was covered by firmly adherent omentum, in the other 2 by firmly adherent duodenum.

Of the remaining 16 dogs, 1 died on the 2nd, 8 on the 3rd, 4 on the 4th, and one on the 8th postoperative day. Two dogs appeared to be moribund, and they were sacrificed on the 3rd and 4th postoperative day. All of these dogs showed severe pathologic changes, with varying amounts of hemorrhagic fluid in the peritoneal cavity and most extensive intra-abdominal fat necrosis, involving mostly the omentum, the mesentery, and the parietal and peri-renal subperitoneal tissue. Pancreas and liver were grossly normal. The duodenal flap was usually somewhat cyanotic, but otherwise intact and easily demonstrable. In the majority of dogs fat necrosis was found in the chest also, mostly on the superior surface of the diaphragm, on the pericardium, in the paravertebral region and on the inner surface of the chest wall, usually along the intercostal spaces. No fat necrosis was found in any other region. Bacteriological tests showed no growth of bacteria from the peritoneal fluid in some dogs, while in others various aerobic and anaerobic bacteria were found.

Sixteen of 20 operated animals showed extensive fat necrosis which, if the 2 moribund animals were included, was fatal on the 3rd or 4th postoperative day in most dogs. Three had no intraperitoneal disease and one showed fat necrosis of moderate degree.

The operation described above appears to be the most simple and efficient one of all methods we have employed for producing fat necrosis in the dog, since it shows a high percentage (85%) of positive result with a rather uniform course. Other procedures are less reliable and results are not as uniform. The technic used by Dragstedt *et al.*(3) for testing the toxicity of pancreatic secretion is similar in principle to the method described above. However, a 2-stage operation, an open flap of jejunum, and a rubber tube from the cannulated pancreatic duct onto the jejunal flap, represent 2 separate operations and introduce complicating factors.

Summary. Excision of the pancreatic duct together with a duodenal flap surrounding its papilla is followed in the majority of dogs by extensive intraperitoneal and marked intrathoracic fat necrosis, and usually leads to the death of the dog on the 3rd or 4th postoperative day. This appears to be the most reliable procedure for producing fat necrosis in the dog.

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Distribution and Excretion of Radioactive Hafnium[181] Sodium Mandelate in the Rat. (18462)

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The advent of radioisotope therapy for malignant disease and other pathological conditions has stimulated the investigation of many elements and compounds in the search for substances with tissue or organ specificity, and for an understanding of principles governing biological localization. Element 72, hafnium, has been studied by us in an attempt to determine its distribution in the body after the intravenous administration of its man-

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delate salt. No previous reports regarding the distribution or toxicity of hafnium compounds have been found. Preliminary experiments indicate that the LD_{50} for a 10 day period of hafnium sodium mandelate when given intravenously to white rats is approximately 75 to 100 mg of hafnium metal per kilo of body weight. When administered in daily intraperitoneal doses to white rats as the gluconate salt, the LD_{50} for a 10 day period is about 2.0 to 3.0 g of hafnium metal per kilo of body weight(1). These values are comparable to those obtained for zirconium salts(2,3).

Chemical properties. Hafnium is a member of the carbon-silicon family and occupies a position in the fifth sub-group of elements with titanium, zirconium, and thorium. It is a metal, usually tetravalent, but in some cases divalent, and closely resembles zirconium in its physical and chemical properties although it is more basic(4,5). It has been estimated to be thirtieth in abundance of elements composing the earth's crust(6) and is contained in all zirconium ores in amounts varying up to 30%. Because of this close association with zirconium and the difficulty of separation, a paucity of knowledge exists regarding its properties.

Radioactive hafnium. Hafnium has not been found in any naturally occurring radioactive form, but 5 radioactive isotopes have been artificially produced: Hf^{172}, Hf^{173}, Hf^{175}, Hf^{179}, and Hf^{181}. Of these, Hf^{181} is most readily available in appreciable quantities being easily formed by the bombardment of stable hafnium with thermal neutrons. Hafnium^{181} possesses a half-life of 46 days. Its decay scheme has not been established with certainty, but most likely its transition to tantalum^{181} is accompanied by the emission of one beta ray (0.4 mev·) and 5 gamma rays (0.087, 0.13, 0.13, 0.34, and 0.48 mev·) (7,8).

Method. Hafnium^{181} oxide (0.900 g) with an estimated activity of 60 mc/g, obtained from the Oak Ridge nuclear reactor, was converted to hafnium tetrachloride by passing chlorine gas and carbon tetrachloride vapor over it at a temperature of 550-600°C. Immersion of the tetrachloride into approximately 250 ml of water formed hafnium oxychloride. This was evaporated to 50 ml. A 10 ml aliquot was then placed in a volumetric flask containing 0.550 g of mandelic acid and a drop of cresol blue indicator. Sodium hydroxide and water were added until a pH of 7.0 and a volume of 25 ml were reached. All procedures were done with necessary precautions for the safe handling of radioactive material. One-half ml of the radioactive hafnium sodium mandelate solution (containing about 3.06 mg of hafnium metal) was injected intravenously into the tail vein of 17 healthy, white, male, inbred, Wistar-stock rats weighing between 250-350 g. These animals were kept in metabolism cages where urine and feces could be collected separately. Daily urinary and fecal samples were taken for analyses with the exception of the first, when 8 hour specimen collections were made, and for the last 4 days when 48 hour samples were obtained.

The animals were sacrificed in groups of 3 at one, 2, 3, 4, 8, and 16 day intervals (only 2 animals comprised the 8 day study). They were lightly anesthetized with an intraperitoneal injection of nembutal and a sample of blood was aspirated from the inferior vena cava. This was subsequently centrifuged and divided into red cell and plasma portions.

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TABLE I. Urinary and Fecal Excretion of Intravenously Administered Hafnium[181] Sodium Mandelate Expressed as % of Total Activity.*†

8 h.	16 h.	1 d.	2 d.	3 d.	4 d.	5 d.	6 d.	7 d.	8 d.	10 d.	12 d.	14 d.	16 d
						Urine							
2.09	.39	.18	.27	.30	.18	.10	.11	.28	.13	.28	.20	.17	.19
‡	2.48	2.66	2.93	3.23	3.41	3.51	3.62	3.90	4.03	4.31	4.51	4.68	4.87
						Feces							
.02	.19	.22	.60	.36	.16	.06	.13	.07	.03	.04	.06	.08	.04
§	.21	.43	1.03	1.39	1.55	1.61	1.74	1.81	1.84	1.88	1.94	2.02	2.06
						Cumulative total excretion							
2.11	2.69	3.09	3.96	4.62	4.96	5.12	5.36	5.71	5.87	6.11	6.45	6.70	6.93

* Avg of 3 animals for each time period except 2 animals for the 8-day study.

† % total activity equals counts per min. for specimen divided by total counts per min. of entire animal plus excretions.

‡ Cumulative urinary excretion.

§ Cumulative fecal excretion.

After the blood had been obtained, the rat was viviperfused with isotonic saline. The animal was then dissected and the following specimens, or aliquot parts, taken for analysis: liver, spleen, pancreas, salivary glands, kidneys, adrenals, testes, urinary bladder, heart, lungs, thymus, thyroid, brain, eyes, trachea, incisor teeth, incisor pulp, prostate, red cells, plasma, muscle, pituitary, bone (femoral shaft, femoral epiphyses, and mandible), stomach, stomach contents, small intestine, small intestinal contents, cecum, cecal contents, large intestine, large intestine contents, tail, and carcass. The tissues were weighed and then gently heated with concentrated nitric acid until dissolution occurred. After this pseudo-ashing, a 10 ml sample was placed in a Petri dish for measurement of the radioactivity using a lead-walled, vertical, counting chamber with a TCG-2, thin mica window, Geiger-Mueller tube. The inside bottom of the dish was 1.6 cm from the tube window. The same geometry was employed for all counting. Radioactivity of the urine was determined by counting an aliquot portion after sulfuric acid digestion of the filter paper on which the urine had been absorbed. The feces was homogenized by incubation with a concentrated papain solution and an aliquot sample counted.

Total blood weight was assumed to be 7% of the total body weight(9). From this and the hematocrit, the plasma and red cell masses were determined. Skeletal weight was calculated as 7% of the total body weight(10). Muscle weight was assumed to be carcass minus skeletal weight. The per cent of the total activity of the animal and excretions in the various organs and body systems was calculated from the radioactivity measurements, after correction to a zero time. Concentration values, or specific activity, for the different tissues were derived and expressed as per cent per gram adjusted to a standard body weight.

Results. The excretion of hafnium[181] sodium mandelate is given by Table I and is illustrated by Fig. 1 in terms of per cent total activity. The daily urinary, daily fecal, cumulative urinary, cumulative fecal, and total cumulative excretion have been tabulated.

Table II shows the per cent of total activity retained in the most important organs and body systems. This was derived from the counts per minute of the structure involved divided by the number of counts per minute in the entire animal and its excretions, with the exception of its tail. The amount of activity in an animal's tail probably represented unabsorbed hafnium[181] and therefore was not included.

Table III lists the concentration values, or specific activity, in the same organs. This was obtained by dividing the per cent total activity by the weight in grams of the organ or body system with each animal corrected to a standard body weight.

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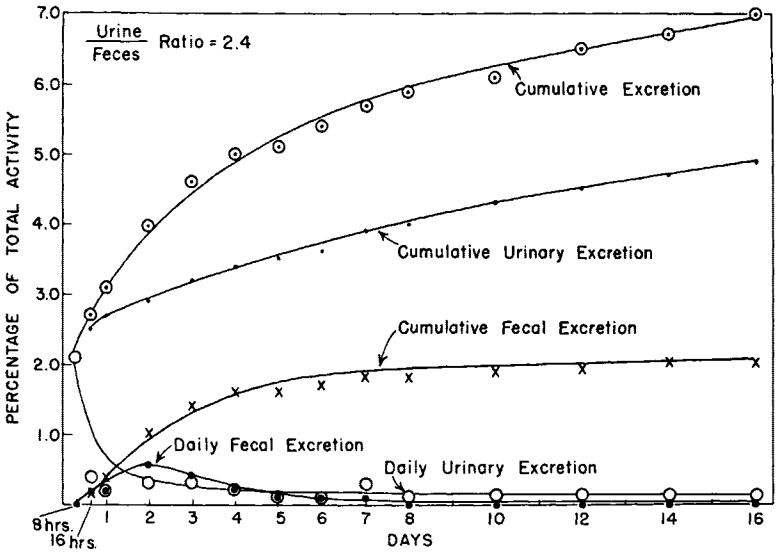

EXCRETION OF INTRAVENOUS Hf^{181} SODIUM MANDELATE

FIG. 1.

Graph illustrating the urinary, fecal, and total excretion of hafnium[181] sodium mandelate for a 16-day period following its intravenous administration to the white rat.

Discussion. After the intravenous administration of hafnium[181] sodium mandelate, the hafnium was slowly excreted, only 7% having been eliminated at the end of 16 days. Of this, 5% was excreted within the first 4 days. A larger portion was removed by the kidneys, the urine/feces ratio being 2.4 in this study. Between 70 and 90% of the total activity was accounted for by the liver, spleen, the skeletal, muscular, and integumentary systems in each of the time intervals studied. The liver and spleen respectively showed highest retention on an organ basis. Slight, but appreciable amounts were found in the adrenals, thyroid, pancreas, salivary glands, and testes. Little, or no activity was contained in the brain, eyes, pituitary gland, teeth, heart, lungs, thymus, trachea, and prostate. The gastro-intestinal tract in general contained small amounts and an occasional high determination was believed to reflect the difficulty in separation of contents from the wall rather than any absorption.

Appreciable amounts of hafnium[181] remained in the blood for the first 3 days, after which only 0.1-0.5% of the total activity was present. At the end of 24 hours, 4% of the total activity was in the blood. In each determination, about 95% of the activity was found in the plasma, with little or none in the red cells.

Expressed as specific activity (Table III) the spleen exhibited the greatest value followed by liver, bone, and kidneys respectively. The pelt which contained a high percentage activity during the first 2 days showed a

TABLE II. Distribution* of Hafnium[181] Sodium Mandelate in Organs Expressed in % of Total Activity.†

Organ	24 hr	48 hr	72 hr	96 hr	8 days	16 days
Liver	19.8	41.3	36.5	37.8	42.8	44.9
Spleen	3.9	9.1	11.8	12.5	7.7	2.1
Bone	13.8	13.0	21.5	15.4	25.8	12.5
Kidneys	2.2	1.4	0.8	1.5	2.1	1.6
Blood	4.0	1.0	0.5	0.2	0.1	0.1
Heart	0.2	0.3	0.3	0.1	0.2	0.2
Lungs	0.7	1.3	1.3	0.4	0.5	0.3
Pelt	14.4	3.2	3.0	3.2	1.6	0.8

* Each column represents avg determinations in 3 animals with exception of 8-day period, when 2 animals were studied.

† % total activity equals organ counts per min. divided by total counts in entire animal and excreta.

TABLE III. Distribution* of Hafnium^{181} Sodium Mandelate in Organs Expressed in % per g Corrected to a Standard Body Weight.

Organ	24 hr	48 hr	72 hr	96 hr	8 days	16 days
Liver	1.8	4.9	4.3	4.3	6.4	6.5
Spleen	5.5	9.4	19.2	23.8	17.4	6.3
Bone	0.8	0.8	1.2	0.9	1.5	0.6
Kidneys	1.5	0.8	0.4	0.8	1.3	0.9
Blood	0.5	0.1	†	†	†	†
Heart	0.3	0.3	0.3	0.1	0.2	0.2
Lungs	0.7	0.7	0.8	0.2	0.2	0.2
Pelt	0.2	0.1	†	†	†	†

* Each column represents avg determinations in 3 animals with exception of 8-day period, when 2 animals were studied.

† Negligible.

marked decline subsequently. Tissue autoradiograms confirm these findings and will be discussed in more detail later(11).

These data indicate that hafnium^{181} sodium mandelate has little specific localization in the body to recommend its consideration for radiation therapy of individual organs or tissues.

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Conclusions. 1. The distribution and excretion of radioactive hafnium^{181} sodium mandelate after its intravenous administration was studied in 17 rats sacrificed at intervals of 1, 2, 3, 4, 8, and 16 days. 2. Seventy to 90% of the total activity was retained in the liver, spleen, the skeletal, muscular, and integumentary (pelt) systems. 3. Specific activities showed the spleen to be highest, followed by the liver, bone, and kidneys. 4. The adrenals, thyroid, pancreas, salivary glands, and testes showed a slight, but appreciable retention. 5. Hafnium^{181} in the blood was found chiefly (95%) in the plasma and remained in appreciable amounts to 4 days. 6. Seven per cent of the total dose was excreted in 16 days with more being eliminated in the urine than in the feces, the urine/feces ratio being 2.4.

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Failure of a Flavonoid to Reduce Radiation Mortality in Mice. (18463)

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Various investigators have reported flavonoids to be beneficial in the treatment of animals after exposure of the whole body to potentially lethal amounts of radiation(1-3). Sokoloff *et al.*(3) have adequately discussed the beneficial reports. Other reports(4,5) have stressed the ineffectiveness of rutin. Further discussion of the rationale behind the use of these compounds is out of the scope of this paper which reports another failure.

Materials and methods. A flavonoid compound isolated from citrus fruit was used.* For injections the material was dissolved in saline (0.9%), pH adjusted to 7.0 and diluted so that 1 ml contained 6.6 mg of flavonoid. The flavonoid was started 5 days before ir-

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* Supplied by Dr. Boris Sokoloff, Florida Southern College, Lakeland, Florida, and reported to contain Quercitin-like substance 4%, eriodictin 15%, chalcone hesperidin-glucose hesperidin 80%, and calcium phosphorus ash 0.38%.