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PHYSIOLOGICAL PARAMETERS FOR ASSESSING THE HAZARD OF EXPOSURE TO RUTHENIUM RADIOISOTOPES

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PHYSIOLOGICAL PARAMETERS FOR ASSESSING THE HAZARD OF EXPOSURE TO RUTHENIUM RADIOISOTOPES

By

R. C. Thompson, M. H. Weeks, O. L. Hollis,
J. E. Ballou and Willa D. Oakley

Biology Section
Radiological Sciences Department

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ABSTRACT

Results are reported from a variety of studies on the absorption by various routes, the distribution, the excretion and the long term retention of ruthenium-106 in various tissues of the rat. Gastrointestinal absorption of ruthenium is much greater than previously assumed; the maximum permissible concentration of Ru^{106} in drinking water should be 4×10^{-3} μc/ml.

PHYSIOLOGICAL PARAMETERS FOR ASSESSING THE HAZARD OF EXPOSURE TO RUTHENIUM RADIOISOTOPES

Like many another relatively rare element, ruthenium has recently become of interest to the biological scientist because of its prominence in the spectrum of products formed in the nuclear fission of uranium. The ruthenium isotopes of major significance among the fission products are Ru^{103} and Ru^{106}. Ruthenium-103 is a beta-emitter (maximum energy, 0.2 Mev) with a half-life of 40 days. At 90 days following instantaneous fission of U^{235} it is responsible for 7.2 per cent of the total fission product radioactivity.[1] Because of its short half-life, its relative hazard significance decreases with time after fission and by one year post-fission it accounts for less than one per cent of the total radioactivity.

Ruthenium-106 is a beta-emitter (maximum energy, 0.04 Mev) with a half-life of 365 days. The daughter of Ru^{106}, rhodium-106, is also a beta-emitter (maximum energy, 3.5 Mev) with a half-life of 30 seconds. The energy release in the $Ru^{106} \longrightarrow Rh^{106} \longrightarrow Pd^{106}$ (stable) chain is therefore attributable largely to Rh^{106}. However, the biological distribution of this released energy will be determined by the physiological behavior of the parent Ru^{106}, because of the extremely short half-life of Rh^{106}. At 90 days following instantaneous fission of U^{235}, Ru^{106} and Rh^{106} are responsible for less than one per cent of the total fission product radioactivity, but after one year, they account for 2.4 per cent.[1]

Very little previous work has been done on the biological behavior of ruthenium. The presently established maximum permissible limits for Ru^{106} in the human body, in air, and in water,[2,3] are based on limited studies with a small number of rats, conducted by Hamilton and his associates at the University of California.[4,5] Studies on the distribution and retention in rats of inhaled Ru^{106} were reported by Dailey, et al.[6] More recently, Scott, et al.[7] reported on the short-term retention in rats of intravenously administered ruthenium.

Our interest in ruthenium was stimulated by the finding of Hanson and Browning[8] that approximately three per cent of intragastrically administered Ru^{106} was absorbed by chickens. This absorption value was so much higher than the value of < 0.05 per cent reported for the rat[4, 5] that an experiment was performed to check the gastrointestinal absorption of ruthenium in the rat. The finding in this experiment of a much higher absorption than was previously reported led to a more complete study of ruthenium metabolism which is detailed in this report. Preliminary reports of some of the results of these studies have appeared in the Biology Section Annual Report.[9, 10, 11] Coincident with our program on the metabolism of ruthenium, studies have been made at the Argonne National Laboratory on the radio-toxicity of the element.[12]

METHODS

Ruthenium Radioisotope Solutions: The isotope employed in all experiments was Ru^{106} obtained from Oak Ridge as "carrier-free chlorides" in 6 N HCl solution. The specific activity was in the range of 4-10 c/g ruthenium. In most of the experiments to be described, the HCl solution as obtained from Oak Ridge was diluted, the pH adjusted, as required, with NaOH, and this solution administered to the animals without further chemical treatment. These solutions probably contained both Ru(III) and Ru(IV), hydrolyzed to varying degrees depending upon the pH. In all experiments, unless otherwise noted, the dilution of the 6 N HCl solution and pH adjustment was made 24 hours prior to administration of the solution to the rats.

The decision to employ the Oak Ridge solution without attempting to standardize the valence state of the ruthenium was reached after experiments with various chemically treated solutions of ruthenium had shown little effect of the treatment on ruthenium absorption from the gastrointestinal tract. In these experiments the ruthenium was oxidized to the tetravalent state with NaOCl, reduced to the trivalent state with $SnCl_2$, and these solutions were fed after various periods of standing.

In studies of the effect of specific activity on absorption of Ru^{106} from the gastrointestinal tract, ruthenium carrier, as the chloride, was added to the 6 N HCl Ru^{106} solution and allowed to stand for two months before dilution, pH adjustment, and administration to the rats. It was felt that this long period of standing in acid solution would insure homogeneity of the stable and radioactive ruthenium. Earlier attempts to obtain homogeneous solutions, by oxidizing the isotope mixture and distilling the volatile tetroxide, were accompanied by such low and variable yields that this method was abandoned in favor of the procedure of prolonged standing in acid solution.

Animal Procedures: All rats employed were of the Sprague-Dawley strain. Except as otherwise noted they were maintained on an *ad libitum* diet of Purina Laboratory Chow. Intragastric administration was accomplished via stomach tube without anesthesia. Light ether anesthesia was employed for intravenous injections which were made via the great saphenous vein. Intratracheal injections were made by surgical exposure of the trachea under nembutal anesthesia. In the chronic feeding studies, Ru^{106} was added to the drinking water which was adjusted to pH 2, and which was continuously available. Water consumption was measured in all such experiments. All-glass metabolism cages were employed in experiments requiring the collection of urine and feces.

Sampling and Counting Procedures: Animals were sacrificed by decapitation. In most cases tissues were minced, and air-dried on stainless steel plates for direct beta counting. Feces samples and tissue samples too large to be totally counted by this procedure were partially digested with nitric acid, care being taken to prevent evaporation to dryness. Under the conditions employed there was no significant loss of Ru^{106} during digestion, and no significant counting error due to self-absorption. All samples were counted with an end-window Geiger tube. Unless otherwise noted, all results were corrected for radioactive decay.

EXPERIMENTS AND RESULTS

SINGLE DOSE GASTROINTESTINAL ABSORPTION STUDIES

Effect of pH: Ruthenium solutions of pH 1, 2, 4, and 6 (± 0.05 pH unit) were intragastrically administered to 24 female rats, six rats per pH level. Approximately 15 μc Ru^{106} were administered to each rat. Each animal was sacrificed after 24 hours; the pelt, feet, tail, and head were discarded and the remainder of the animal analyzed. The results are shown in Table 1.

Total absorption was essentially the same at pH 2 and pH 4. The somewhat lower value at pH 1 is of doubtful significance. Absorption is very definitely decreased, however, at pH 6.

The distribution of ruthenium among the various organs and tissues is typical of that seen at a short time interval following ruthenium administration. The value of approximately 0.75 per cent for ruthenium absorbed and retained for a 24-hour period is somewhat lower than the figure which we have usually obtained in 24-hour experiments with pH 2 solutions. Variation in absorption results by as much as a factor of two, among different experiments has been quite typical, although agreement of results for animals in the same experiment is usually much better. This variability is quite possibly due to differences in the chemical or physical state of ruthenium in the solutions fed.

Values for gastrointestinal absorption such as obtained in this experiment are, of course, not a true measure of total absorption, since absorption and excretion are occurring throughout the 24-hour experimental period. More precise values for total absorption were obtained from chronic feeding experiments.

Effect of Chemical State: Because of the complexity of ruthenium chemistry, concern was felt over the reproducibility of experiments employing ruthenium solutions which might differ in the proportion of valence states present,

TABLE 1

Effect of pH on Gastrointestinal Absorption of Ruthenium
(Average values from six rats)

Tissue	Retention 24 hours post feeding (per cent of dose/g tissue)			
	pH 1	pH 2	pH 4	pH 6
Kidney	.077	.11	.12	.017
Liver	.021	.025	.025	.0040
Ovaries	.0077	.0096	.0066	.0012
Spleen	.0048	.0074	.0057	.0014
Bone	.0037	.0046	.0044	.0013
Lungs	.0034	.0058	.0053	.0012
Heart	.0033	.0044	.0039	.0008
Fat	.0018	.0022	.0021	.0003
Muscle	.0014	.0016	.0020	.0004
Brain	.0003	.0003	.0003	.00009
Blood	.0050	.0066	.0066	.0014
Residual Carcass	.0022	.0029	.0029	.0007
Total Animal (% of dose ± std. dev.)	.66±.18	.75±.09	.78±.07	.14±.02

the extent of hydrolysis, or in some other subtle manner. In the experiments performed to evaluate this problem, no effort was made to explore thoroughly these various factors. The sole object was to determine whether major changes in the methods of solution preparation might significantly affect the absorption or distribution of the ruthenium in the animals to which these solutions were fed. By employing oxidizing and reducing agents, and aging the solutions for various time periods before feeding, it was hoped to obtain solutions which differed significantly in the chemical and physical properties of the contained ruthenium. The nature of these differences was not measured but can be estimated from what is known of the chemistry of ruthenium.

The six solutions employed are described in Table 2. These solutions were fed, each to a group of six female rats, which were sacrificed and analyzed for Ru^{106} content after 24 hours. Results for representative tissues and for the total animal are shown in Table 2. The pattern of ruthenium distribution is essentially the same for all solutions fed. There is an indication that total absorption was affected by the method of solution preparation; however, this effect results in no more than a two-fold difference. The conclusion seems justified that the gastrointestinal absorption of ruthenium from pH 2 solutions is relatively insensitive to the ionic form, or valence state of the ruthenium contained.

Effect of Specific Activity of Ru^{106} Fed: The effect of Ru^{106} specific activity on gastrointestinal absorption was studied in an experiment in which non-radioactive ruthenium was added to the solutions fed, in amounts equal to 10, 100, and 1,000 times the total ruthenium content of the Oak Ridge "carrier free" solution. Six female rats were fed approximately 20 μc Ru^{106} at each concentration level, and sacrificed after 24 hours. Results of the experiment are summarized in Table 3. There appears to be no very significant effect of ruthenium concentration on either absorption or distribution.

TABLE 2

Effect of Chemical and Physical State on Gastrointestinal Absorption of Ruthenium

(Average values from 6 rats)

Solutions fed*	A	B	C	D	E	F
Ox. or Red. Agent	None	None	NaOCl	NaOCl	$SnCl_2$	$SnCl_2$
Aging of soln.	30 m	6 d	30 m	6 d	30 m	6 d
Prob. valence state	3 and 4	3 and 4	4	4 (?)	3	3 (?)
Prob. physical state	ionic	coll.	ionic	coll.	ionic	?
Tissue	Retention 24 hours post feeding (per cent of dose/g tissue)					
Kidney	.19	.16	.20	.28	.12	.12
Liver	.041	.029	.038	.048	.026	.025
Spleen	.012	.008	.011	.015	.007	.007
Bone	.012	.008	.012	.014	.008	.008
Muscle	.004	.003	.004	.004	.002	.002
Residual carcass	.005	.003	.005	.006	.003	.003
Total Animal (% of dose ± std. dev.)	1.3±.3	1.3±.4	1.0±.5	1.7±.7	1.1±.5	.86±.17

*pH of all solutions was 2.05 ± 0.1

TABLE 3

Effect of Specific Activity on Gastrointestinal Absorption of Ruthenium-106

(Average values from six rats)

Tissue	Retention 24 hours post-feeding (Per cent of dose per g tissue)			
	Solution A .005 mg/20 μc	Solution B .05 mg/20 μc	Solution C 0.5 mg/20 μc	Solution D 5.0 mg/20 μc
Kidney	.17	.13	.087	.12
Liver	.035	.025	.019	.025
Spleen	.0099	.0076	.0049	.0063
Bone	.0097	.0058	.0040	.0054
Muscle	.0031	.0021	.0020	.0020
Residual Carcass	.0042	.0033	.0025	.0026
Total Animal (% of dose, ± std. dev.	1.28±.14	.79±.35	.62±.07	.72±.17

CHRONIC FEEDING STUDIES

Four chronic feeding experiments were performed, one of which is still in progress at the time of this writing. The salient features of these experiments are summarized in Table 4.

Excretion of Ru^{106} During and Following Chronic Feeding: In Experiment I (Table 4) complete excretion data were obtained over a 71-day feeding period and a subsequent period of 149 days following cessation of Ru^{106} feeding. While excretion data following a single administration of isotope are, for most purposes, most readily interpreted, the data from this chronic feeding experiment are of particular interest because they give the most accurate value for total gastrointestinal absorption of ruthenium.

The daily excretion of Ru^{106} in urine and feces during the feeding period showed marked decreases over each weekend, when feedings were not given. To smooth out the curve, the excretion during the 24 hour periods following each feeding were averaged for each five consecutive days of feeding, and this "average daily value" plotted for each week. Excretion curves for the duration of the experiment are shown in Figure 1. Data, as plotted, were not corrected for radioactive decay.

Of primary interest, from the standpoint of calculating ruthenium absorption, is the ratio of urinary to fecal excretion. This ratio, during the latter three-fourths of the feeding period was quite constant at 0.024. Therefore, at least 2.4 per cent of the ruthenium fed was absorbed from the gastrointestinal tract (the very small fraction of the total ruthenium fed which is retained in the animal can be ignored in this calculation). An additional fraction of the ruthenium fed may have been absorbed and re-excreted via the feces. This fraction can be evaluated from the ratio of urinary to fecal excretion following cessation of ruthenium feeding. Within ten days after feeding of the ruthenium was terminated, all residual fed ruthenium had apparently been cleared from the gastrointestinal tract, and from this time on, the ratio of urinary to fecal ruthenium excretion was

TABLE 4

Design of Chronic Feeding Experiments

Expt. No.	Animals			Method of Administration	Total Feeding Period (d)	Average Daily Dose (μc)	Sacrifice Schedule		Remarks
	No.	Sex	Initial wt. (g)				Group Size	Time on Feeding (d)	
I	86	M	248	Stomach tube 1.8 μc/d, 5 d/wk	71	1.3	3-5	1, 10, 17, 24, 31, 52, 71	Daily urine and feces collections from 5-8 animals. Additional rats sacrificed at intervals up to 149 days after feedings stopped.
II	5	M	396	Stomach tube 0.12 μc/d, 5 d/wk	71	0.085	5	71	
	4	F	259				4		
III	10	M	402	Drinking water ad lib, 0.11μc/ml	71	4.3	10	71	
	10	F	252		144	4.3	10		
IV	50	M	484	Drinking water ad lib, 0.01μc/ml	400	.30-.36*	5-8	50, 125, 200, 300, 400	Experiment in progress, sacrifices completed through 200 days.
	50	F	247			.22-.26*	8-10		

*Average varies somewhat between different sacrifice groups.

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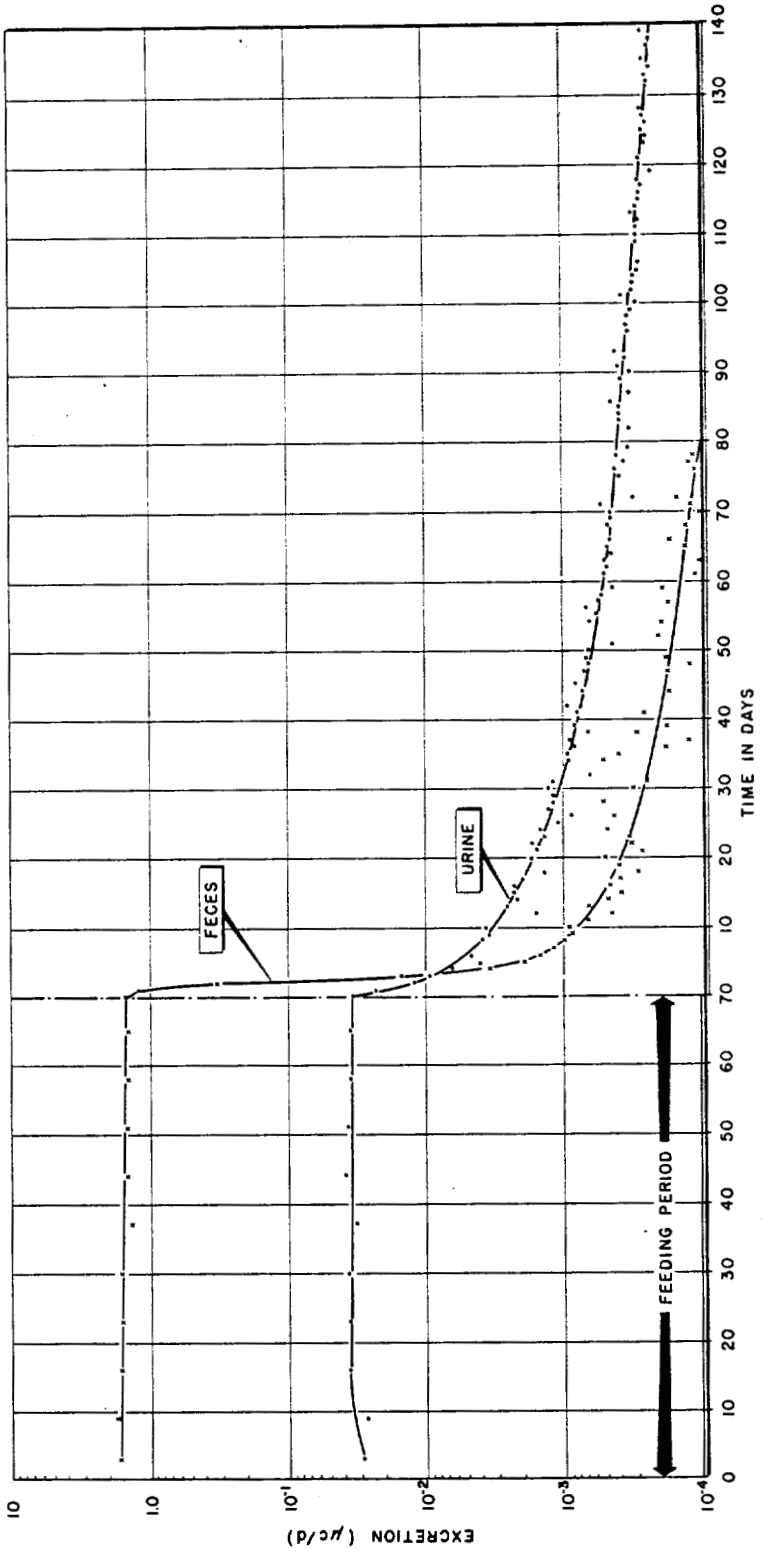

FIGURE 1

EXCRETION OF Ru^{106} DURING AND FOLLOWING CHRONIC FEEDING

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quite constant at 4.0. Therefore, 20 per cent of absorbed ruthenium is excreted via the gastrointestinal tract, and the total absorption must be 25 per cent greater than that indicated by the ratio of ruthenium in urine and feces during the feeding period. This leads to a total absorption value of 3.0 per cent of the amount fed.

For the period from about 70-149 days post-feeding, the semi-logarithmically plotted urinary excretion data (Fig. 1) are well fitted by a straight line. The slope of this line corresponds to a half life of 70 days. Since these data were not corrected for radioactive decay, this is an effective half life combining the effects of the 365 day physical half life of Ru^{106} and a biological half life of approximately 85 days for elimination of ruthenium from the animal.

Build-up of Ruthenium in Tissues During Chronic Feeding: Data on the tissue ruthenium levels attained after various periods of chronic feeding are shown in Tables 5-8. To facilitate comparison between the different experiments, all results are expressed as the per cent of average daily dose per gram of tissue, and all results have been normalized by multiplying the experimental results by the fraction, "average weight of rats in sacrifice group/400." This normalization is justified, since ruthenium dosage was not varied with animal weight. In the stomach tube feedings the dosage was exactly the same for all animals in a given experiment, and in the spiked drinking water experiments the measured daily water intake, while varying somewhat among the animals, was not correlated with animal weight.

Data covering the early portion of the build-up curves were obtained only in Experiment I (Table 5). These data indicate a continued increase in tissue ruthenium concentration throughout the 71 day feeding period, although most tissues are increasing to a much smaller extent after the 31 day sacrifice. Spleen and bone are notable for their continued marked increase in ruthenium content during the interval from 31 to 71 days.

TABLE 5

Ruthenium Build-up in Tissues During Chronic Feeding - Experiment I*

Time on feeding (d)	1	10	17	24	31	52	71
Avg. wt. at sacrifice (g)	200	263	288	308	310	376	402
Tissues	Ruthenium concentration (% of avg. daily dose/g tissue - normalized to 400 g rat)						
Kidney	.088	.34	.47	.46	.57	.67	.57
Liver	.019	.078	.098	.10	.13	.15	.17
Testes	.0020	.013	.022	.023	.032	.043	.049
Spleen	.0053	.027	.047	.054	.089	.16	.19
Bone	.0067	.049	.066	.080	.088	.12	.15
Lungs	.0067	.028	.039	.032	.044	.063	.056
Heart	.0041	.018	.020	.028	.027	.043	.044
Fat	.0026	.011	.013	.017	.018	.018	.026
Muscle	.0020	.011	.013	.014	.022	.027	.032
Brain	.0003	.002	.001	.001	.002	.002	.002
Blood	.0049	.017	.022	.019	.025	.034	.034

*See Table 4 for description of experiment.

TABLE 6

Ruthenium Build-up in Tissues During Chronic Feeding - Experiment II*

Tissues	Ruthenium Concentration after 71 Days Chronic Feeding (% of avg. daily dose/g tissue - normalized to 400 g rats)	
	Males (Sac. Wt. 430 g)	Females (Sac. Wt. 260 g)
Kidney	1.06	1.32
Liver	.26	.30
Testes - Ovaries	.073	.18
Spleen	.30	.56
Bone	.15	.21
Lungs	.10	.20
Heart	.068	.12
Fat	.022	.067
Muscle	.044	.066
Blood	.058	.068

*See Table 4 for description of experiment.

TABLE 7

Ruthenium Build-up in Tissues During Chronic Feeding - Experiment III*

Tissues	Ruthenium Concentration (% of avg. daily dose/g tissue - normalized to 400 g rats)	
	Males (Sacrificed at 71 days, sac. wt. 493 g)	Females (Sacrificed at 144 days, sac. wt. 293 g)
Kidney	1.06	.44
Liver	.20	.13
Testes-Ovary	.074	.18
Spleen	.30	.41
Bone	.23	.22
Lungs	.14	.094
Heart	.096	.076
Fat	.030	.030
Muscle	.055	.063
Brain	.004	.003
Blood	.060	.020

*See Table 4 for description of experiment.

TABLE 8

Ruthenium Build-up in Tissues During Chronic Feeding - Experiment IV*

Time on feeding (d)	50		125		200	
Sex	Male	Female	Male	Female	Male	Female
Avg. wt. at sacrifice (g)	545	270	528	268	507	252
Tissues	Ruthenium concentration (% of avg. daily dose/g tissue - normalized to 400 g rats)					
Kidney	.44	.57	.63	.64	.45	.55
Liver	.090	.12	.13	.11	.11	.12
Testes - Ovary	.037	.12	.072	.12	.061	.18
Spleen	.13	.20	.23	.27	.17	.24
Bone	.058	.050	.083	.063	.056	.068
Lungs	.040	.048	.079	.069	.057	.076
Heart	.039	.036	.072	.053	.057	.055
Fat	.014	.016	.023	.018	.020	.034
Muscle	.023	.022	.041	.038	.039	.043
Brain	.077	.022	.003	.003	.003	.003
Blood	.024	.029	.030	.026	.018	.022

*See Table 4 for description of experiment.

Considering the data beyond 31 days, from all experiments, the four tissues showing the highest ruthenium content, with minor exceptions, were kidney, spleen, liver, and bone, listed in order of decreasing concentration. This order was consistently altered in the case of females by interposition of the ovaries between spleen and liver, or between liver and bone.

The 71 day results of Experiments II (Table 6) and III (Table 7) are quite consistently higher than the 71 day results of Experiment I. The 144 day females of Experiment III also show higher ruthenium concentrations for most tissues, with the notable exception of the kidney which, relative to the other tissues, is much lower than in any of the other experiments. These variations between experiments are no larger than a factor of two, and are not surprising considering the differences between experiments and the rather large normalizing factors required.

The results thus far obtained in Experiment IV (Table 8) correspond well with the data of Experiment I, with the single exception of bone which is consistently lower by a factor of approximately 2 in Experiment IV. The slight decrease in ruthenium content of all tissues of the male group sacrificed at 200 days is probably due to an epidemic of virus infection which resulted in the death of several animals and moderate weight losses in nearly all of the males. Females were relatively unaffected by the infection.

For reasons which will be discussed later the two most interesting tissues from the hazard standpoint are kidney and bone. Data on these two tissues, from all four experiments, are plotted in Figure 2. Curves are drawn through the points from Experiments I and IV. In Experiment IV, the points for females are most heavily weighted in drawing the curves because of the uncertain effect of the previously discussed infection on the male values. The immediately obvious impression from Figure 2 is the close agreement in kidney ruthenium level between Experiments I and IV

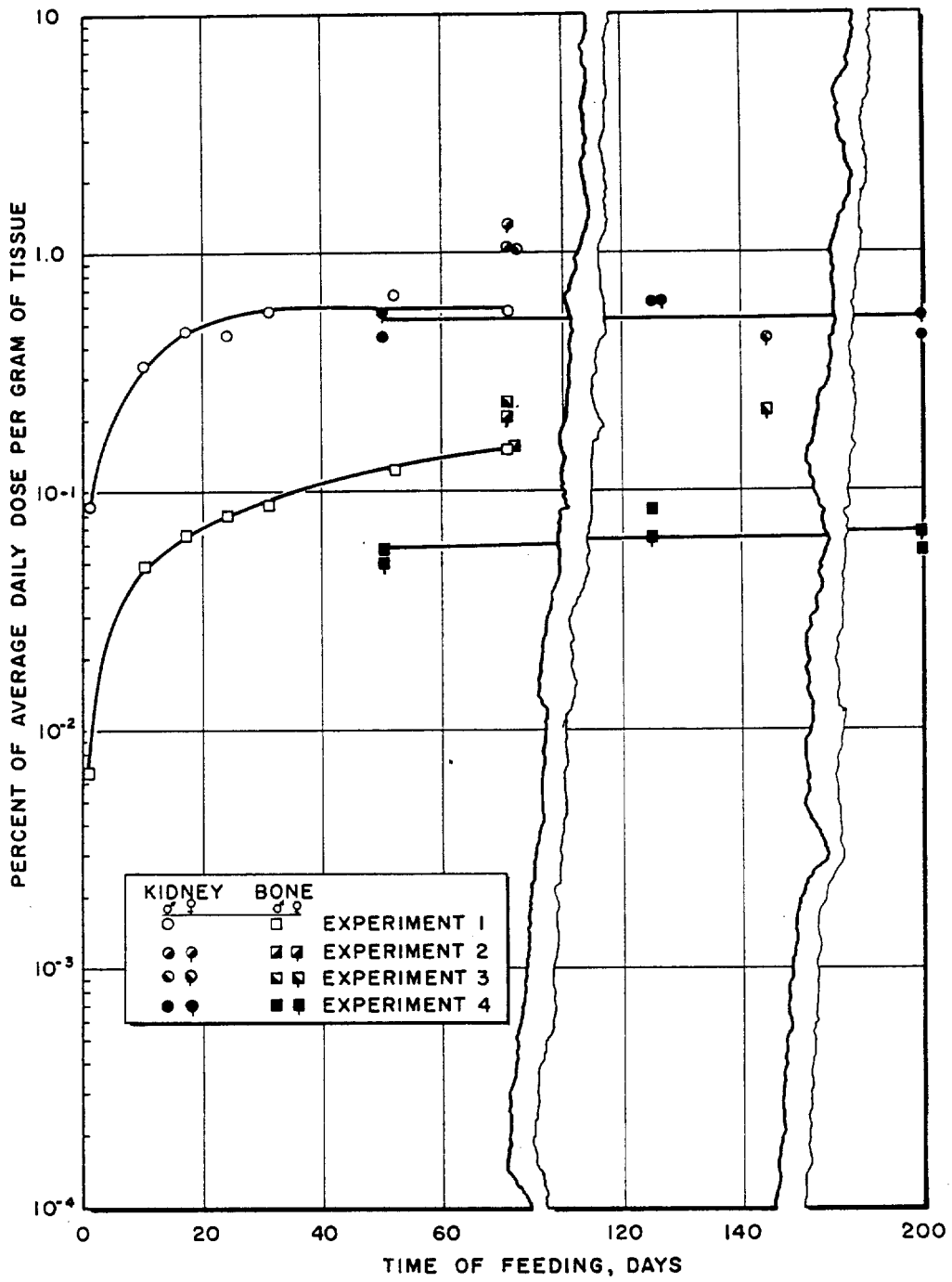

FIGURE 2

RUTHENIUM BUILDUP IN KIDNEY AND BONE
DURING CHRONIC RUTHENIUM FEEDING

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and the equally obvious lack of agreement in the bone levels of these two experiments. The kidney to bone concentration ratio at 71 days, from Experiment I is 3.6, whereas this same ratio at 50, 125, and 200 days, from Experiment IV is quite constant at a value of approximately 8. This discrepancy is in all likelihood related to the difference in weights of the animals at the beginning of feedings in the two experiments. The animals in Experiment I (males) averaged 248 g at the start of feedings, and the 71 day sacrifice group averaged 402 g. In Experiment IV the male rats averaged 484 g at the start of feedings and had gained no more than 60 g by the time of sacrifice. Thus extensive growth occurred during the feeding period of Experiment I and very little growth during the feeding period of Experiment IV. The greater ruthenium deposition in bone in Experiment I is therefore probably due to the more extensive formation of new bone.

This effect of growth on bone deposition is also apparent in the comparison of Experiment II with Experiments I and IV. The male rats in Experiment II at the beginning of feedings were 150 g heavier than the animals in Experiment I and gained only 34 g during the 71 day feeding period. The kidney to bone concentration ratio for the Experiment II males was 7.0, in close agreement with the "non-growing" rats of Experiment IV and much higher than the "growing" rats of Experiment I. The females of Experiment II showed no growth during the 71 day feeding period and exhibit a kidney to bone concentration ratio of 6.3.

The results of Experiment III are somewhat anomalous. The males, growing from 402 g to 493 g during the 71 day feeding period, show a kidney to bone ratio of 4.6, which is somewhat higher than the ratio of the faster growing animals of Experiment I and considerably lower than the ratio of the slower growing animals of Experiment IV. However, the females, which gained only 41 g during 144 days of feeding show a kidney to bone ratio of 2.0 the lowest ratio observed in any experiment. As previously noted, the kidney ruthenium concentration in these animals was unusually low, not only in relation to bone but to most of the other tissues as well.

Rentention of Ruthenium in Tissues Following Chronic Feeding: Following the chronic feeding phase of Experiment I, rats were sacrificed in groups of 3-5 at intervals up to 149 days. The results of tissue ruthenium analyses are shown in Table 9. All results are corrected for radioactive decay and normalized to a 400 g rat in the manner previously described. Retention curves for representative tissues are shown in Figure 3. Retention curves for most tissues were fairly accurately represented by a single exponential function, or by the sum of two exponentials. The biological half lives associated with these exponential functions are listed for each tissue in Table 10.

Excluding blood, the tissues which lose their ruthenium most rapidly are those which have the highest ruthenium concentration at the end of the feeding period: kidney, spleen and liver. The majority of kidney and liver ruthenium is lost with a half life of the order of 5-6 days and most of the remainder with a half life of 40-50 days. There is some indication that a small fraction of the ruthenium in kidney and liver may be retained with a longer half life. The remaining tissues all have long-lived components with half lives in the range of 100-250 days; all show substantial shorter lived components, with the exception of bone and muscle. Kidney and bone are clearly the tissues of greatest hazard significance; kidney because of its high initial ruthenium content, and bone because of the long biological half life of its ruthenium.

DISTRIBUTION AND RETENTION OF RUTHENIUM FOLLOWING INTRA-PERITONEAL ADMINISTRATION

Thirty-six female rats, average weight 249 g, were injected intra-peritoneally with 7.7 μc of Ru^{106}. Groups of four animals were sacrificed at intervals of 1, 2, 4, 8, 16, 31, 64, 128, and 256 days following injection. The tissue ruthenium concentrations at these time intervals are shown in Table 11. Data are expressed as per cent of injected dose per gram tissue and normalized to a 250 g rat.

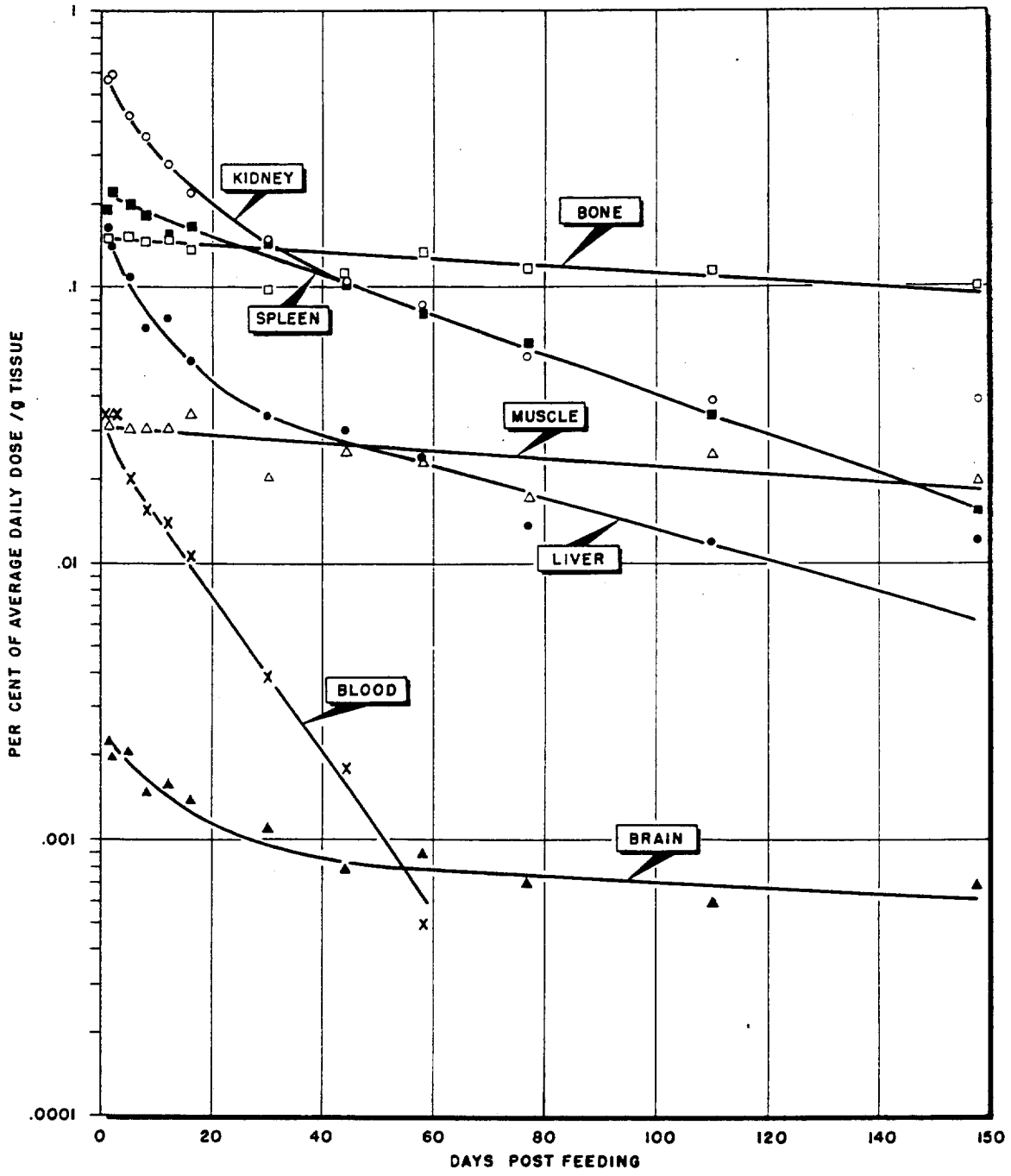

FIGURE 3

RETENTION OF RUTHENIUM IN REPRESENTATIVE TISSUES FOLLOWING CHRONIC FEEDING

TABLE 10

Biological Half-Lives for Ruthenium in Tissues as Determined Following Chronic Ruthenium Feeding

Tissue	Shorter Lived Component		Longer Lived Component	
	Fraction of Total Ruthenium	Half-life (days)	Fraction of Total Ruthenium	Half-life (days)
Kidney	.65	5	.35	40
Liver	.70	6	.30	50
Testes	.20	?	.80	120
Spleen	0		1.0	40
Bone	0		1.0	250
Lungs	.30	?	.70	180
Heart	.30	?	.70	140
Fat	.60	10	.40	110
Muscle	0		1.0	250
Brain	.60	10	.40	250
Blood	.20	?	.80	12

TABLE 11

Retention and Distribution of Ruthenium Following Intraperitoneal Injection

Days post injection	1	2	4	8	16	31	64	128	256
Avg. wt. at sacrifice (g)	248	240	246	255	256	259	264	286	301
Tissue	Tissue Ruthenium Concentration (% of injected dose/g tissue)*								
Kidney	2.2	2.9	3.1	2.9	2.2	1.4	0.68	0.27	0.084
Liver	1.8	1.9	1.6	1.6	0.90	0.37	0.14	0.090	0.031
Ovaries	1.2	1.1	1.4	1.3	0.90	0.47	0.34	0.16	0.088
Spleen	2.2	1.8	2.6	2.8	1.6	1.1	0.50	0.20	0.080
Bone	0.31	0.29	0.32	0.24	0.27	0.20	0.15	0.11	0.10
Lungs	0.77	0.52	0.50	.035	.021	0.12	0.058	0.033	0.014
Heart	0.38	0.29	0.22	0.16	0.14	0.087	0.048	0.031	0.012
Muscle	0.10	0.11	0.086	0.076	0.052	0.028	0.018	0.013	0.0068
Brain	0.034	0.022	0.015	0.0069	0.0036	0.0022	0.0016	0.0011	0.0005
Stomach	0.41	0.33	0.32	0.34	0.20	0.11	0.065	0.055	0.026
Lg. Intestine	0.77	1.1	--	0.68	0.36	0.16	0.068	0.068	0.026
Sm. Intestine	0.83	0.67	0.62	0.51	0.31	0.15	0.072	0.041	0.025
Blood	0.94	0.64	0.26	0.086	0.017	0.0038	0.0004	0.0002	--
Residual Carcass	0.17	0.15	0.14	0.11	0.081	0.085	0.035	0.027	0.018

*Normalized to 250 g rat.

Retention curves were plotted on semi-log paper and resolved into two or more exponential components. The biological half lives associated with these components are shown in Table 12. These values may be compared with the ruthenium retention half lives derived from the chronic feeding experiment (Table 10). Following chronic feeding a much larger proportion of the ruthenium is present in long-lived components. This is to be expected, since the long-lived components are accumulating ruthenium throughout the feeding period, while the shorter-lived components soon attain an equilibrium level. In the intraperitoneal injection experiment, 70 per cent or more of the ruthenium in all tissues except bone is present in components of relatively short half-life.

The half lives listed in Table 12 should be considered as approximations only. Resolution of the short-lived component of the retention curves was complicated by the fact that during the first few days following injection, deposition of ruthenium in the tissues was proceeding concurrently with loss from the tissues. Thus in the case of kidney, maximum ruthenium content was not attained until four days after injection, and in the case of spleen, not until eight days after injection.

There was no pronounced tendency for retention of ruthenium in the peritoneal cavity following injection and such ruthenium as was retained could not have significantly affected the half-lives of ruthenium in other tissues. One day after injection, less than 3 per cent of the administered dose remained in the muscular tissue surrounding the peritoneal cavity, and at the later sacrifice periods the concentration of ruthenium in these tissues was comparable to that in the total residual carcass.

Half-lives listed in Table 12 for the long-lived components are in fair agreement with those determined in the chronic feeding experiment. The values must be considered only approximate because of the small number of animal groups sacrificed at the longer time intervals, and because of the evident departure from linearity of many of the curves when

TABLE 12

Biological Half-Lives for Ruthenium in Tissues as Determined Following Intraperitoneal Injection of Ruthenium Chloride Solution

Tissue	Shorter Lived Component		Longer Lived Component	
	Fraction of Total Ruthenium	Half-life (days)	Fraction of Total Ruthenium	Half-life (days)
Kidney	.75	16	.25	80
Liver	.85	10	.15	80
Ovary	.75	13	.25	120
Spleen	.70[1]	17	.15	100
Bone	.50	15	.50	340
Lungs	.90	9	.10	100
Heart	.80	8	.20	100
Muscle	.80	9	.20	140
Brain	.35[1]	6	.06	120
Stomach	.70	8	.30	120
Sm. Intestine	.90	10	.10	140
Lg. Intestine	.90	8	.10	120
Residual Carcass	.75	10	.25	220

[1]Additional component of shorter half-life present but could not be resolved.

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plotted semi-logarithmically. Figures 4 and 5 present the retention data for several tissues plotted as log retention vs log time. Data are shown only for the time interval from 16 to 256 days post injection. Within these time limits reasonably linear retention curves are obtained when plotted in this manner. The data can therefore be represented by a power function of time having the form[13]

$$R = Bt^{-m}$$

where: R = retention at time t following isotope administration,
B = constant proportional to the extent of deposition of the isotope in a given tissue,
and m = constant determined by the rate of loss of the isotope from the tissue.

Equations of this type for each of the tissues considered are shown in Figures 4 and 5. The dimensions of R are per cent of administered dose per gram of tissue. These equations, while not applicable to the early portion of the retention curves, describe the later portions more accurately and more simply than could be done by a sum of two exponential terms.

EXCRETION STUDIES FOLLOWING SINGLE ADMINISTRATION BY VARIOUS ROUTES

Groups of 4 or 5 female rats were administered a single dose of ruthenium intragastrically, intravenously, intraperitoneally, or intratracheally. Urine and feces were collected daily and at 60 days the animals were sacrificed and tissues analyzed for ruthenium. Table 13 shows the distribution of ruthenium in the animal tissues plus a summary of total excretion from the four groups of animals, for the 60 day period. All data are corrected for radioactive decay. Total recovery of ruthenium was satisfactory except in the intragastrically fed group, where over 40 per cent of the ruthenium was not accounted for. This unaccounted for ruthenium must have been missed in the early feces collections, since approximately 97 per cent of fed ruthenium is not absorbed. The urinary excretion of 2.7

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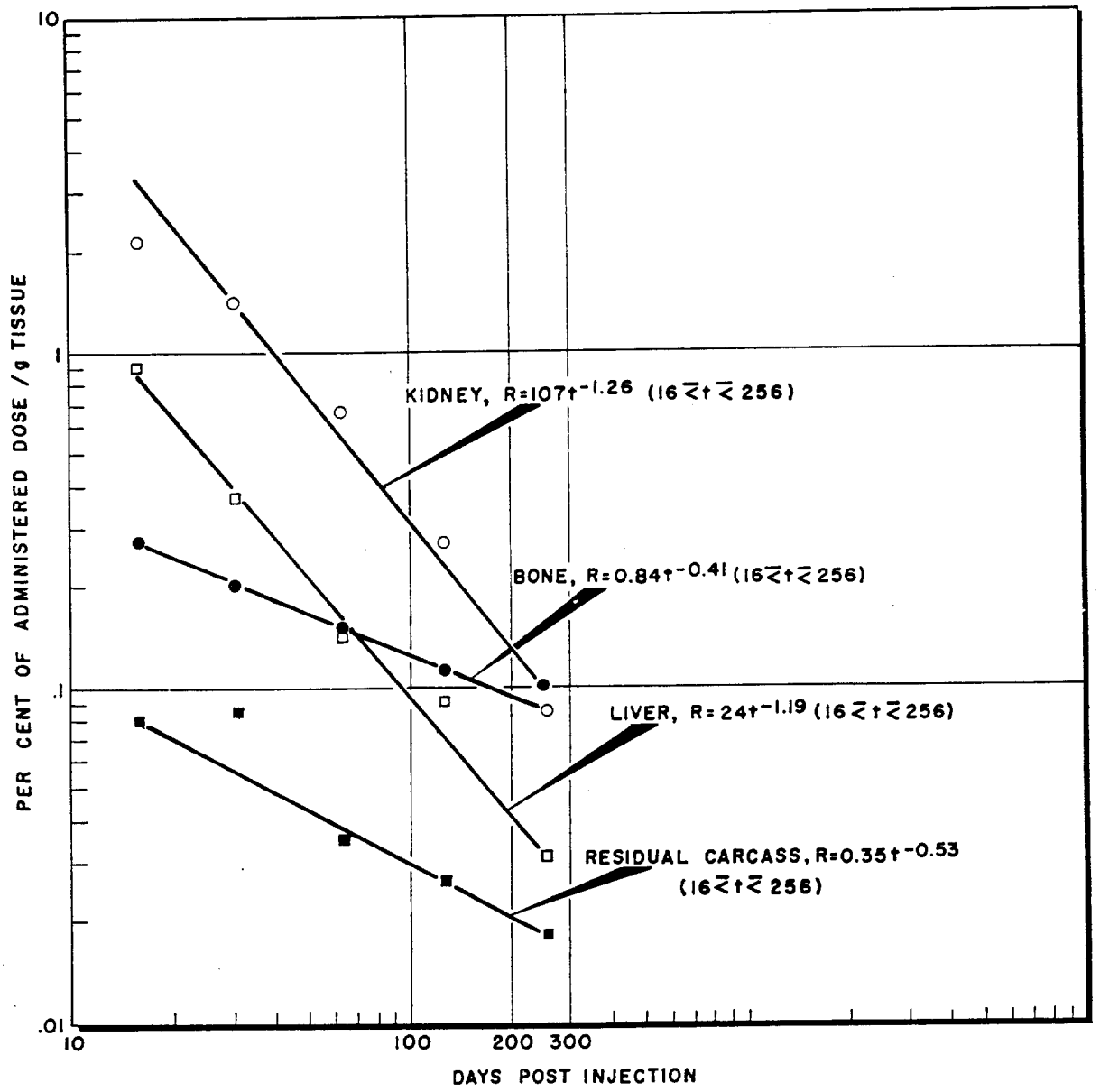

FIGURE 4

RETENTION OF RUTHENIUM IN REPRESENTATIVE TISSUES
FOLLOWING INTRAPERITONEAL INJECTION

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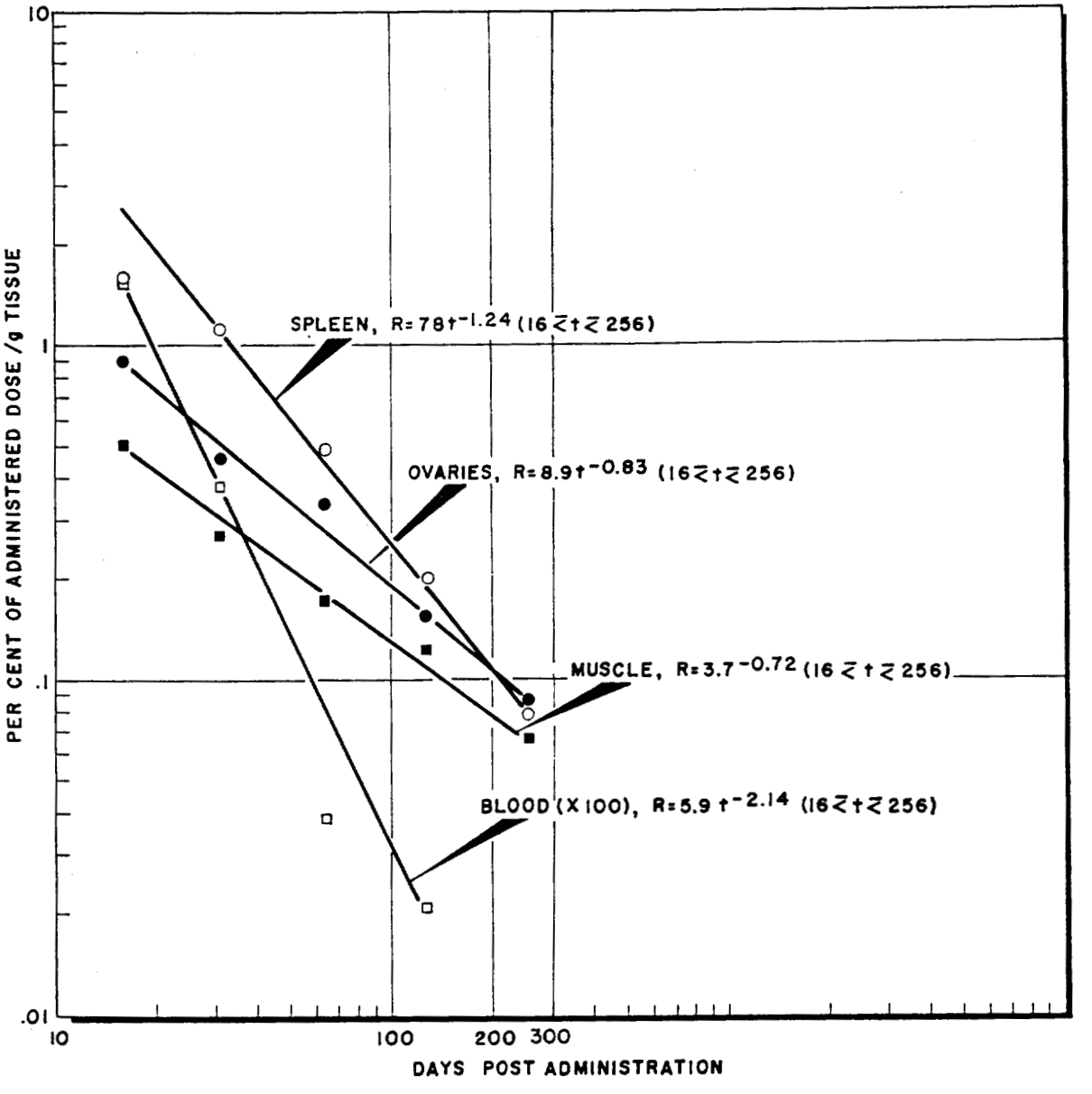

FIGURE 5

RETENTION OF RUTHENIUM IN REPRESENTATIVE TISSUES FOLLOWING INTRAPERITONEAL INJECTION

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TABLE 13

Distribution of Ruthenium in the Rat 60 Days after Administration by Various Routes (Per Cent of Administered Dose per Tissue)

Tissue	Intravenous	Intraperitoneal	Intragastric	Intratracheal
Kidney	.46	.98	.0085	.42
Liver	.59	1.30	.0085	.096
Ovaries	.018	.039	.00027	.0019
Spleen	.16	.32	.0024	.023
Bone	3.35	3.62	.066	.50
Lungs	.45	.10	.0016	1.50
Heart	.048	.047	.00076	.0052
Fat	.28	.91	.0066	.045
Muscle	3.87	2.54	.073	.54
Brain	.015	.001	.00005	.0005
Stomach	.098	.14	.0021	.019
Sm. Intestine	.22	.44	.0037	.036
Lg. Intestine	.18	.27	.0037	.040
Blood	.005	.010	.00039	.0070
Pelt	4.13	2.55	.109	1.09
Trachea				.19
Total Retained	13.9	13.3	.29	4.5
Excreted, urine	53.8	51.8	2.7	28.8
Excreted, feces	19.2	21.4	55.5	66.1
Total accounted for	86.9	86.5	58.5	99.4

per cent checks well with the value of 2.4 per cent obtained in chronic feeding experiments.

Total retention in the intravenous and intraperitoneal injection groups is very nearly the same. There are significant differences in the distribution, however. The lungs are notably high in the intravenous group, whereas most of the abdominal organs, and particularly abdominal fat, are significantly higher in the intraperitoneal group. These differences are what one might expect from the nature of the injections and the path taken by the ruthenium in the blood stream. The distribution of excreted ruthenium between urine and feces is virtually identical in the intravenous and intraperitoneal groups.

The intratracheally injected group differs in several notable respects from the intravenous group. The high fecal excretion indicates that a major portion of the injected material was carried up the trachea and excreted via the gastrointestinal tract. Comparing urinary excretion in the two groups (intravenous and intratracheal) one would estimate that about half of the injected ruthenium was absorbed into the blood stream. However, the ruthenium content of most tissues in the intratracheal group was considerably less than half that of corresponding tissues in the intravenous group. Kidney is relatively very high in the intratracheal group. This may be due to the fact that absorption of ruthenium from the lungs continued at a relatively high rate throughout the experimental period, thus maintaining high ruthenium levels in this excretory organ. About 1.7 per cent of the injected dose remains in the lungs and trachea 60 days after administration.

Table 14 shows the same data expressed in terms of ruthenium concentrations in the various tissues at 60 days post administration. Kidney, spleen, bone, and ovaries show high concentrations in all groups. Lungs show a disproportionately high concentration in the intravenous group, and kidney in the intratracheal group. The high concentrations of ruthenium

TABLE 14

Distribution of Ruthenium in the Rat 60 Days after Administration by Various Routes (Per Cent of Administered Dose per Gram Tissue)

Tissue	Intravenous	Intraperitoneal	Intragastric	Intratracheal
Kidney	.28	.59	.0051	.26
Liver	.078	.19	.0012	.014
Ovaries	.13	.30	.0019	.028
Spleen	.31	.65	.0045	.046
Bone	.22	.23	.0044	.031
Lungs	.36	.078	.0013	1.21
Heart	.061	.056	.00097	.0070
Fat	.016	.053	.00039	.0026
Muscle	.034	.022	.00066	.0048
Brain	.001	.001	.00003	.0003
Stomach	.081	.12	.0017	.017
Sm. Intestine	.049	.091	.00081	.010
Lg. Intestine	.075	.12	.0017	.018
Blood	.0003	.0007	.00003	.0004
Pelt	.099	.063	.0027	.029
Trachea				1.27

in lungs and trachea of the intratracheal group is, of course, due to unabsorbed ruthenium deposited on these tissues.

Table 15 shows the ruthenium concentration in the various tissues expressed as a percentage of the total retained dose. Expressed in this manner the essential similarity in distribution, following administration by various routes, is emphasized. Three significant differences between the four groups are apparent: 1) the higher concentration of ruthenium in the abdominal organs of the intraperitoneal injection group, 2) the high lung concentration in the intravenous injection group, and 3) the high kidney concentration in the intratracheal injection group.

The detailed excretion data are presented graphically in Figures 6 to 9. The logarithm of daily ruthenium excretion via urine and feces is plotted against time following administration. During the latter half of the experimental period the urine and feces curves are essentially parallel in all groups. During this period the ratio of ruthenium in urine to ruthenium in feces is about 5:1 following intraperitoneal and intragastric administration and about 3:1 following intravenous administration. These ratios compare with the 4:1 ratio observed in the previously discussed chronic feeding experiment. Following intratracheal injection the ratio of ruthenium in urine and feces during the latter portion of the experimental period is only 2:1 and for the first 15 days following injection, fecal excretion of ruthenium exceeds urinary excretion. This is due, of course, to removal of ruthenium from the lungs via the bronchi, trachea, and gastrointestinal tract.

Beyond about the eighth day post injection, all of the semi-logarithmic retention curves can be well fitted by equations consisting of two exponential terms. The slower component exhibits a biological half life of from 16-20 days, except for the intratracheal group, where the half life is 12.5 days. The shorter half life in the intratracheal group is reasonable in view of the continued introduction of ruthenium from the unabsorbed reservoir in the lungs. The faster components in all groups exhibit half lives of from 2.5

TABLE 15

Distribution of Ruthenium in the Rat 60 Days after Administration by Various Routes (Per Cent of Retained Dose per Gram Tissue)

Tissue	Intravenous	Intraperitoneal	Intragastric	Intratracheal*
Kidney	2.0	4.4	1.8	9.0
Liver	.56	1.4	.41	.48
Ovaries	.94	2.3	.66	.97
Spleen	2.2	4.9	1.6	1.6
Bone	1.6	1.7	1.5	1.1
Lungs	2.6	.59	.45	--
Heart	.44	.42	.38	.24
Fat	.12	.40	.13	.090
Muscle	.24	.17	.23	.17
Brain	.007	.008	.010	.010
Stomach	.58	.90	.59	.59
Sm. Intestine	.35	.69	.28	.35
Lg. Intestine	.54	.90	.59	.62
Blood	.002	.005	.010	.014
Pelt	.71	.47	.93	1.0

* Per cent of retained dose exclusive of that in lungs and trachea.

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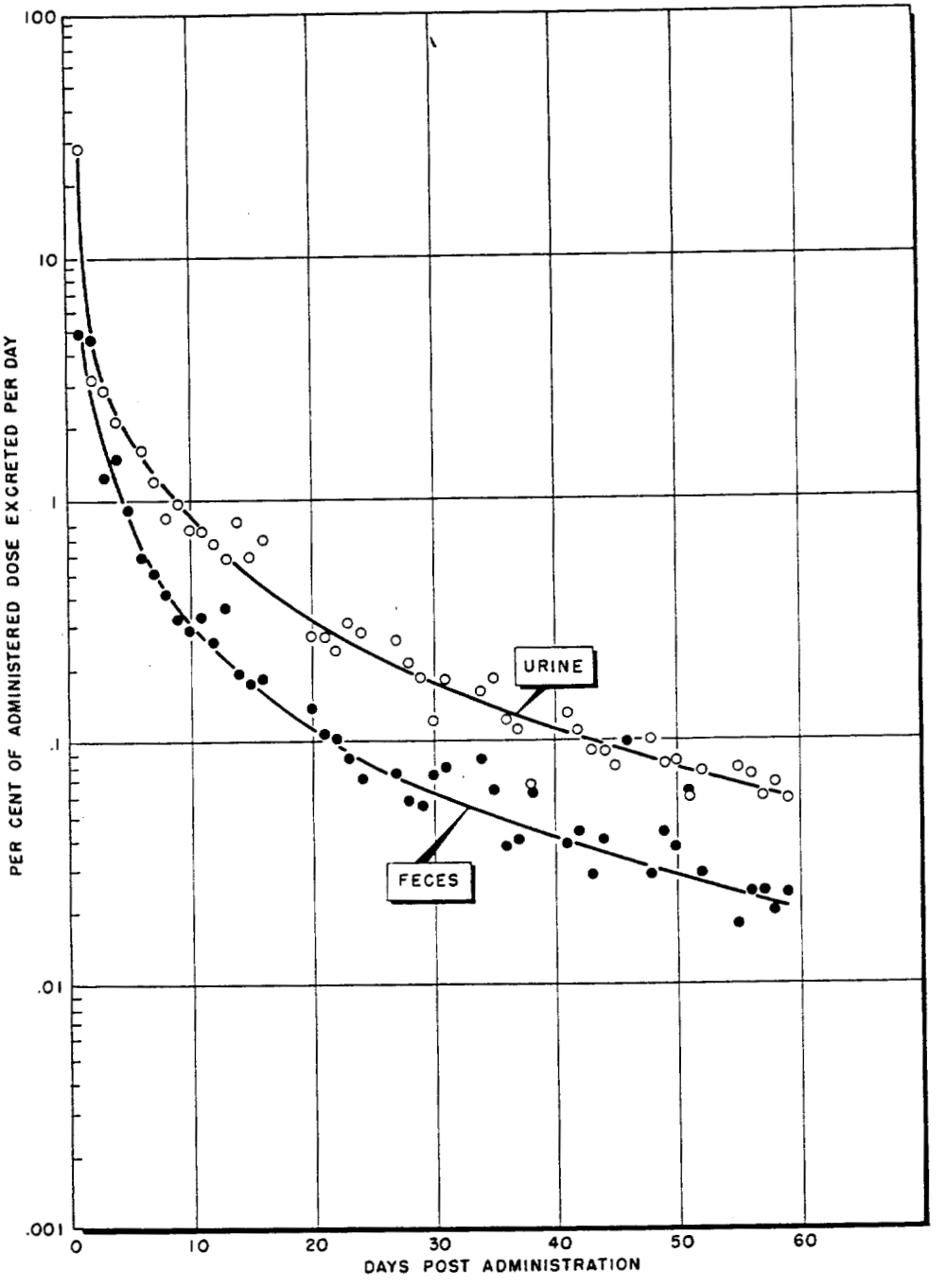

FIGURE 6

EXCRETION OF RUTHENIUM FOLLOWING SINGLE INTRAVENOUS INJECTION

(Semi-logarithmic Plot)

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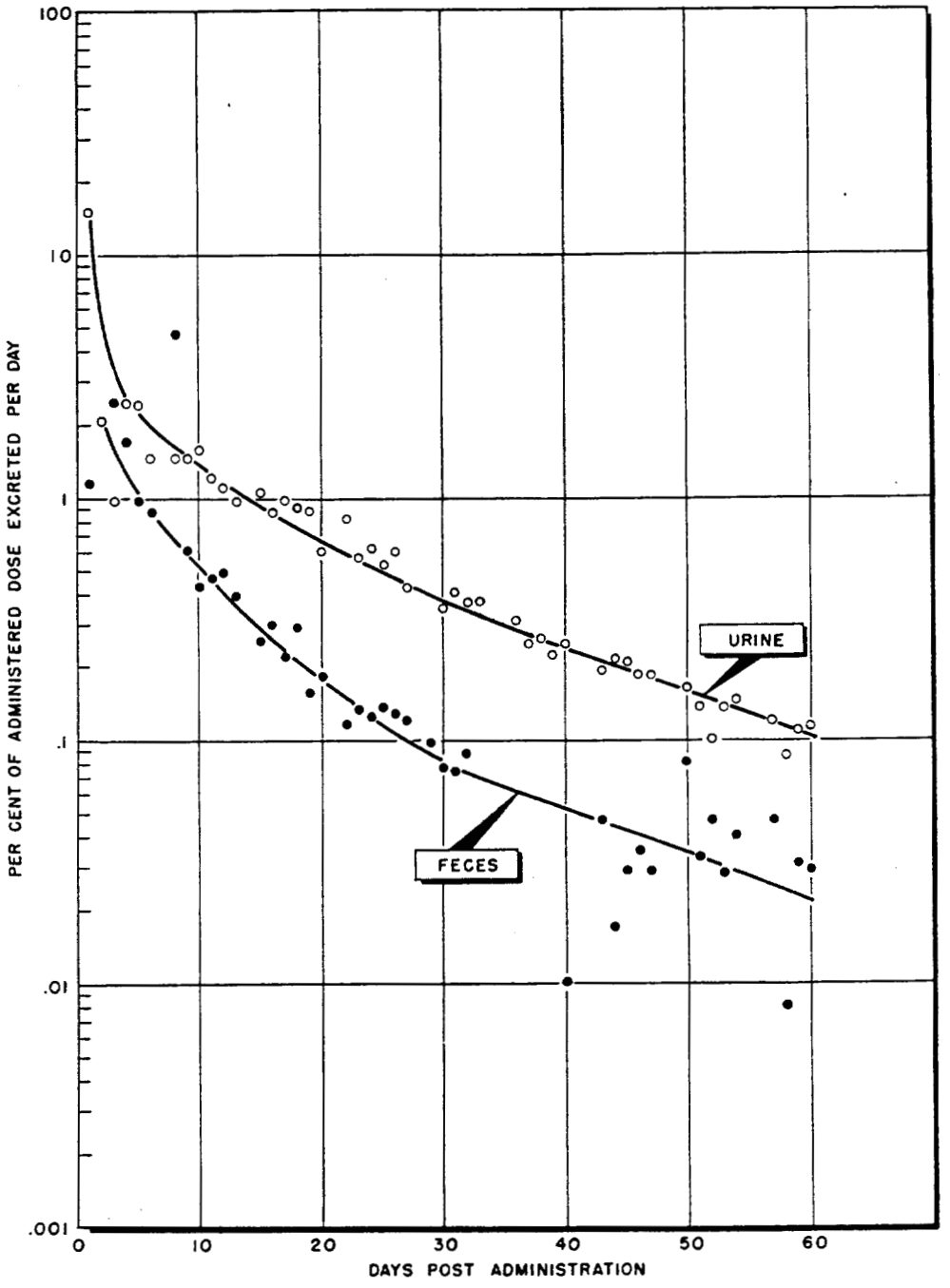

FIGURE 7

EXCRETION OF RUTHENIUM FOLLOWING SINGLE INTRAPERITONEAL INJECTION
(Semi-logarithmic Plot)

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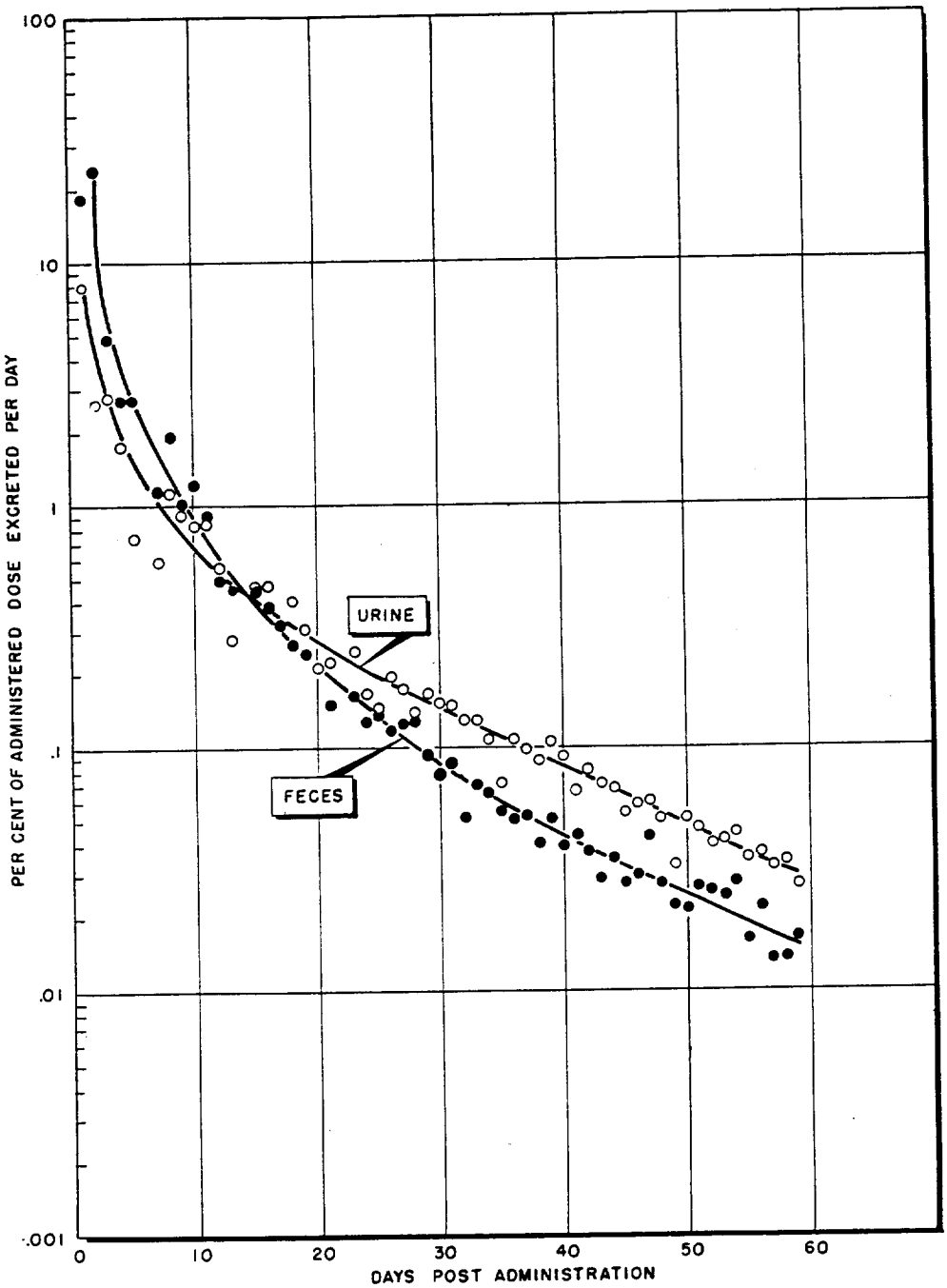

FIGURE 8

EXCRETION OF RUTHENIUM FOLLOWING SINGLE INTRATRACHEAL INJECTION
(Semi-logarithmic Plot)

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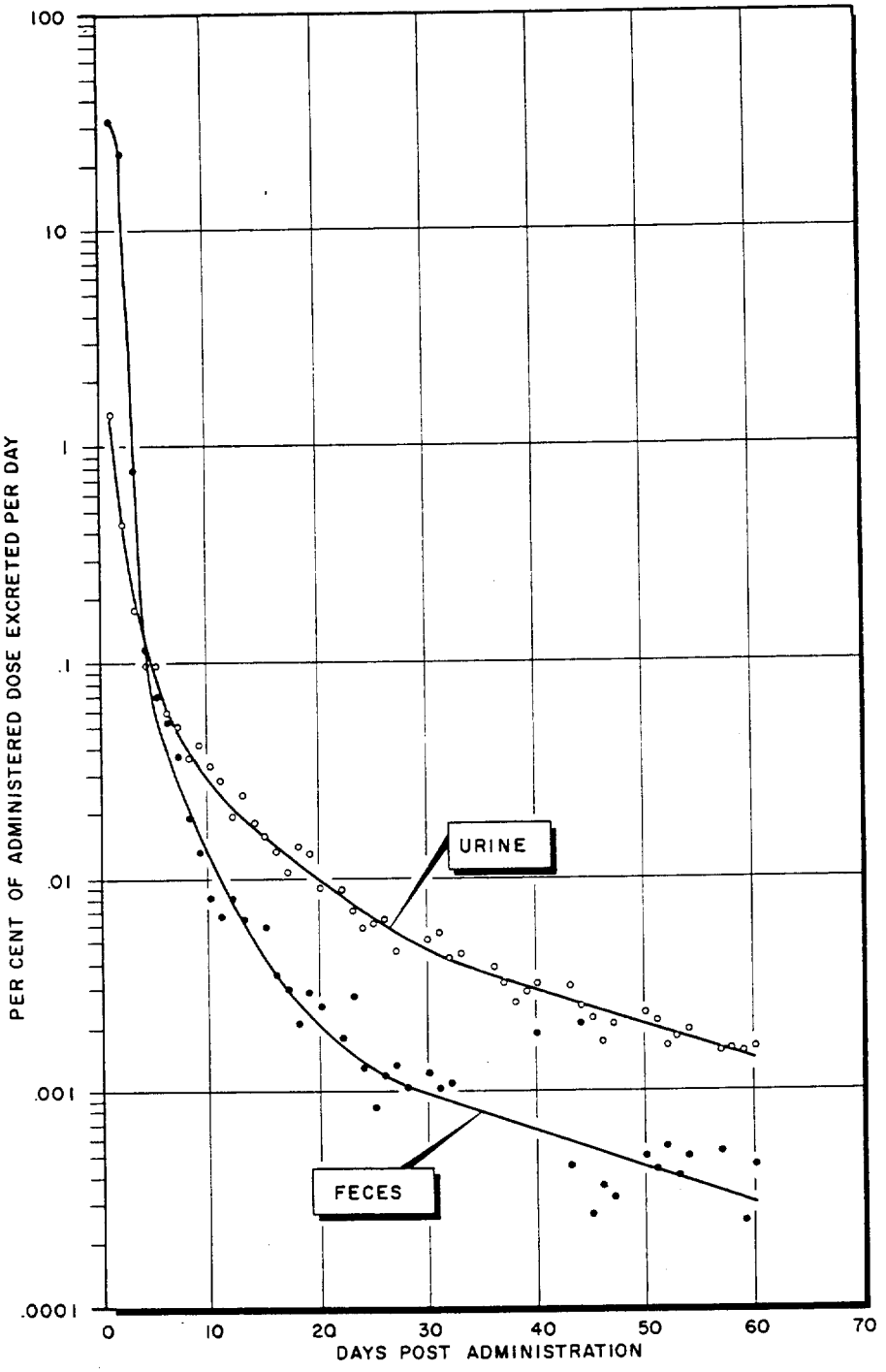

FIGURE 9

EXCRETION OF RUTHENIUM FOLLOWING SINGLE INTRAGASTRIC FEEDING
(Semi-logarithmic Plot)

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to 4.5 days. While these two exponential components for each group adequately describe the excretion over most of the time period studied, they account for only a small portion of the total ruthenium excreted. The bulk of ruthenium excretion occurs during the first few days after administration. Any attempt to resolve this early portion of the excretion curve into additional exponential components would be necessarily quite inaccurate due to the discontinuous nature of the excretion process. It is also apparent from longer term studies, previously discussed, that the 16-20 day half life components would not accurately represent excretion beyond the 60 day limit of the present experiments.

In an effort to find simpler, more accurate expressions for the ruthenium excretion curves, the data of Figures 6 to 9 were replotted logarithmically, i.e., log excretion vs log time. A straight line resulting from such a plot can be represented by a simple power function of time. These logarithmic plots for the four types of administration are shown in Figures 10 to 13. Both urinary and fecal excretion data from the intravenously injected animals (Figure 10) form reasonably straight lines when thus plotted. Urinary ruthenium excretion following intragastric administration fits a straight line very closely (Figure 13), and fecal excretion from the second day following intratracheal injection is well fitted by a straight line (Figure 12). The remaining data all fit straight lines during the latter portion of the experimental period, but diverge to a greater or lesser degree during the early period following administration.

In Table 16 derived equations are presented for all of the excretion curves. For each curve, a two term exponential equation, and an equation involving a power function of time are given, together with the time limits within which each equation is applicable. It is evident that the simpler power function provides a better description of the results in many cases. It can also be predicted with confidence that excretion data beyond 60 day post administration would be reasonably well represented by the power functions listed, but would not be adequately represented by the exponential equations unless additional terms were added.

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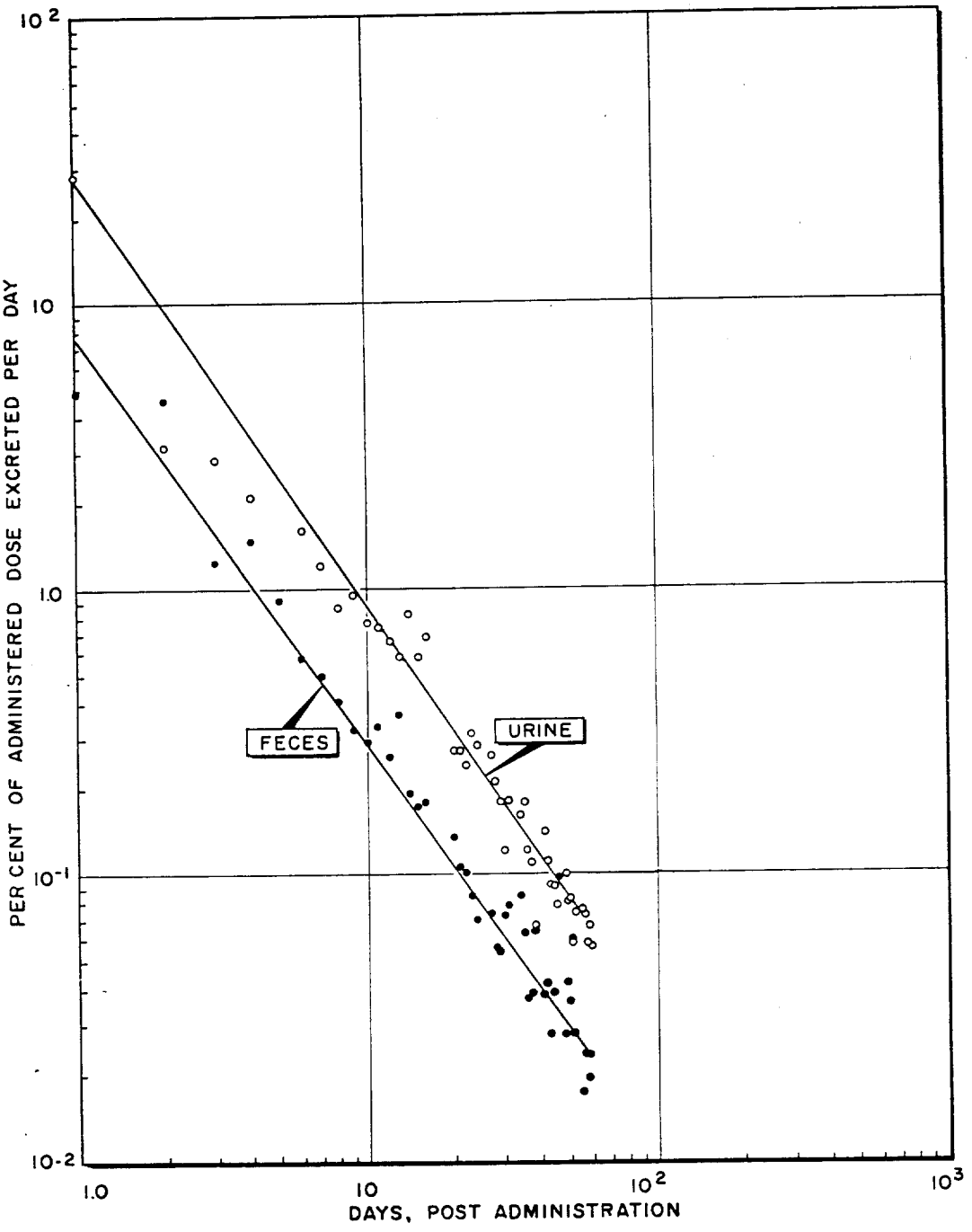

FIGURE 10

EXCRETION OF RUTHENIUM FOLLOWING SINGLE INTRAVENOUS INJECTION
(Logarithmic Plot)

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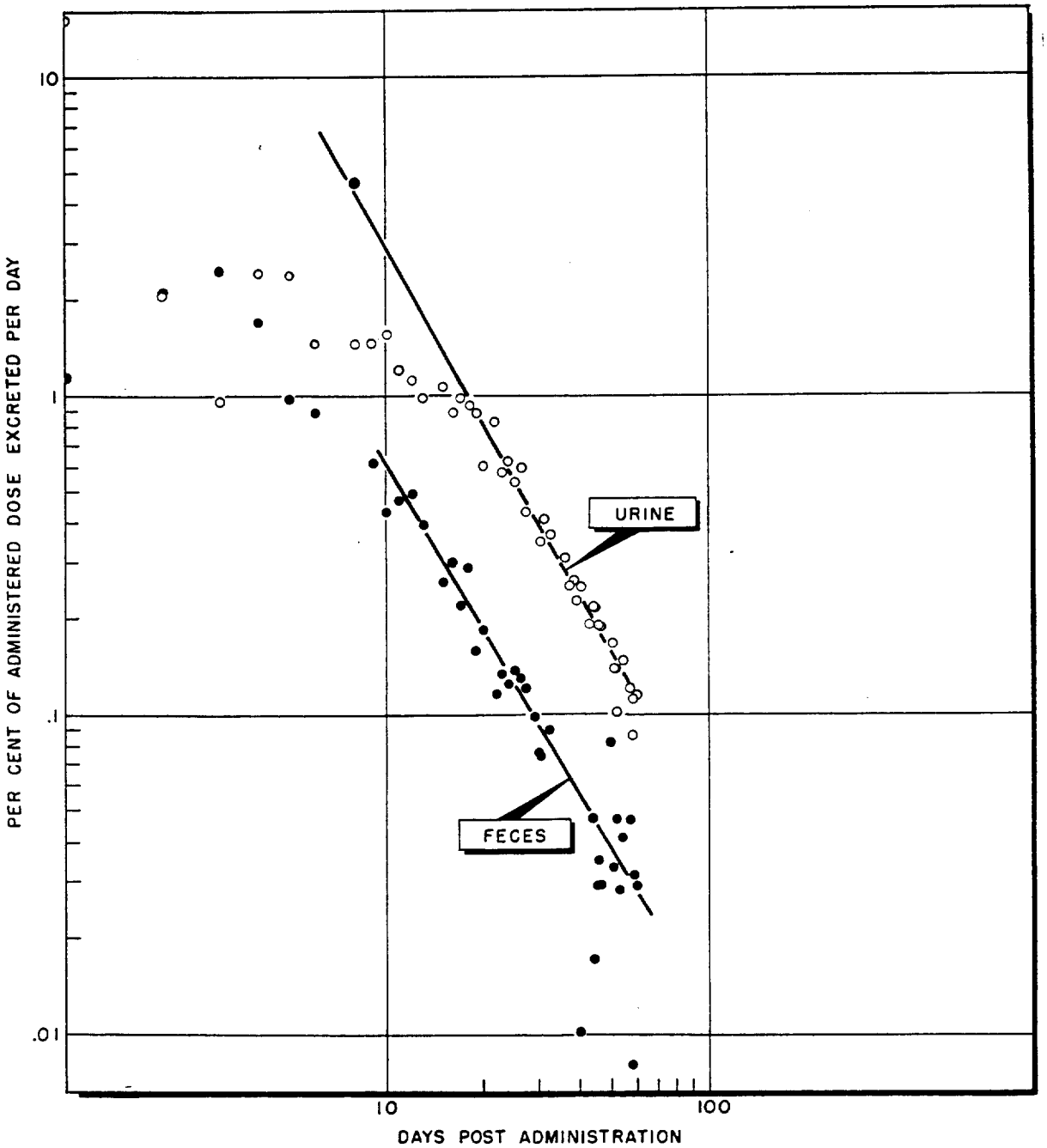

FIGURE 11

EXCRETION OF RUTHENIUM FOLLOWING SINGLE INTRAPERITONEAL INJECTION
(Logarithmic Plot)

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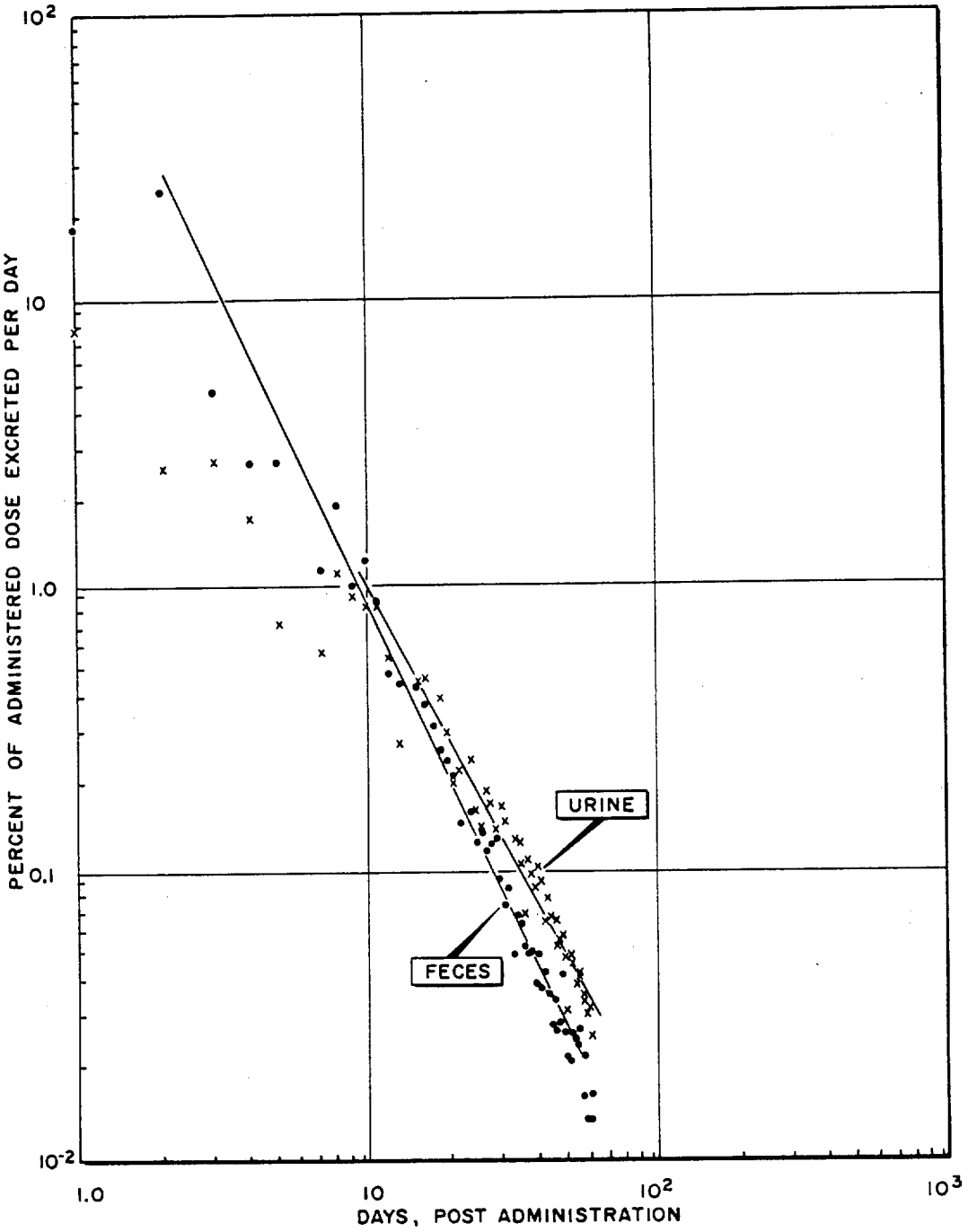

FIGURE 12

EXCRETION OF RUTHENIUM FOLLOWING SINGLE INTRATRACHEAL INJECTION
(Logarithmic Plot)

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TABLE 16

Equations for Excretion of Ruthenium Following Administration by Various Routes

Route of Administration	Exponential Function*	Limits of Applicability	Power Function*	Limits of Applicability
Intravenous	$E_u = .036e^{-0.17t} + .0046e^{-0.035t}$	$5 \leq t \leq 60$	$E_u = .29t^{-1.48}$	$1 \leq t \leq 60$
	$E_f = .012e^{-0.18t} + .0016e^{-0.035t}$	$6 \leq t \leq 60$	$E_f = .08t^{-1.42}$	$1 \leq t \leq 60$
Intraperitoneal	$E_u = .025e^{-0.15t} + .012e^{-0.041t}$	$4 \leq t \leq 60$	$E_u = 1.7t^{-1.81}$	$15 \leq t \leq 60$
	$E_f = .018e^{-0.17t} + .0030e^{-0.043t}$	$5 \leq t \leq 60$	$E_f = .29t^{-1.71}$	$8 \leq t \leq 60$
Intratracheal	$E_u = .045e^{-0.29t} + .0075e^{-0.055t}$	$4 \leq t \leq 60$	$E_u = .78t^{-1.88}$	$8 \leq t \leq 60$
	$E_f = .050e^{-0.21t} + .0040e^{-0.055t}$	$8 \leq t \leq 60$	$E_f = 1.2t^{-2.15}$	$2 \leq t \leq 60$
Intragastric	$E_u = .0010e^{-0.17t} + .00013e^{-0.036t}$	$8 \leq t \leq 60$	$E_u = .014t^{-1.64}$	$1 \leq t \leq 60$
	$E_f = .0020e^{-0.29t} + .00003e^{-0.038t}$	$7 \leq t \leq 60$	$E_f = .0066t^{-1.82}$	$8 \leq t \leq 60$

*E_u = Fraction of administered dose excreted in urine per day, t days after dosage.
E_f = Fraction of administered dose excreted in feces per day, t days after dosage.

PERCUTANEOUS ABSORPTION STUDIES

A single experiment was performed comparing the absorption of ruthenium from 2.0 N and 0.01 N HCl solutions, after exposure to the skin for 1, 5, or 24 hours. Five animals were exposed in each group. The area to be contaminated on the right thigh was shaved a day prior to exposure. Ten microliters of the ruthenium solution, containing approximately 2 μc Ru^{106}, was spread over an area of 1 cm^2. The contaminated areas were not covered during the exposure period.

At sacrifice, the exposed skin area and underlying tissue was removed for separate analysis. The remainder of the animal was dissected and the various tissues analyzed for ruthenium content. Results are shown in Table 17.

The values listed as "total absorbed" do not include ruthenium in the gastrointestinal tract or pelt. The gastrointestinal tract will contain largely ruthenium ingested by the animal during the exposure period, and the pelt is likely to be grossly contaminated externally. It is obvious that the amount of ruthenium ingested, as indicated by the gastrointestinal tract analyses, could not have resulted in significant absorption, compared to the amount absorbed through the skin.

The total recovery of ruthenium in the 5 and 24 hour exposure experiments was very poor. This is inevitable in experiments of this type. While the calculation of any exact absorption coefficients is precluded, the results are nonetheless of practical interest since the conditions of exposure closely simulate those to which humans might be subjected.

Total absorption is clearly a function of acidity and increases with increasing length of exposure. The distribution of the absorbed ruthenium among the various tissues is similar to that observed following other methods of administration, except for the much higher concentration of ruthenium in the exposed thigh. This is presumably due to absorbed ruthenium which has not yet found its way into the general circulation.

TABLE 17

Absorption of Ruthenium Chloride through the Skin of Rats
(Average values from five animals)

Tissue Assayed	Per Cent of Administered Dose per Tissue					
	2.0 N HCl Solution			0.01 N HCl Solution		
	1 hr.	5 hr.	24 hr.	1 hr.	5 hr.	24 hr.
Kidney	.070	.32	.55	.0035	.026	.058
Liver	.11	.27	.66	.0048	.028	.051
Ovaries	.0012	.0042	.061	.0002	.0003	.0003
Spleen	.0027	.0090	.032	.0003	.0002	.0016
Bone	.050	.13	.13	.0059	.010	.019
Lungs	.014	.052	.055	.0006	.0082	.0053
Heart	.0047	.011	.021	.0002	.0010	.0009
Fat	.030	.12	.18	.0020	.027	.025
Muscle	.18	.38	.85	.018	.17	.13
Brain	.0012	.0040	.0049	.0001	.0008	.0004
Blood	.18	.57	.79	.0051	.033	.041
Exposed thigh	.29	.64	.89	.0031	.043	.061
Total absorbed	.93	2.51	4.22	.044	.35	.49
GI tract and contents	.66	1.90	.92	.0005	.24	.88
Pelt	.18	.62	.77	.021	.30	.26
Exposure area	97.	46.	49.	84.	88.	15.
Total recovery	99.	51.	55.	84.	89.	17.

GENERAL DISCUSSION AND CONCLUSIONS

It is not the purpose of the present report to consider in great detail the many implications of these data as they may relate to such general problems as the best manner of representing mathematically the various curves obtained, the correlation of data from acute and chronic experiments, and the correlation of data from experiments involving different routes of administration. It is intended that these subjects shall be thoroughly explored in a subsequent document. For the present we shall restrict ourselves to the conventional application of the data obtained to the problem of establishing internal exposure limits for Ru^{106}.

Table 18 compares the most recent recommendations of the ICRP[3] with the results of the present study. In this comparison it is assumed that kidney is the critical organ. This assumption is justified on the basis of our chronic feeding studies with mature animals. As pointed out previously, however, bone is a close contender and might well prove to be critical in rapidly growing animals.

The various physiological parameters involved in the establishment of permissible limits are listed in Table 18 and will be considered individually in the discussion to follow. The notation employed is that of the ICRP.[3]

f_1 = Fraction Going from Gastrointestinal Tract to Blood: There seems little question but that the presently recommended value of <0.0005 is much too low. Our value of 0.03 is based primarily on the ratio of urinary to fecal ruthenium excretion during and following chronic feeding, but is also consistent with the results of many other experiments.

The fraction 0.03 may be questioned on the basis that it is derived from experiments employing solutions considerably more acidic than are usually encountered in a drinking water supply. Most experiments were performed at pH 2. Single feeding experiments showed no decrease in

absorption at pH 4, but a significant decrease by a factor of about 5, at pH 6. Because of our very limited knowledge of the chemical state of ruthenium in these solutions, and because of the possibility of increased absorption in very young animals, we feel that the use of the higher absorption figure is justified.

f_2 = Fraction in Critical Organ of That in Total Body: The data in this report on organ distribution of ruthenium during chronic feeding were uniformly presented in terms of per cent of average daily dose per gram. The value of f_2 is therefore not apparent from the tabulated results. In chronic feeding experiment IV (Tables 4 and 8) residual carcass ruthenium was determined in addition to the various organ contents. Gastrointestinal tract and pelt were not analyzed because of the probability of gross contamination from drinking water and excreta; however, a fairly good estimate of total body ruthenium should be obtained by multiplying the residual carcass concentration per gram by the live weight of the animal. On this basis the average value of f_2 after 50 days chronic feeding was 0.11; after 125 days, 0.077; and after 200 days, 0.065. Further data to be obtained after 300 and 400 days feeding may be expected to reduce further this figure to a slight extent, but on the basis of present information a value of 0.07 seems most justifiable.

f_2' = Fraction Going from Blood to Critical Organ: Since ruthenium is lost from the kidney more rapidly than from most other tissues, the value of f_2' must be substantially larger than f_2. The value of f_2' may be approximated from the 24 hour retention data of single administration experiments. The kidney data of Tables 1, 2, and 3, when converted to total organ content and compared with the total body content, lead to an average value of 0.23 for f_2'. This method of evaluating f_2', of course, neglects the loss of absorbed ruthenium from the kidney and from the total body during the 24 hour experimental period. Because of this uncertainty the value of f_2' is expressed to only one significant factor.

f_w = Fraction Taken Orally That Arrives in Critical Organ: This parameter is elsewhere defined in the ICRP report[3] as "fraction taken into the body that is retained in the critical organ," and it is pointed out that when derived from acute exposure animal data in which a simple exponential curve is fitted to the critical organ retention data, f_w is best considered as the intercept of the extrapolation of this exponential curve with the zero time axis. Since our kidney retention data for ruthenium is poorly represented by a simple exponential curve, and since chronic feeding data are available which obviate the necessity for making any assumptions with regard to the exponential nature of the retention curve, we list in Table 18 a value for f_w which is the product of f_1 and f_2', and which is literally the fraction taken orally that arrives in critical organ. This value of 6×10^{-3} is therefore a physiologically significant figure, but not one which would result from the conventions usually employed in deriving f_w from acute exposure animal data.

f_a = Fraction Inhaled That Is Retained in Critical Organ: Because of the general paucity of data on the redistribution of inhaled radioisotopes, this parameter is frequently calculated from the formula:[3]

$$f_a = (0.25 + 0.5\, f_1)\, f_2',$$

which assumes that one-fourth of the inhaled radioisotope is absorbed directly from the lung to the blood, and that one-half of the inhaled radioisotope is removed from the lung up the bronchial tree and swallowed. In the present case this calculation leads to a value for f_a of 0.05. In our experiments it was found that urinary excretion (and therefore, presumably, total absorption to the blood) was ten times greater following intratracheal injection than it was following intragastric administration (Table 13). Assuming that distribution of ruthenium from the blood is the same following either method of administration, f_a should be ten times as large as f_w, or $f_a = 6 \times 10^{-2}$. While our experiments were not specifically designed to yield a value for f_a, the agreement between these two estimated values is encouraging.

T_b = Biological Half Life in Critical Organ: Tables 10 and 12 list values for the half life of ruthenium in the kidney which were derived by "forcing" the data to fit a double exponential equation. The shorter lived component from the chronic feeding experiment (Table 10) was assigned a half life of 5 days and accounted for about two-thirds of the total ruthenium. The shorter lived component from the intraperitoneal injection experiment (Table 12) has little significance because of the prolonged build-up in the kidney which coincided with the early loss of ruthenium from the organ. The longer lived component was assigned a value of 40 days in the chronic feeding experiment and 80 days in the intraperitoneal injection experiment. The discrepancy is undoubtedly due to the longer period of retention studied in the intraperitoneal experiment. The conclusion must be that the retention of ruthenium in the kidney over any extended period cannot be described adequately by one, or even two biological half lives. Since this parameter is not essential to the calculation of MPC's for water, no value is listed in Table 18 for T_b.

mC/I = Fraction of Daily Intake Chronically Present in Critical Organ: This composite parameter is not separately listed in the ICRP report. For most radioisotopes the value is unavailable. It can be determined directly from chronic feeding experiments of sufficient duration, and when known, leads directly to an evaluation of the MPC. This parameter is related to others, previously considered by the expression:[3]

$$T_b = \frac{0.693\ mC}{I\ f_w}$$

where m = mass of critical organ, C = concentration of the element in the critical organ, and I = daily intake of the element. Inserting ICRP values for T_b and f_w, mC/I becomes 5.8×10^{-4}. Values of mC/I derived from the chronic feeding experiments detailed in Tables 4-8 are summarized in Table 19. As will be seen, the values from different experiments range from 0.01 to 0.03. A value of 0.02 is taken as most representative of the total information available.

q = Maximum Permissible Total Body Burden: The quantity of ruthenium uniformly distributed in 300 g of kidney (standard man) which will result in a radiation dose rate of 0.3 rad per week is 0.18 μc. Dividing this figure by f_2, we obtain a permissible body burden of 2.6 μc.

$(MPC)_w$ = Maximum Permissible Concentration in Water: If the fraction of daily intake chronically present in the kidneys (mC/I) is 0.02, and the maximum permissible kidney content is 0.18 μc, then the maximum permissible daily intake is 0.18/0.02, or 9.0 μc/day. This is consumed in 2200 ml of water (standard man), so the maximum permissible concentration in water becomes 9/2200, or approximately 4×10^{-3} μc/ml. It should be noted that this calculation involves only the single directly measured parameter, mC/I, and avoids completely the uncertainties inherent in the assumption of a value for T_b.

It is interesting to note the value of T_b which would be required to yield an MPC of 4×10^{-3} μc/cc when calculated from the conventional equation:[3]

$$(MPC)_w = \frac{3.1 \times 10^{-4}\, q\, f_2}{T f_w (1 - e^{-0.693\, t/T})},$$

using values from the present investigation for q, f_2 and f_w. The value derived for the effective half life, T (which in this case is equivalent to the biological half life, T_b) is 2.3 days. The discrepancy between this value and the range of measured values for T_b is indicative of the pitfalls involved in uncritical application of the conventional approach to MPC calculations.

Work is in progress to calculate MPC's from these data by other methods of analysis, such as the description of retention by means of power functions of time.[13] Preliminary results indicate that the MPC's obtained will not differ from those presented in this report by more than a factor of two. A detailed account of these further calculations will be published separately.

It should be emphasized again that the values presented for the various parameters in Table 18, are those which, from the experimental data obtained, best fit the formal definition of the parameter. These are not necessarily the most appropriate values for use in any particular method for calculating MPC's. If $(MPC)_w$ were to be calculated in the conventional manner, using some experimentally determined value for the effective half life, T, the value of f_w employed in this calculation should be that which corresponds to the fraction of total ruthenium in the kidney whose turnover is described by the chosen value for T. If a value of 40 days were used for T, the appropriate value for f_w would be much smaller than 6×10^{-3} since only a relatively small fraction of the ruthenium which arrives in the kidney is lost with a half life as long as 40 days.

$(MPC)_a$ = Maximum Permissible Concentration in Air: We have no data on chronic pulmonary exposure which would permit a direct calculation of $(MPC)_a$, similar to that made for $(MPC)_w$. Falling back on the conventional equation:

$$(MPC)_a = \frac{3.5 \times 10^{-8}\, q\, f_2}{T f_a\, (1-e^{-0.693t/T})},$$

and employing the value for T (2.3 d) which would have given the proper result in the conventional calculation of $(MPC)_w$, we calculate, $(MPC)_a = 5 \times 10^{-8}$ μc/cc. The rather close agreement between this result and the ICRP value is fortuitous, being occasioned by changes in the various parameters which largely cancel out in the final calculation.

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