrease from the original blood radium content. Daels et al.[27] also reported a few autoradiographic studies of blood samples from rats and guinea pigs sacrificed 5 to 7 hr after the last of two or three daily subcutaneous injections. Their descriptions indicate that the activity of blood at that time was either lower than the most active tissues, such as bone, kidney, and liver, or in approximate equilibrium with them.

The radium content of blood in the later phase of radium poisoning was determined quantitatively by Aub et al.[5] in their patient No. 2. The average of repeated analyses was of the order of 1×10^{-12} g/ml in whole blood. If a total blood volume of 5 liters is assumed, it can be calculated that only about 0.03 per cent of the total body radium was in the circulation 14 years after beginning exposure. After a month and a half of decalcifying therapy the blood activity was reduced to about half that value, but it soon returned to the previous level when the treatment was discontinued. The concentration of radium in red blood cells was slightly less than in serum.

Aub and his coworkers,[5] in discussing radium distribution by analogy with lead and similar heavy metals, point out that it is scattered through soft tissues as well as in bone soon after intake and afterward is gradually stored preponderantly in bone. Concerning this redistribution from soft tissue to bone and into different areas of bone itself, they state: "At first a heavy metal is stored largely in the bone trabeculae, there being from 10 to 16 times as much per gram in the trabeculae as in the cortex of the bone. During the following months there is a redistribution, and the concentration becomes equal in both trabeculae and cortex. Because the cortex is far heavier than the trabeculae, this means that most of the radium is stored in cortical bone. This distribution indicates an explanation for the variation in radium excretion. The wide distribution in soft tissues and then the accumulation in the bones imply considerable circulation in the

blood and, therefore, a chance for rapid excretion. The first large storage in the trabeculae (where inorganic salts are readily deposited and also readily liberated) would allow a continued though less rapid excretion. When the radium finally accumulates in the cortex, it is to be expected that excretion would be slow and relatively poorly influenced by therapy."

Table 4.7—Distribution of Radium in Human Tissues

	3½ months after injection of 1 mg of radium*	5 years after beginning exposure as dial painter†	5½ years after beginning ingestion of 2.8 mg of radium‡
Skeletal tissues:			
Vertebrae, μg Ra/g ash		0.0212	0.0342
Femur, μg Ra/g ash		0.0101	0.0092
Tibia, μg Ra/g ash		0.0063	
Lower jaw, μg Ra/g ash		0.0016	0.0076
Upper jaw, μg Ra/g ash		0.0119	
Teeth, μg Ra/g ash			0.0149§
Skull, μg Ra/g ash		0.0037	
Average, μg Ra/g ash	0.10	0.0115	0.0139
Estd. average, μg Ra/g fresh wt.	0.05	0.0058	0.007
Estd. total Ra in skeleton, μg	380	48.26	73.27
% of total body Ra in skeleton	95	94.7	99.4
Soft tissues:			
Liver, μg Ra/g ash	0.16	0.0069	0.0012
Lung, μg Ra/g ash	0.042	0.0276	0.0008
Spleen, μg Ra/g ash	0.019	0.0103	0.0009
Kidney, μg Ra/g ash	0.00094		0.0046
Heart, μg Ra/g ash	0.00103		0.0008
Brain, μg Ra/g ash		0.0101	
Bone marrow, μg Ra/g ash	0.25		
Average, μg Ra/g ash	0.076¶	0.0091**	0.0016
Estd. average, μg Ra/g fresh wt.	0.0006	0.00007	0.00001
Estd. total Ra in soft tissue, μg	20.0	2.68	0.39
% of total body Ra in soft tissue	5.0	5.3	0.6

*From Cameron and Vlol.[28]

†From St. George, Gettler, and Muller.[29]

‡From Gettler and Norris.[14] Ingested in drinking water over a five-year period.

§Possibly an artificially high value. Autoradiographs of these teeth showed a uniform distribution in the roots but an appearance of localization in parts of the crown that could only be explained as heavy uptake by metallic fillings.

¶From 10 specimens, including those used in this table, and a sample of

all expressed on a wet-weight basis, since the average ash content of bone is 50 per cent whereas in soft tissues it is only about 0.8 per cent. The localization in the skeleton is extremely important in the eventual lethality of apparently minute quantities of radium. The first set of data from an experimental subject with a terminal carcinoma, reported by Cameron and Viol[28] in 1915, has always been taken to indicate a wide distribution of radium still in the soft tissues 3½ months after intravenous administration, thus implying a slower uptake by the skeleton than the preponderance of data indicates. From a simple reconsideration of these data on the basis of Viol's own findings[2] on the excretion of radium administered intravenously, it is apparent, even though no bone samples were analyzed at that time, that the total soft-tissue content really represented a minor portion of the radium in the body.

A rough indication of the early distribution of radium may be seen in the qualitative autoradiographic post-mortem studies made by Van Hove[26] on dried tissue samples from three hopeless cases used for experimental radium injection. One month after the injection of 260 μg of radium the liver showed the highest activity; the rib, kidney, spleen, lung, bronchus, adrenal, pancreas, and uterus activities were moderate; the bladder, heart, muscle, stomach, and esophagus were low; and the thyroid and ovary were negative. Two and three months after 100- and 300-μg injections the bone, liver, spleen, and lung showed the same order of activity as the low group of tissues in the first case, but 16 other tissues, including tumors, either were negative or gave very faint exposures.

The few observations made by Martland[30,31] in 1925 on two other fatal cases, former dial painters, are of interest. In one patient, who died of acute anemia eight years after the beginning of exposure, he found gamma radiation present in all the organs and alpha emission most marked from the spleen, bone marrow, cortical bone, and liver but not detectable from the lung, heart, and kidney. In the other subject, after a nine-year retention period, the alpha electroscope measurements on one month's emanation from incinerated organs were reported to be in excess of the normal drift per hour by 365 divisions for bone, 40 for the spleen, 30 for the liver, and 23 for gastrointestinal tissue. Other organs showed almost no activity. However, of the 150 μg of radioactive substance estimated in the entire skeleton of this case, 70 per cent was accounted for by mesothorium. This was also the first case in which the unequal distribution in bone was noted. Autoradiographs showed the outer border of the cortex to be the most active part of the femur at this late stage.

Schlundt and Failla[3] gave some evidence of the general variability of deposition in different parts of the skeleton. Gamma-ray measure-

ments on a patient with incipient bone necrosis in the jaw indicated a body radium content of 14 μg when the reading was taken near the jaw, as compared with 11.6 μg near the lumbar spinal region and 9 μg near the ankle. Analyses showed 5.2×10^{-9} g of radium per gram of air-dried vertebral bone, 3.4×10^{-9} g per gram of rib, and an average value of 2.67×10^{-9} g per gram of humerus.

In one of Aub's cases,[5] clinical evidence of the relatively specific localization of radium in growing epiphyses is given. The patient's heaviest exposure had been during the period from 16 to 20 years of age, and the marked rarefaction and bone destruction in the heads of the femur and humerus 14 years later obviously resulted from the greater uptake in these regions. Also, in the same case, the average radium content of bone, calculated from the radium/calcium ratio in the excreta and the known calcium content of bone, was 5.4×10^{-9} g per gram of bone. However, analyses of necrotic spicules extruded from the jaw gave values of 13.6 and 19.6×10^{-9} g of radium per gram of dried trabecular bone. Another case, whose total body radium was about 5 μg, did not show such variation between trabecular and cortical bone. Tibia and fibula trabecular values ranged from 0.86 to 1.75×10^{-9} g per gram, similar to shaft values of 1.06 to 1.79×10^{-9} g. The retention period was not known in this case, but, judging by the amount of radium present, the development of sarcoma of the knee,[16] and the ensuing death, it was probably at least 12 or 15 years.

The distributions that have been described for two fatalities, thought to be due chiefly to inhalation of radioactive dusts, indicate an appreciably higher retention in the lungs than from other routes of intake. Reitter and Martland's subject,[32] in whom both radium and mesothorium were present, had the equivalent of 14 μg of radioactive substance in the whole skeleton, 5 per cent of this amount being radium itself; 1.8-μg radium equivalents in the lungs, 43 per cent due to radium; 0.001-μg radium equivalent in spleen; and no detectable radium equivalents in liver, gastrointestinal tract, heart, or kidney. The actual values for radium element were 4.75×10^{-10} g per gram of bone, 3.25×10^{-9} g per gram in the right lung, and 5.0×10^{-9} g per gram in the left lung.

From analyses on a case also involving a mixture of radium and thorium, Janitzky et al.[17] report two sets of values, namely, a lower limit of activity based on alpha determinations by the emanation method, and an upper limit, about three times higher, derived from alpha-counter measurements on tissue ash. Expressed in terms of radium equivalents per gram of fresh tissue, according to the former method, they found concentrations of about 300 $\mu\mu$g in the spinal marrow and rib, 200 $\mu\mu$g in the femur, 90 $\mu\mu$g in the lung, 30 $\mu\mu$g in the liver, 7 $\mu\mu$g in the spleen, and 0.7 $\mu\mu$g in the heart. In another inha-

lation-poisoning case, reported by Toenges and Kalbfleisch,[33] it was not quite clear how high the lung retention was, but it was higher, at any rate, than that of the liver, spleen, or heart and lower than that of the spinal marrow, rib, or femur cortex.

The mechanism and extent of radium deposition in the skeletal systems of experimental animals is essentially similar to those in human subjects. The relatively high localization at first in the actively calcifying parts of the rat skeleton has been demonstrated by an autoradiographic examination of a few bone specimens,[18,34,35] as well as by the high incidence of osteogenic sarcoma in the continuously growing lumbar and pelvic regions of rats with chronic radium poisoning.[6] Later, according to epiphysis and shaft analyses on a rat 383 days after the beginning of the experiment, the higher concentration shifts toward the cortical bone.[6]

The only quantitative data on the relative radium concentration in various organs and tissues of rats long after the initial radium intake are those of Thomas and Bruner[19] and of Evans and his coworkers.[6] The animals on which the most complete set of analyses was reported are included in Table 4.8. The percentage of the body content of radium found in each whole organ or tissue system has been used as a common basis of expression for these results. In terms of radium concentration per gram of fresh tissue in those of Evans's rats which were fed radium, the lungs were usually the highest among the organs; muscle, analyzed separately in three instances, was very low; and the bones showed at least 100 times the concentration of the richest soft tissue. Usually no marked variations in concentration were noted from one region of the skeleton to another, but in some animals the rib and spine values were somewhat lower. In the intradermally injected animals, in which a large portion of the dose was retained in the skin and was slowly absorbed therefrom, the kidney, spleen, and liver concentrations were at least 10 to 20 times higher than in animals with comparable total retentions from radium administered orally.

Thomas and Bruner's findings,[19] expressed in terms of the dry weights of soft tissues, showed that the kidney, lung, heart, and intestine, in the order named, were the most active organs in this one animal that had received radium subcutaneously. The concentration in bone ash from different parts of the body was fairly uniform, with the exception of the mandibles. When the teeth of another animal were analyzed separately, their activity per gram of ash was found to be only 27 per cent as high as that of the tooth-free portion of the jaw, thus accounting for the low activity of intact mandibles. The fetuses of one radioactive female had accumulated some radium, but the con-

centration per gram of fetal ash was only 3.6 per cent of the concentration found in the total ash of the parent.

The early studies on rabbits (see references 21, 22, 24, 25, 36), a report on one dog,[37] and the photographic analyses of rat and guinea pig tissues[27] served only to indicate that radium appeared in bone as soon as three days after administration; that, among the soft tissues,

Table 4.8—Distribution of Radium in Rat Tissues

Route of intake	Subcutaneous*	Intradermal†		Oral†			
Retention period, days	163	224	302	455	462	462	537
Total Ra retained, μg	15.46	4.9	3.0	0.62	0.42	0.68	0.67
Tissue	Percentage of total radium						
Kidney	0.144	0.012	0.002	0.003	0.0001	0.022	0.0045
Intestine	0.104			0.12	0.017	0.053	0.087
Lungs	0.079	0.008	0.015	0.03	0.06	1.05	0.268
Testes	0.041	0.006			0.004	0.006	0.07
Heart	0.034	0.00002	0.003	0.006	0.001	0.001	0.0007
Brain	0.027						
Submaxillary glands	0.008						
Liver	0.004	0.045	0.015	0.005	0.023	0.008	
Spleen	0.003	0.0015	0.009			0.003	0.0064
Muscle, skin, and fur	0.1	69.5	70.0	10.3	8.0	8.8	2.34
Vertebrae (spine and tail)	45.6	6.54	8.8	30.5	24.3	26.5	42.2
Skull and teeth		8.67	8.3	25.9	29.2	28.1	18.95
Mandibles	3.9						
Hind legs	29.8	6.8	5.7	19.2	18.1	16.6	16.1
Pelvis		2.4	4.4	7.7		8.1	9.1
Forelegs and scapulae	20.1	3.57	2.5	5.1	9.5	6.6	9.85
Ribs		2.2	1.6	1.3	2.85	3.97	6.27
Entire skeleton	99.46	30.2	31.2	89.7	84.0	90.0	94.3

*From Thomas and Bruner.[18]
†From Evans, Harris, and Bunker.[9]

the liver, kidney, and fetal tissues were most often relatively high during the first few days; and that the muscle, brain, heart, stomach, uterus, adrenal, and tumor tissues were usually almost negative. When retention times were longer, the lung, spleen, and brain were sometimes found among the more active soft tissues. One report[38] seemed to indicate that rabbit bone marrow has a higher activity per gram than bone two or three days after prolonged radium injections and that it still retains about the same concentration as bone four months after injection.

In any consideration of the possible significance of the experimental work discussed, whether in distribution or in excretion studies, it must be kept in mind that probably very little investigation was done

with accurate control of the dosages. The experience of Evans and his group[16] of getting sometimes as little as 10 per cent of the calculated dose into their animals throws some light on the apparent discrepancies found between many of the results.

Krebs has repeatedly written about what he calls the "basal radioactivity" of organisms. Various radioactive materials are taken into the body in air, water, and food, so that the blood has a constant normal activity equivalent to 10^{-13} or 10^{-12} g of radium per milliliter.[39] The normal content of these substances in human tissue is of the order of 10^{-12} gram equivalent per gram, and although it increases with age it never exceeds this order of magnitude.[40] From analyses of crematory ash of 18 presumably normal individuals, Krebs[41] found an average total body content equivalent to 1.4×10^{-8} g of radium, ranging from 1.9 to 17.9×10^{-12} g per gram of ash. He further suggests that accumulation in excess of this amount, if it should reach the concentration of 10^{-10} g in any tissue, may lead to serious injury and ultimately to death.[39] Analyses made in the Project laboratory on two samples of crematory ash indicated the total body content of radium to be of the order of 0.01 per cent of the figure reported by Krebs.

REFERENCES

1. H. E. Silberstein, Radium Poisoning; A Survey of the Literature Dealing with the Toxicity and Metabolism of Absorbed Radium, Report M-1695, May 26, 1945.
2. H. A. Seil, C. H. Viol, and M. A. Gordon, Radium, 5: 40 (1915); N. Y. Med. J., 101: 896 (1915).
3. H. Schlundt and G. Failla, Am. J. Roentgenol. Radium Therapy, 26: 265 (1931).
4. R. D. Evans, J. Ind. Hyg. Toxicol., 25: 253 (1943).
5. J. C. Aub, R. D. Evans, D. M. Gallagher, and D. M. Tibbetts, Ann. Internal Med., 11: 1443 (1938).
6. R. D. Evans, R. S. Harris, and J. W. M. Bunker, Am. J. Roentgenol. Radium Therapy, 52: 353 (1944).
7. F. E. Hoecker, J. Ind. Hyg. Toxicol., 26: 289 (1944).
8. H. Schlundt, J. T. Nerancy, and J. P. Morris, Am. J. Roentgenol. Radium Therapy, 30: 515 (1933).
9. F. B. Flinn and S. M. Seidlin, Bull. Johns Hopkins Hosp., 45: 269 (1929).
10. F. B. Flinn, J. Am. Med. Assoc., 96: 1763 (1931).
11. L. F. Craver and H. Schlundt, J. Am. Med. Assoc., 105: 959 (1935).
12. B. Rajewsky, Strahlentherapie, 69: 438 (1941).
13. H. H. Barker and H. Schlundt, Am. J. Roentgenol. Radium Therapy, 24: 418 (1930).
14. A. O. Gettler and C. Norris, J. Am. Med. Assoc., 100: 400 (1933).
15. E. Neitzel, Z. ges. Schiess- u. Sprengstoffw. Nitrocellulose, 37: 74, 94, 114, 132, 155 (1942).
16. J. C. Aub, H. S. Martland, and R. D. Evans, personal communications, 1944.
17. A. Janitzky, A. Krebs, and B. Rajewsky, Strahlentherapie, 61: 254 (1938).
18. C. E. Dunlap, J. C. Aub, R. D. Evans, and R. S. Harris, Am. J. Path., 20: 1 (1944).

19. H. E. Thomas and F. H. Bruner, Am. J. Roentgenol. Radium Therapy, 29: 641 (1933).
20. W. Salant and G. M. Meyer, Am. J. Physiol., 20: 368 (1907).
21. H. Dominici, Mme A. Laborde, and A. Laborde, Compt. rend. soc. biol., 75: 108 (1913).
22. H. Dominici, S. Laborde, and A. Laborde, Compt. rend., 156: 1107 (1913).
23. T. Hosokawa, Strahlentherapie, 19: 546 (1925).
24. H. Dominici, G. Petit, and A. Jaboin, Compt. rend., 150: 726 (1910).
25. H. Dominici, G. Petit, and A. Jaboin, Compt. rend., 153: 1509 (1911).
26. Van de Putte-Van Hove, Strahlentherapie, 61: 300 (1938).
27. F. Daels, H. Fajerman, and Van de Putte-Van Hove, Strahlentherapie, 63: 545 (1938).
28. W. H. Cameron and C. H. Viol, Radium, 4: 57 (1915).
29. A. V. St. George, A. O. Gettler, and R. H. Muller, Arch. Path., 7: 397 (1929).
30. H. S. Martland, P. Conlon, and J. P. Knef, J. Am. Med. Assoc., 85: 1769 (1925).
31. H. S. Martland, Arch. Path., 2: 465 (1926).
32. G. S. Reitter and H. S. Martland, Am. J. Roentgenol. Radium Therapy, 16: 161 (1926).
33. E. Toenges and H. Kalbfleisch, Frankfurt. Z. Path., 50: 100 (1936-1937).
34. M. Rosenthal and E. J. Grace, Am. J. Med. Sci., 191: 607 (1936).
35. M. Rosenthal, Am. J. Med. Sci., 193: 495 (1937).
36. H. Dominici and M. Faure-Beaulieu, Compt. rend. soc. biol., 68: 46 (1910).
37. C. van Eweyk, M. Gurwitsch, C. Gottheil, and I. Gasiunas, Strahlentherapie, 19: 789 (1925).
38. H. Wada, Strahlentherapie, 19: 383, 779 (1925).
39. A. Krebs, Kolloid-Z., 89: 309 (1939); Chem. Abstr., 34: 2466 (1940).
40. A. Krebs, Fundamenta Radiol., 5: 89 (1939); Chem. Zentr., 1: 224 (1940); Chem. Abstr., 35: 5919 (1941).
41. A. Krebs, Strahlentherapie, 72: 164 (1942).

Chapter 16

STUDIES ON HUMAN EXPOSURES TO URANIUM COMPOUNDS

By Joe W. Howland*

1. INTRODUCTION

As has been stated in the introductory chapter of this volume, the primary purpose of this entire study on the toxicology of the uranium compounds was directed toward the protection of both workers and scientists engaged in carrying out that work necessary for the success of the Manhattan District operation in its development of atomic energy for military purposes. During the course of these activities numerous observations were made on the possible toxic reactions of human beings to these compounds either as the result of acute exposure or following long-continued chronic exposure. In this chapter these observations are summarized as completely as possible. Obviously since all these individuals were engaged either in research on uranium purification processes or in the processes themselves, much detail of their work must be omitted for security purposes.

Following a brief review of the related literature on human exposure to uranium compounds, a discussion will be given of the clinical effects of the few accidental acute exposures, a résumé of the clinical studies made in several installations on the effect of known chronic uranium exposure, and finally a review of the laboratory observations made on the industrial medical program carried out in the manufacturing laboratories and plants in various parts of the country.

In an examination of the following data it is quite obvious that, except for the acute exposures in which the individual was heavily contaminated with the uranium compound, no evidences of a chronic toxicity for any of the uranium compounds could be demonstrated by the methods used in the examination.

*This work is a summary of a portion of the control activities of the medical section of the Manhattan District.

2. REVIEW OF THE LITERATURE

There is very little scientific literature on the effect of uranium and its compounds on the human body. The few papers that have appeared are primarily reports on the therapeutic effect of uranium compounds on diabetes mellitus, dermatological disorders, and neoplastic diseases.

Kennedy,[1] West,[2] Walsh,[3] Tylecote,[4,5] and Wilcox[6] treated large numbers of diabetics orally with uranyl nitrate hexahydrate in doses ranging from ½ to 60 grains daily (0.011 to 3.9 g) for periods up to 1 year. The occurrence of transient albuminuria was noted by Tylecote only.

Gailleton,[7] Clark,[8] and Truttwin[9] used uranyl nitrate topically in the treatment of a variety of skin disorders, including lupus, psoriasis, eczema, trychophytosis, and senile atrophy. No toxic symptoms were noted.

Clark[8] and Hocking[10] used uranium or uranium-thorium preparations in the treatment of neoplastic growths with supposedly successful results. No urinary changes were noted. Pack and Stewart[11] studied the effects of intravenous colloidal uranium-thorium preparations in eight patients with carcinoma, all receiving approximately 60 ml of a 1 per cent solution of each of these metals. Questionable benefit was noted in one case. Two patients showed evidence of renal damage, although at autopsy no changes were noted in the kidneys of the single case examined.

Only a single paper is found in the literature on the potential hazard of uranium compounds used in industry. DeLaet and Meurice[12] reported four cases in a Belgian ceramics plant in which changes in the peripheral blood (anemia, leucopenia) were interpreted as due to the effect of the uranium compounds. No urinary abnormalities were noted.

3. EXPOSURE OF PERSONNEL TO URANIUM COMPOUNDS IN THE LABORATORIES AND PLANTS OF THE MANHATTAN PROJECT

The ultimate value of an industrial toxicological program can be measured only by the success obtained in the application of the laboratory findings for the protection of workers in industry. Hence an attempt is made in this final section to present a concise over-all picture of the type of exposures to uranium compounds that occurred in all phases of the experimental and industrial work and the results obtained in the study of exposed personnel for positive evidences of exposure.

In the preceding chapters many data have been presented on the toxicological findings following animal exposures to various uranium compounds by inhalation, ingestion, and skin absorption. It is quite important to state early in this account that such observations can be applied to man only in a relative fashion, inasmuch as the human being is anatomically, physiologically, and biochemically somewhat different from the animal, and his susceptibility to toxic substances may be different.

As has been stated, the urgency of the project demanded that work on the isolation and purification of various potentially toxic uranium compounds be rushed to completion as rapidly as possible. Hence it was not feasible to defer such activity until preliminary toxicity tests could have been conducted. Again, the earlier work on the toxicity of uranium had been conducted largely for the production of experimental toxic kidney diseases in order to study the physiology of this condition. Consequently, little was known about the relative toxicity of varied doses of even uranyl nitrate, the most studied compound. Nothing was known about the toxicity of doses absorbed through the lung, the most common industrial exposure. Obviously, if even temporary protection was to be effected, some sort of a value for the maximum allowable concentration of the metal suspended in air was necessary. Hence, after careful study, the data originally obtained on the toxicity of lead, a heavy metal of atomic weight 207, were used for establishing a temporary maximum allowable concentration of these compounds in air. This amount was 150 μg of uranium dusts per cubic meter of factory air. Following the adoption of this provisional standard the experimental program was rushed to completion to determine whether this level was within safe limits. At the same time the concentration of the dusts in factory air was reduced to this recommended value by means of improvements in existing ventilation, housekeeping, etc.; redesign of processes and handling methods; and, in areas where concentrations continued to exceed this value, the use of recommended protective equipment. The results of the experimental program as given in previous sections indicate that this predicted safe allowable concentration of uranium compounds in air was indeed a wise one.

It cannot be too strongly emphasized that the evaluation of the total exposures to uranium dusts in factory and in laboratory air is entirely different from evaluation of the exposures of animals by inhalation of uranium dusts. In the toxicological chambers the animal is exposed constantly 6 hr daily to a known concentration range of a single uranium dust of high purity, unmixed with appreciable nuisance dust. The particle size of the dust and resultant absorption are, relatively, known. The humidity and temperature are controlled. The animals

are healthy specimens of known age, sex, and weight. Even the normal reaction of the animal to incarceration in exposure chambers is controlled by a similar study in a chamber to which no uranium dusts are added.

The worker in a uranium-processing plant undergoes an entirely different experience. In any given location under operating conditions, concentration of uranium dusts may vary many thousandfold (from approximately 100 μg to 100 mg of the heavy uranium dust per cubic meter of air). Owing to the nature of the work in a chemical purification process, the dust is usually not a pure compound but is composed of a mixture of the dusts from various processes being carried out in that building or buildings. The particle size of the compounds will vary over a very wide range and fluctuate constantly. Humidity and temperature are usually uncontrolled. In addition to all these physicochemical variables, the problem of the worker himself is encountered, perhaps the most unstable factor of the entire group. All ages and races are employed; both sexes are employed; selectivity as to a state of health, except for the elimination of obvious pathology, is rarely allowable if employment is to be maintained. The action of individuals in following safety and precautionary rules for the prevention of exposure, such as the use of gas masks and other protective equipment, is always unpredictable.

With the foregoing considerations in mind, it becomes important to state the comparative value of animal toxicological data as applied toward the protection of the worker. The relative toxicity of a compound for a group of animal species is in almost all instances well above the recommended 150 μg/cu m of air. This difference between the recommended and toxic levels is called a "factor of safety" for the compound in question and will give a wide margin of protection for another species (including the human) that might be unusually susceptible. Again, animals in their exposure chambers undoubtedly receive much higher concentrations of the toxic compound than do workers in the processing plants and laboratories, owing to the use of preventive devices, shifting of work stations, and the psychological fear of a possibly dangerous material. Finally, the relative toxicity of a series of similar compounds usually shows that the susceptibility or resistance of any species bears the same relationship to other species, the sensitive species to one compound (such as the rabbit to nitrate) being again the sensitive species to a related compound.

The general aim of the toxicological program is of course to protect against the insidious development of toxicity from a chronic exposure. That acute exposures will and do occur is an expected event in most

industrial medical programs, and the prevention of such acute exposures (usually to high concentrations of material) falls within the realm of the combined medical and safety departments. In the following discussion of human exposures to uranium compounds, the only two instances of acute exposure encountered will first be given in some detail, followed by a general account of observations made on an over-all survey of chronically exposed personnel.

3.1 Acute Uranium Poisoning. Fortunately, in spite of the very large numbers of individuals working on uranium compounds, the acute toxic effects have been observed in only two instances. Both of these exposures were accidental in nature and involved the same compound, uranium hexafluoride. Inasmuch as this is the first report of any acute injury to the human body by uranium compounds, the details and findings will be discussed at considerable length.

A. Report of First Accident. An accident occurred at an experimental laboratory where a very large amount of uranium hexafluoride escaped, resulting in the death of two employees, serious injury to three others, and slight injury to thirteen additional persons.

(a) Description of the Accident. The cause of the accident was the sudden rupture of a large tank containing the hexafluoride as a gas with the simultaneous rupture of high-pressure steam lines. This resulted in a very dense cloud of the compound and its hydrolysis products, uranium oxyfluoride and hydrofluoric acid, plus steam released from the broken lines.

One of the two engineers was working 5 to 6 ft away from the site of the explosion, and the other was observing the procedure from immediately behind him.

The two fatally injured were directly in the path of the released chemical cloud. One was unable to find his way out of the laboratory for about 5 min and expired 10 min later; the other escaped quite rapidly and died in about 70 min from the time of the accident. Two of the three seriously injured men were in the vicinity of the fatal cases; the third was just outside the building within a few feet of the place where the tanks containing the hexafluoride were stored.

The three seriously injured cases required 10 to 14 days of hospitalization before recovery was complete. The 13 other cases received only minor injuries and required little or no treatment other than that which could be given in a dispensary.

A study revealed that the exposure of the various individuals differed

was about 17 sec. The characteristics of the individual exposures varied somewhat because of the different actions taken on the part of the individuals, e.g., holding the breath, closing the eyes, and removal from contaminated areas. A further variation in exposure resulted from the individuals' actions in showering and removal of clothes.

There was a considerable variation in the CT level (concentration times time of exposure) that the different individuals experienced. In general the most severe injuries occurred in those nearest the site of the explosion. There appeared to be less variation in the length of exposure than in the concentration of the exposure.

The steam lines were broken by the explosion of the storage tank and the atmosphere of the room contained a mixture of uranium hexafluoride, hydrofluoric acid, uranium oxyfluoride, and live steam. The combination of the moisture and heat undoubtedly facilitated the hydrolysis of the uranium hexafluoride and from a toxicological viewpoint aggravated both the systemic and vesicant action of these substances.

(b) Case Reports of Fatally Injured Workers. (1) Case No. 1. Clinical Observation. He was the more seriously injured of the two fatal cases and nearer to the point of explosion. He was in extremis when first seen, apparently having been sprayed with live steam containing liquid, solid, and gaseous material in large quantities. He died 16 min after the accident.

Gross Pathological Findings. The skin revealed extensive third-degree burns, and over 70 to 80 per cent of the body surface showed some degree of injury. The areas covered by his underwear (shorts only) were free from burns except for the skin above the anus and that of the scrotum. The hair on the scalp also seemed to afford protection. The areas of mottled blue, green, and cyanotic red distributed in the skin of all parts of the body were thought to be related to chemical irritants and to the fluid ("citrated-like") character of the blood. The conjunctivas were edematous and injected. The corneas were frosted. The oral and pharyngeal mucous membranes were edematous and gray-green in color. There was generalized edema of the subcutaneous tissue beneath the burns, varying considerably in degree. This is typical of chemical burns as opposed to thermal burns (suggesting the invasiveness of the chemical-type burn). Other positive findings were:

1. Small petechial hemorrhages in the epicardium.
2. The pulmonary tissue was bulging into the intercostal spaces. The surfaces of the lungs were dark red, and the organs only partially floated in water. On section, the bronchial mucosa was a dirty-gray necrotic mass with partial desquamation. The parenchyma was unchanged except for increased fluid content.

3. The blood resembled citrated blood.

4. The intima of the blood vessels was tinted with hemoglobin.

5. The external surfaces of the neck organs (thyroid, larynx, trachea, and proximal esophagus), together with the surrounding fascia, had a green-blue fluorescent sheen. The mucosa of the larynx and trachea was necrotic, dirty green in color, and sloughing. The submucosa was edematous. The mucosa of the esophagus down as far as the region of bifurcation of the trachea was likewise necrotic and sloughing. Upon section the thyroid parenchyma was a dark reddish green in color and appeared to be necrotic.

Microscopic Pathological Findings. 1. Skeletal muscle taken from superficial areas showed considerable edema.

2. The lungs showed marked vascular congestion and patchy alveolar edema. Red cells were present in the alveoli.

3. The kidneys showed tubular swelling and marked vascular and glomerular congestion. The tubular epithelium was detached in some areas from the basement membrane. Coalescence of the epithelium was present in many tubules.

Table 16.1—Uranium Analysis on Autopsy of N.E.*

Sample	In alcohol, μg U/g	In formalin, μg U/g
Lung	800	570
Bronchi	750	320
Tongue	25	
Heart		22
Kidney	18	35
Liver	17	
Stomach wall	42	4
Spleen		0
Ribs		0
Esophagus		1
Testis		0
Fresh skin, outer layer	270	
Fresh skin, inner fat layer	35	
Urine	0.10	
Alcohol (blank)	0	
Formalin (blank)		0

*Separate portions of organs were preserved in alcohol and in formalin.

Laboratory Findings. The autopsy material was analyzed for uranium by spectrographic means (see Table 16.1).

(2) Case No. 2. Clinical Observations. Following the accident his condition appeared to be good. A short time after admission to the

hospital (20 min) he developed a progressive respiratory distress associated with considerable generalized pain. He expired 70 min after the explosion.

Gross Pathological Findings. 1. Approximately 70 to 80 per cent of the body surface was burned. Most of the burns appeared to be third degree in type. The scalp was not involved, being protected by the hair, which was brittle and dry.

2. The conjunctiva of the right eye was edematous and red.

3. The mucosa of the mouth and nasopharynx was necrotic and gray-red in color.

4. Numerous petechial hemorrhages were noted in the epicardium.

5. The blood was fluid and of a citrated-like nature.

6. The intima of the arteries was stained with hemoglobin.

7. The bronchi were filled with undigested food. The bronchial mucosa was intensely injected but not necrotic. The lung parenchyma was diffusely red and bloody without any focal lesions.

8. Lobulation of the liver was indistinct.

9. Petechial hemorrhages were present in the right kidney.

10. The laryngeal, tracheal, and esophageal mucosa were injected and edematous but not necrotic.

Microscopic Pathological Findings. 1. The superficial skeletal muscle was edematous.

2. The heart showed myocardial fragmentation and an area of subepicardial hemorrhage.

3. The lungs showed marked vascular congestion, moderate alveolar edema, and some alveolar hemorrhage.

4. The kidneys showed tubular swelling, marked vascular and glomerular congestion, and a separation of the tubular epithelium from the basement membrane. Coalescence of the epithelium was observed in many tubules.

Laboratory Findings. Analysis for uranium in the autopsy material was carried out by the spectrographic method (Table 16.2).

(c) Description of Findings in the Nonfatal Cases. In addition to the two fatal cases previously described, 19 men were exposed to the huge chemical cloud that enveloped almost everything within a radius of approximately 100 yd of the center of the explosion. This cloud required several minutes to dissipate.

Three of these individuals developed no symptoms. Fourteen were immediately hospitalized for observation and treatment (besides the one that died almost immediately and the other who died in slightly more than 1 hr). Two additional men reported to the dispensary 36 hr

after the incident because of minor symptoms. Except for three men who were more seriously injured, all the hospitalized patients were ready for discharge within 48 hr after hospital admission.

Table 16.2 — Uranium Analysis on Autopsy of B.R.*

Sample	In alcohol, μg U/g	In formalin, μg U/g
Lung	0	0
Bronchi	0	0
Tongue	0	
Heart	0	
Kidney	0	0
Liver	0	1.1
Stomach wall	1.3	0.3
Spleen		0
Ribs		0
Esophagus		0
Testis		0
Fresh skin, outer layer	310.0	
Fresh skin, inner fat layer	8.0	
Alcohol (blank)	0	
Formalin (blank)		0

*Separate portions of organs were preserved in alcohol and in formalin.

(1) Clinical Findings. For brevity a résumé of the effects of the chemical exposure on the various body structures and systems is given.

Eyes. Eleven of 16 surviving patients experienced an intense burning sensation of the eyes with profuse lacrimation. A chemical conjunctivitis occurred in 8 of these 11 patients. A severe corneal ulceration occurred in one case and was described by the ophthalmologist as a chemical burn of the entire corneal epithelium. A slit-lamp examination of the eyes of this patient 2 months later revealed a diffuse haze of the epithelium of the lower half of both corneas. No staining or change in sensitivity was noted. Prognosis was given for the complete disappearance of this pathology.

Respiratory Tract. Of the 16 surviving patients, nine complained of throat irritation, six of hoarseness, and six of nasal "stuffiness." Respiratory distress of a transient nature occurred in 10 of the 18 patients. This was described as a shortness of the breath, inability to "catch a breath," or just as an uncomfortable sensation in the chest. In 10 patients severe coughing spells occurred, often of paroxysmal

nature. On examination nine patients showed numerous râles in the chest, suggestive of a chemical bronchitis; one, a typical pulmonary edema; and one, a suggested pulmonary edema. The patient with pulmonary edema raised blood-streaked sputum for 3 days after the accident. This sputum had a glistening reddish-orange appearance and in areas unstained by blood resembled hydrolyzed uranium hexafluoride.

Skin. Ten patients complained of burning of the skin shortly after exposure. Some of these individuals noted intense pain in the scrotum and penis and around the anus (probably because of the hydrolysis of the hexafluoride in these moist areas and a release of the irritant hydrofluoric acid). Eight patients showed definite second-degree burns. Two had coagulative necrosis of the skin of the legs, which healed very slowly, more than 1 month elapsing before complete epithelialization took place. The burned regions at that time were pigmented and of a parchmentlike appearance. Most of the severe burns were on the lower legs, the area of the burn starting abruptly at the top of the shoes. The burns were treated with vaseline gauze dressings with mild compression. No calcium gluconate (prescribed for hydrofluoric acid burns) was necessary.

Gastrointestinal Tract. Six of the 16 patients had nausea and vomiting in some degree. Three of these had in addition abdominal cramps with or without some distention. The symptoms disappeared spontaneously in 12 to 24 hr. No diarrhea was observed in any patient.

Urinary Tract. Two of the three seriously injured individuals showed transient albuminuria. One excreted from 39 to 100 mg of albumin (per 100 ml of urine) daily for a period of 7 days after the accident. Thereafter he showed only an occasional trace of albumin, which disappeared entirely by the time of his discharge from the hospital. All three of the seriously injured had a 3-day period of transitory urinary suppression. One showed a mild rise in the blood urea and nonprotein nitrogen level. These blood constituents were still somewhat elevated 3 weeks after the accident, after which a gradual reduction to normal levels was noted. Five of the group of 16 continued to excrete uranium 18 days after the accidental exposure.

Nervous System. All the seriously injured individuals were unusually nervous and apprehensive for 4 to 5 days after the accident. One individual was definitely overstimulated for about 3 days, exaggerating all facial expressions and being unusually verbose and talkative. At times he was almost incoherent. The other seriously injured patient, although normally quiet and placid, became very apprehensive with a similar tendency toward the exaggeration of statements. The opinion of all observers held that the mental reactions were more than could possibly be explained on a fear-reaction basis.

(2) Laboratory Data. The laboratory data collected on these cases consisted of complete blood counts with differential smears, blood urea nitrogen and nonprotein nitrogen, blood chlorides, serum cholesterol, plasma carbon dioxide, total proteins, and complete urine analysis, including frequent analysis for the uranium content of the urine by the spectrographic method.

The significant findings follow:

1. Temporary fall in the plasma protein level (mild hemodilution).
2. Transitory type of albuminuria.
3. Elevation of blood nonprotein and urea nitrogen.
4. Uranium present in urine in amounts from 0.00 to 0.51 mg/liter (Table 16.3). The persons having the highest exposure showed the highest uranium excretion. In addition their urinary abnormalities were the most severe, consisting of albuminuria plus red cells and casts in the urinary sediment, and their blood urea and nonprotein nitrogen were elevated for several weeks.

Table 16.3—Uranium Analyses of Urines on Five Nonfatal Cases

Date	Initials of victim	Uranium, mg/liter	Total urinary output, ml
Sept. 4	T.O.	0.51	1,000
5	T.O.	0.15	2,370
6	T.O.	0.18	3,900
9	T.O.	0.10	?
10	T.O.	0.10	?
11	T.O.	0.07	?
12	T.O.	0.14	?
20	T.O.	0.00	?
Sept. 16	H.A.	0.07	?
Sept. 20	B.L.	0.05	?
Sept. 4	L.E.	0.15	1,395
5	L.E.	0.09	1,800
6	L.E.	0.00	2,150
9	L.E.	0.00	1,725
10	L.E.	0.00	1,775
11	L.E.	0.21	?
12	L.E.	0.16	?
20	L.E.	0.02	?
Sept. 4	K.R.	0.00	820
5	K.R.	0.05	2,655
6	K.R.	0.15	2,000
9	K.R.	0.06	1,635
10	K.R.	0.11	1,765
11	K.R.	0.10	1,925
12	K.R.	0.11	?
20	K.R.	0.05	?

The roentgenographic films of the exposed individuals showed a diffuse inflammatory process of mild nature radiating out from the hilus of each lung. Involvement of the upper lung fields was more marked. Findings present in the lower lobes suggested those seen in mild pulmonary edema with an increase in the prominence of the lung markings. No consolidation was noted.

Bacteriological cultures of the sputum contained only normal flora.

B. Report of Second Accident. The patient became suddenly surrounded by vapor as the result of a sudden development of a leak on a cylinder containing uranium hexafluoride. In the cloud he was unable to find an exit rapidly so that the period of his exposure in the cloud may have been as much as 10 min. When taken to the dispensary he complained of burning of his eyes and throat. Coughing and retching were quite marked with vomiting on one occasion.

Discussion of Findings. He was immediately hospitalized, and during the following month his clinical course was studied in considerable detail. The important findings were related to the respiratory tract, urinary tract, and the eyes.

The lower respiratory tract showed clinical evidence of a chemical pneumonitis. Râles were present throughout the chest, and the patient produced a thick tenacious black sputum for about 10 days. The X-ray findings immediately after the accident showed no abnormalities but 5 days later revealed an increase in the density of the bronchovascular markings and hilus shadows. Ten days after exposure the chest was clear both clinically and radiographically. There was a hemorrhagic involvement of the left arytenoid cartilage and vocal cords on laryngoscopic examination. Thirteen days later this involvement was resolving favorably.

There was a rapid rise in the quantity of the solid elements in the urine followed by a gradual decrease as the patient improved. The single constituent appearing in largest amount was a coarsely granular cast. Epithelial cells of various types were noted. Occasional large mononucleated phagocytes containing red cells and cellular debris were also found.

The eyes showed a chemical conjunctivitis with necrosis of the corneal epithelium. Within 5 days under conservative treatment the corneal epithelium had almost completely regenerated. Visual acuity at the time of discharge was normal.

The mental status for the first 5 or 6 days following the accident was marked by general sluggishness with transient periods of restlessness, irascibility, and nervous tension with occasional silliness and loss of contact. All symptoms of this type cleared up within a week after admission to the hospital.

C. Discussion. The typical picture of the acute poisoning of human subjects by the inhalation of a soluble uranium compound (uranium hexafluoride) is one of an initial chemical injury to the respiratory tract followed almost immediately by evidences of kidney injury. At the onset there is almost immediate development of marked weakness and prostration. The patient complains of suffocation and retrosternal pain and on examination exhibits dyspnea, cyanosis, and numerous wet râles and rhonchi throughout the chest. The latter findings are associated with the development of an annoying irritative cough, often producing a greenish-gray sputum that frequently contains blood. In severe exposures, signs of pulmonary edema are often seen. X rays of the chest show a soft infiltration along the bronchovascular markings and an increased width of the intercostal spaces. At times areas of consolidation may be noted. The circulatory system immediately following the exposure shows signs typical of the onset of traumatic or secondary shock plus secondary signs related to the cyanosis or pulmonary edema. The body temperature is usually elevated for a period of 12 to 72 hr, the highest observation being 103°F. The burns of the skin resemble those following hydrofluoric acid exposure but are almost without exception less severe. A similar latent period of two or more hours between exposure and development of the chemical burn is noted. With conservative treatment the burns are self-limiting in type, although as much as 6 weeks may be required for the healing of the injured area. The exposure is usually associated with a change in sensorium, states of depression or agitation being quite common in all individuals. Corrosive action of the chemical results in a coagulation necrosis of the epithelium of the cornea, at times accompanied by deeper ulceration. Healing is spontaneous and complete. The renal changes as observed in human beings have been entirely those of laboratory observation and have never been associated with clinical findings such as anuria, costovertebral pain, colic, or the like. Maximum changes as observed have been transient albuminuria, increase in solid elements in the urine, and moderate retention of nitrogenous products in the blood.

An analysis as to the probable cause of the various clinical findings indicates that in all probability the injurious effects observed on the skin, eye, mucous membranes of upper respiratory tract, esophagus, larynx, and bronchi were all directly caused by the action of the fluoride ion on the exposed tissues. The uranium as such had its only effect in the production of the transient urinary-tract changes.

D. Conclusion. The acute effects of exposure to high concentrations of uranium hexafluoride have been demonstrated to consist of corrosive changes in the skin, eyes, and respiratory mucosa, probably

caused by direct action of the contained fluoride, and transient kidney changes related to toxic action of the absorbed uranium.

3.2 Chronic Exposure to Uranium Compounds. The previously discussed reports of accidental exposures to uranium hexafluoride are the only known instances of acute high-concentration exposures to uranium compounds. The most important problem, however, to the medical group supervising such activities in the Manhattan District, was the possibility of the existence of a chronic toxicity to uranium compounds that might develop in workers in the important laboratories and plants of the project.

After operations on these possibly toxic substances had been carried out for several months, it was evident either that no toxic changes had occurred or that their development was of such an insidious nature that the methods used for their detection were insufficiently sensitive to show changes. Hence it was necessary to set up some plan of examination that could detect the presence of abnormalities as they developed.

In the following section the problem will be stated, followed in turn by discussion of the type of examination, method of analysis, and experimental observations.

The Problem. The selection of the tests used in the exposure of workers in industry followed these criteria: (1) the test should use the most sensitive index of injury to the human organism; (2) it should be of the highest reliability and applicable to all types of individuals; (3) all known and specific types of damage known to be caused by uranium compounds should be tested for; (4) the test should not alarm the subject psychologically so that he would suspect presence of damage where none exists; (5) the test should be sufficiently simple to be capable of being performed in a routine clinical laboratory.

A review of the available data indicated that at that time the only definite damage known to be caused by uranium compounds was restricted to the development of a toxic necrosis, with resultant damage to kidney tubules in varying degrees depending, in so far as could be determined, on the susceptibility of the animal species and the size of the dose. Suitable tests for this type of damage had already been known and consisted simply of tests on the urine for excreted albumin as well as evidences of the actual tubular damage in the form of excreted cells and cellular debris either singly or in the composite casts. Other tests such as urinary specific gravity were also of value in predicting renal abnormalities. Therefore use of the common urinary tests satisfied the foregoing conditions for the detection of any kidney abnormality. Inasmuch as uranium, like other heavy radioactive materials, was suspected of being deposited in excessive amounts

in bone, it was possible that the small amount of radiation to which the bone marrow would be exposed over an extended period of time might result in a depression of the red and white marrow coupled with a production of abnormal white-cell elements. Inasmuch as this possibility could exist, suitable tests were necessary in order to detect this possible pathological development. As to the nature of these events, the only evidence that could be used was the development of changes in the cells of peripheral blood. For this reason, routine analyses of the circulating blood elements, namely, red cells, hemoglobin, and white cells, were necessary plus a differential examination of the white-cell elements. Serial examination of these should indicate the development of any depressive state or abnormality that might occur following radiation exposure from the deposit of uranium.

It was suspected also that some liver damage might occur. However, in the absence of suitable clinical tests it was decided that the clinical evidence of liver disease should suffice as an index of the development of this condition.

Hence the examination of personnel exposed to uranium compounds resolved itself into serial examination of the blood and urine at specific intervals. Development of any unusual state or abnormality in an individual was checked upon with additional, more specific tests as will be outlined below.

Examination of Human Subjects. Before employment of an individual in any of the laboratories or industries using or engaging in the production of uranium compounds, a preliminary screening for obvious physical abnormalities was carried out. This consisted of a complete physical examination by a competent observer, X ray of the chest, a Wasserman test, and special tests thought to be necessary for any clinical purpose. In addition a laboratory examination of the blood and urine was carried out. The blood examination consisted of a hemoglobin test by the Sahli method, erythrocyte count, leukocyte count, and a complete differential examination of the white-cell elements. The urine examination consisted of the testing for specific gravity, the reaction (acid or alkaline), the qualitative analysis for albumin and sugar, and a microscopic examination of the centrifuged sediment for cells and abnormal elements.

Inasmuch as the war emergency had caused marked diminution in available labor throughout the entire country, it was necessary to accept individuals for employment whose physical status would not meet the requirements for peacetime industry. In addition, certain individuals, particularly scientists, were of such value to the project that their presence was necessary in spite of obvious physical defects. Hence it was necessary to limit the refusal of possible employees to

the minimum, and disqualification was made only in those showing obvious kidney pathology, extreme cardiovascular disease, and various pulmonary conditions, particularly chronic bronchial asthma. The latter condition is well known in industry to result in considerable difficulty, particularly when noxious materials and gases are present.

Following the screening examination the individual was employed and placed in the laboratory or industrial process where needed. At intervals, urine and blood examinations were carried out for the detection of changes. Although there was variation in the frequency of these examinations at first, the following schedule was soon decided upon: urines were examined once a month, and, inasmuch as blood changes were presumed to develop relatively slowly, a 3-month interval was used between blood tests.

Special examinations were later carried out after an individual had been exposed to uranium compounds for an extended period of time. One consisted of an analysis at suitable intervals of a 24-hr specimen of urine by the fluorophotometric method for uranium content. It was soon discovered that only the individuals exposed to high concentrations of the soluble compounds showed an increased urinary excretion. Considerable difficulty was encountered in this type of examination because of the instances of contamination of the urine from dust on the clothing and skin. For this reason, accurate analyses of excreted uranium were limited largely to those individuals showing only high exposure over an extended period of time. Where possible, analyses of teeth and also of bone samples for deposited uranium were made. The latter study, although very limited, tended to show that little deposition was occurring in the processing plants where the instituted precautionary measures had been followed. This observation agreed with the presence of low uranium excretion in these individuals.

All individuals in the laboratories and plants were examined as

detection of gross errors. Any markedly abnormal finding in the laboratory study was checked back with the laboratory where the finding originated in order that any possible pathological cause for this variation would be eliminated. At times it was necessary to repeat physical examinations and related studies to solve the problems. Final data were grouped in such a form as to facilitate statistical evaluation. The data were punched on cards and analyzed according to the methods given in Chap. 3 on Statistics.

Experimental Observations. The program described above was carried out in all the laboratories and processing plants working on hazardous uranium compounds. Inasmuch as these sites were extremely varied in type and purpose it would be difficult to submit the findings collectively. Hence a subdivision of the various types of work has been made with a representative example of each group selected for exposition. The various types selected included (1) laboratories, (2) small uranium-processing plants, (3) large ore- and uranium-processing plants, and (4) large uranium-processing plants. A brief description of each of these installations will be made including statements as to the types of work, the physical status of the workers, the types of exposure, and, finally, the results of the laboratory data obtained in a study of such a group. The exposition related to the process itself must be rather general, inasmuch as both the processes and specific materials used in them must be kept secret for purposes of security.

(1) Laboratories. Type of Work. The laboratory selected for extensive study was one in which several hundred people were engaged in the study of various uranium compounds.

Physical Status of Workers. Employed in this installation was a large group of professional and academic scientists either directing large groups or acting as leaders of smaller research sections. Under them were routine laboratory workers engaged in the actual operation of the specific processes. In addition maintenance and housekeeping workers were employed.

Type of Exposure. The exposures were to uranium compounds both wet and dry with resultant hazard by inhalation and skin absorption. The amounts of material used were so small as to eliminate possible toxicity by ingestion. The types of exposure may be classified in several ways. Many workers were exposed to several, and others to only single, compounds. Many had a relatively heavy exposure as gauged by the many hours of work daily with these compounds. Others had only moderate or casual exposures, the latter term being used to indicate less than 1 hr daily. Still others had no exposure whatever and were used as controls.

The medical program was closely combined with a safety program to ensure the use of all protective methods known for the prevention of injury due to specific uranium compounds as well as those other materials ordinarily used in large laboratory and industrial practice.

The Results of the Analyses. The serial analyses of data obtained on this group of individuals can best be described, because the amount of data accumulated on these workers over a period of 2 years of observation is so voluminous that it would be impossible to tabulate sufficient data to illustrate the study even briefly. Although several hundred individuals were employed at all times, serial examinations on all individuals were obviously not possible owing to the continual turnover of labor and transfer of personnel common to all war installations. However, sufficient analyses were obtained covering an extended period of time to demonstrate conspicuously the fact that no pathological abnormalities that were within the range of statistical significance did occur. This finding is highly important, inasmuch as it is obvious that statistical analysis of data on sufficiently large groups of people may indicate changes that are not apparent on direct examination of the data of a single individual. Urinary abnormalities were not observed even after the heaviest exposure. Blood variations that occurred were well within the normal range of individuals in the studied locality. In conclusion it can be said that, within the limits of the method employed, no detectable changes were observed following chronic exposure of these individuals to uranium compounds.

(2) Small Uranium-processing Plants. Type of Work. The work carried out in this installation involved the processing of chemically pure uranium metal. The larger portion of the work is that classed as heavy labor in a metallurgical plant and involves exposures to a limited extent to the radiation from the metal itself as well as inhalation and ingestion of insoluble uranium compounds.

Physical Status of Workers. Several professional chemical engineers assisted by routine laborers engaged in the plant processing were employed. The office staff in this installation was used as the control group. A small number of individuals were working in an analytical laboratory engaged in the analysis of the insoluble uranium compounds. Much direct handling of the metal was encountered.

The Types of Exposure. The types of exposure encountered were (1) the dust of insoluble compounds in a relatively limited locality and (2) direct exposure to the uranium metal by skin contact. All the material used was in a dry form and insoluble as well, so that the possibility of ingestion again was considerably reduced. The safety program and medical program to all intents and purposes were identical and were under the supervision of the plant chief.

Analysis of Data. The statistical analysis of the laboratory data obtained from these individuals again showed no conspicuous change in either urine or blood. An additional study of the urines of this group was carried out with the catalase method as discussed in a previous section. Results of this study indicate that even to this very delicate test little change is noted.

This installation was also subjected to another type of study not mentioned previously. This is the study of changes in the contour of the fingerprints as caused by the exposure to beta radiation from handling of the uranium metal itself. Such changes were observed in individuals exposed to continuous radiation for long periods either from X rays (particularly fluoroscopy) or the direct handling of radium. These changes require months for development, but within the period covered by this study they would form a positive index of this type of exposure. The results of the fingerprint examination for the detection of this type of skin injury were completely negative.

In conclusion this study indicates that, again within the limits of the method, no detectable damage to any individual at this installation could be demonstrated.

(3) The Large Ore- and Uranium-processing Plant. The Type of Work. The type of work carried out at this installation consisted of the extraction of uranium from uranium ore (pitchblende) containing varying amounts of radium. The uranium was purified by a series of processes employing both alkali and acids, resulting in the formation of such compounds as uranyl nitrate (acid) and sodium diuranate salt (alkaline) plus many intermediaries. The processes involved solution of uranium compounds in many different ways with the precipitation, extraction, and filtration of the collected salts. Hence the hazards were not only from the dusty ore but also from the wet filter cakes and final dried compounds. Both soluble and insoluble compounds were included in the processing stages.

The Physical Status of the Workers. The physical status of the workers, except for a few professional engineers working in a supervisory capacity, was that consistently found in the group classed as routine laborers. A small laboratory was maintained.

The Type of Exposure. The type of exposure was, as in the large laboratory, a mixed one with exposures to the ore and to a large number of uranium compounds existing in both wet and dry states. Much individual handling of the wet compounds took place, which made possible exposure by ingestion and skin absorption in addition to inhalation of the dried material suspended in the plant air. Exposures to potentially dangerous acids (particularly hydrofluoric) and alkali used in the process also occurred. A full-time safety program was

maintained at this installation. It cooperated in the enforcement of specific handling methods for special uranium compounds and ore. Monitoring schedules both for uranium and for radiation (largely for radium and radon) were carried out for the over-all control of the amount of hazardous material to which workers in each of the plant localities were exposed.

Analysis of Data. Analysis of the data from these installations is complicated by turnover of labor and shifting of personnel so that, although several hundred individuals were employed at all times, a consecutive record of laboratory data covering 2 years of study is available on only a small percentage of this group. In spite of the fact that a certain number of individuals were also exposed to radium radiation (and possible deposition in bone) no significant abnormalities in the examination of blood laboratory data could be attributed to the exposure. Additional analyses were made on the urinary excretion of uranium in selected individuals receiving heavy exposure. These results were not abnormal. Urinary-catalase-excretion studies were also carried out and, as shown elsewhere, gave no positive results in the absence of obviously chronic renal abnormalities from causes unrelated to the exposure. These included chronic nephritis, cardiorenal disease, and the like.

In conclusion it must be stated that, again within the limits of the method, no demonstrable changes that could be attributed to the uranium exposure were observed.

(4) Large Uranium-processing Plant. Type of Work. The type of work carried on in these plants differed from that described previously in that only one or two uranium compounds were used, and, more important, the operating procedures were such that very little material was allowed to escape into the factory air. Hence, although many people were employed, actual moderate to heavy exposure occurred in relatively few individuals. Such exposure was for the most part accidental in type. In addition to the routine plant processing, a research laboratory was maintained for the investigation of changes in processing methods as well as analyses of the product. This involved problems somewhat similar to those already discussed in Sec. 3.2 (1).

Physical Status of the Workers. The physical status of the workers for the most part was that characteristic of any labor population recruited from a large portion of the United States and brought with it certain specific problems that would influence any analysis of laboratory data. Such a problem was exemplified by the presence of

hookworm disease in individuals recruited from the South, and the effect of this parasitism in producing abnormalities in the white-blood-cell count. A high percentage of women was employed here also. This is somewhat different from the condition existing in the other smaller installations.

Type of Exposure. The type of exposure was confined to inhalation and skin absorption of a single compound, plus the exposure to certain special compounds occurring as by-products. Certain special materials that in themselves are toxic and capable of producing kidney abnormalities were developed for the processes. Combined engineering and special safety procedures reduced all hazards to a minimum. Coupled with this was the high monetary value of the purified uranium, which made it imperative that all steps be taken against its loss in the plant in any way and therefore reduced the secondary exposure of the plant personnel.

Analysis of Data. The analysis of the data obtained on these thousands of individuals has been carried out elsewhere. Results, however, show that any existing abnormalities occurring in either blood or urinary examination would be completely explainable on the basis of extraneous causes and cannot be attributed to the uranium. No instance has been found in this area of injury to an individual's health primarily due to specific uranium toxicity.

Elaborate monitoring procedures have been carried out. These included the regular scheduled examination of air for concentration of uranium dust by the electrostatic precipitator or filter methods. Analyses of the 24-hr concentration of uranium in the urine have also been carried out on possible high-exposure cases. Correlations between the degree of exposure by inhalation and the urinary uranium content have been attempted. No consistent relationship has been demonstrated in the studies carried out to date.

In conclusion it is again evident that, within the limits of the method, no demonstrable changes that could be attributed to the uranium exposure were observed.

4. SPECIAL EXAMINATIONS AND STUDIES

A series of studies of more extensive type have also been carried out on groups of individuals employed in the various processing plants discussed in the previous section. Some of these, the catalase studies, have been described elsewhere in connection with the reports on the animal experiments (Chap. 14). All such studies demonstrate that

injury by uranium compounds to the normal kidney is almost nonexistent in the uranium-processing plants of the Manhattan District.

Two other studies that have not been mentioned were also carried out. It was obvious that the routine laboratory studies carried out on all personnel exposed to hazardous compounds would not include many of the elaborate analytical procedures used by clinical medicine and physiology to demonstrate minimal changes in the function of the kidney, blood-forming organs, and liver. Studies of this type were necessary. The general plan consisted of the selection of a group of individuals who had received known heavy exposure to certain uranium compounds over a known period of time, and the use of all the most selective tests on them to determine whether any damage could be demonstrated. Two such studies were carried out and will be discussed in detail.

4.1 Study 1. The purpose of this first study was to evaluate as completely as possible the physiological status of 10 men who had been working for 5 to 9 months in an industrial plant processing hexafluoride. As has been discussed under the acute cases reported in this chapter, this compound has hazardous properties, probably largely caused by its hydrolysis products, uranium oxyfluoride and hydrofluoric acid. The number of men used in this study was small, but, inasmuch as they held a variety of positions in the plant, they could be considered to roughly represent what might be termed a small cross section of the employees. The men were hospitalized for 2 days and the following procedures carried out:

a. Medical histories
b. Physical examinations
    1. Dental examinations
c. X rays of chest
d. Electrocardiograms
e. Hematopoietic system evaluation
    1. Hemoglobin
    2. Erythrocyte count
    3. Leucocyte count
    4. Differential examination
    5. Hematocrit
f. Liver-function evaluation
    1. Electrophoretic study of serum protein
    2. Prothrombin time
    3. Bromsulfalein liver excretion test
    4. Total plasma bilirubin
    5. Fasting sugar

g. Renal function
   1. Blood metabolites
      Nonprotein nitrogen
      Urea nitrogen
      Calcium
      Phosphorus
      Chlorides
   2. Metabolites in urine
      Urinary amino acid nitrogen
      Urinary creatinine excretion
   3. Routine urinary analysis
   4. Renal-clearance tests
      Chloride clearance
      Urea clearance
      Creatinine clearance

h. Special tests
   1. Urinary catalase
   2. Quantitative uranium content of urine excreted in a 24-hr period
   3. Quantitative fluoride content of urine excreted in 24-hr period

An analysis of these studies showed no discernible serious toxic effects that might have occurred as a result of exposure to the uranium hexafluoride.

It might be of interest to mention that the concentration of uranium in the urine ranged from 0.01 to 0.04 mg/liter per 24-hr period. From these figures it seems very doubtful that these men incurred high exposures to the uranium.

The urinary fluoride concentration ranged from 0.22 to 0.44 mg/liter per 24-hr period. This is well below the upper limit of the normal range of fluoride in urine (1.5 mg/liter).

4.2 Study 2. This study concerned itself with the examination of 31 individuals who had been exposed to uranium trioxide, tetraoxide, or tetrachloride in dust form for periods of more than 1 year. During a portion of this time all were exposed to concentrations of these compounds in excess of the recommended 150 μg of uranium per cubic meter of factory air.

The following studies were carried out:
   a. Medical histories
   b. Physical examinations
   c. X rays of chest

d. Hematopoietic system evaluation
    1. Hemoglobin
    2. Erythrocyte count
    3. Differential examination
    4. Leucocyte count
    5. Sedimentation rate
e. Renal function
    1. Blood metabolites
        Nonprotein nitrogen
        Urea nitrogen
        Chlorides
        Total protein
    2. Routine urinary analyses
    3. Renal-clearance tests
        Chloride clearance
        Urea clearance
        Creatinine clearance
f. Icteric index
g. Special tests
    1. Urinary catalase
    2. Urinary uranium

An analysis of these studies revealed no abnormal findings that could be considered to be due to chronic exposure of these workers to uranium compounds.

Mention must also be made of the analyses of teeth and bone removed from exposed workers for uranium content. These indicate that the amount of uranium absorbed and stored by the human being working in such industry is quite small. The hazard that might occur from such storage is in all probability negligible.

5. CONCLUSION

In conclusion this study indicates that, within the limits of the methods employed, no specific evidence of chronic injury to workers employed in any phase of the uranium industry has occurred as the result of the peculiar toxicity of uranium. It is of course possible that changes may develop in some individuals at a later date, but the experience already gained in animal observations indicates that this is unlikely.

Hence the standards set for the industry on the basis of 150 μg of uranium dust per cubic meter of factory air and the maintenance of this by suitable engineering and safety procedures have resulted in the protection of the industrial worker in the uranium industry as far as can be determined by the most selective methods.

BIBLIOGRAPHY

1. Kennedy, Case of Diabetes Mellitus Treated with Uranium Nitrate, Lancet, 1: 835 (1874).
2. S. West, The Treatment of Diabetes Mellitus by Uranium Nitrate, Brit. Med. J., II: 467-721 (1895).
3. D. Walsh, Multiple Medication with Uranium, Trans. Med. Press, 128: 444 (1904).
4. F. E. Tylecote, The Pharmacology and Therapeutics of Uranium, Med. Chron. Manchester, 40: 379 (1904).
5. F. E. Tylecote, The Action of Uranium Salts, Edinburgh Med. J., 58: 459 (1904).
6. R. W. Wilcox, The Therapeutics of Uranium Nitrate, Med. Record, 92: 361 (1917).
7. Gailleton, Lupus Treated with Uranium Nitrate, Lyon Med., 103: 123 (1904).
8. A. Clark, The Use of Uranium as a Radioactive Therapeutic Agent, Brit. Med. J., II: 716 (1912).
9. H. Truttwin, The Use of Uranium in Dermatology, Arch. Dermatol. u. Syphilis, 160: 132 (1930).
10. F. D. M. Hocking, The Employment of Uranium in the Treatment of New Growths, Internl. Conf. on Cancer, pp. 253-258, Wright, Bristol, England, 1928.
11. G. T. Pack and F. W. Stewart, Uranium-Thorium Colloid in the Treatment of Carcinoma, J. Cancer Research, 14: 152 (1930).
12. M. DeLaet and C. Meurice, Ing. chim., 9: 247 (1925).

gical data in later sections that each
idered. Uranium has been studied in
in various physical states. Animals
eyes, lungs, skin, peritoneal cavity,
venous injection. The principal toxic
ited to the uranium.

ffects. One of the first correlations
s is to establish some measurable
al effect that is an index of the degree
nent on the desirability of establish-
in the blood stream as a measure of
of the degree of injury. Once these
mple analysis of a blood sample can
rognosis of the poisoning. Unfortu-
venient procedure is not applicable

mation about any poison is its state
to concentrate on what the poison
studying what the body does to the
s, the distribution of uranium in the
tes and rates of excretion, and the
ave all been studied. These values
to be made about the treatment of
unds. Something of the metabolic
scovered, and a reasonably satis-
dum by the body has been worked

enzyme chemistry is growing so
stion should arise: Does uranium
rtue of its ability to inactivate or
n? From the tissues of poisoned
tracts of various sorts have been
determine what circumstances,
anium, destroy the normal activity
e correlated with concentrations

If a human population suffers an
rial, one of the desiderata is an
detection of the earliest signs of
rious diagnostic procedures may
e, the degrees of change can be
In such a search the blood count
sefulness. Plant personnel have

by now become more or less accustomed to occasional routine blood counts. In many plants it is easy to obtain urine samples, when desired, from cooperative employees. Thus, methods of detecting early changes in the blood or in the urine not only serve as criteria for following the acute and chronic toxic effects in exposed animals but also have a special value as possible aids to the medical supervision of plant employees.

4.7 Restriction of Survey Studies on Human Beings. The importance of good animal experimentation is emphasized by the fact that experimental groups of human subjects are unavailable under any circumstances. On several occasions when an especially promising and delicate method for detecting early signs of uranium poisoning was perfected in the laboratory, volunteers from among the laboratory workers would come forward asking that they be permitted to take small amounts of uranium and apply these tests to themselves. Such exposures were never allowed.

There is one group of human beings, the industrial personnel handling the uranium compounds, in which there was a necessary and unavoidable exposure. This exposure was always maintained at the least possible level, and frequent medical checkups protected the health of these workers. The medical findings were so consistently negative that most of the basic information on the health practices for employees in uranium plants would not be known if experimental animals had not been used.

4.8 Prophylaxis. The practices of vaccination and immunization against certain erstwhile dangerous infections have been so successful that inevitably some reliable protection was sought against uranium poisoning. The questions were: Is such protection possible? If so, what is the mechanism by which the body achieves this degree of resistance? Are there any practical methods that would improve the safety of working conditions? Although to date these investigations have not been fruitful in the prophylaxis of uranium poisoning, the diligence of inquiry is plainly visible in the following pages.

4.9 Treatment of Uranium Poisoning. Accidents do happen, and it seemed inescapable that now and then some series of misfortunes would provide a sufficient exposure to produce some evidence of poisoning. Attempts were therefore made to find any agents that would alleviate or improve the condition of animals either acutely poisoned or undergoing a long-term chronic exposure. Studies of the mechanism of poisoning shed light on the methods by which treatment might be instituted. A number of agents were examined and evaluated as to the efficacy and danger of the antidote in comparison with the danger of the poisoning.

Uranium (2)

Vol. VI-1, Ch. 16, pages 993-1017
National Nuclear Energy Series

"Studies on Human Exposures to Uranium Compounds" by Joe W. Howland

Report on cases of accidental exposures.

Uranium (3)

Vol. VI-1 National Nuclear Energy Series by Harold C. Hodge
pg. 11

1. Restriction of Survey Studies on Human Beings

Radium

(1)

From Vol. VI-3 (Fink) National Nuclear Energy Series (Biological Studies with Polunium, Radium and Plutonium)
Chapter 4

1. Discusses radium poisoning in work with animal, human occupational exposures, and human experimentation.

2. Single intravenous injection in man by Seil in 1915.

3. Series of patients given radium chloride orally on I.V. by Schlundt in early 1930's.

4. Group of 25 mental patients given radium chloride I.V. in 10 ug doses weekly for 2 to 10 mo. by Schlundt in 1933.

5. One mg of radium injected in human - by Cameron and Viol (1915).