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STUDIES OF THE METABOLISM OF RADIUM IN MAN

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INTRODUCTION

SINCE the advent of nuclear reactors, the ever increasing use of radioactive isotopes has demonstrated the practical necessity for a clear understanding of the metabolism of the various elements in man. Such information is essential to the establishment of realistic values for permissible concentrations of radioactive elements deposited in the body as well as to provide a basis for therapeutic removal. The long-lived radioelements that deposit in bone present a particularly difficult problem, since they have thus far proved refractory to efforts to accelerate their normal low rate of excretion.

Following the early observations of Blum,[5] Hoffman,[13] and Martland[28] in 1924 and 1925, who showed that internally deposited radium and mesothorium produce severe necroses, there have been several reports of the clinical course of radium poisoning.[2,6,20,25,26,27,29,34,42] Radium has been shown to be retained tenaciously by bone[1] in which its distribution remains highly heterogeneous during the entire lifetime of the host.[12,22] It is excreted so slowly that its presence in the body may be readily detected many years after a significant initial exposure. Experiences with radium poisoning in man during the last thirty years provide the only good information on the long term effects of radioactive elements deposited in the human skeleton and consequently form the primary basis for the estimation of tolerable concentrations of bone-seeking isotopes in general.

The earliest cases of radium poisoning were observed among employees of the luminous dial painting industry,[28] where the now long-outmoded practice of tipping the brush in the mouth was responsible for the ingestion of dangerous quantities of radioactive paint. This source of patients, however, did not provide clear cut instances of poisoning with radium alone, since the luminous paint contained mixtures of mesothorium (Ra^{228}), radiothorium (Th^{228}), and radium 226. Because of the relatively short half-lives of mesothorium (6.7 years) and radiothorium (1.9 years) and the complexity of their decay schemes, it has been difficult to obtain proof of their original proportions sufficient to assess their contributions to the total biological damage produced.[2]

Since radium was regarded as a useful therapeutic agent until about twenty years ago, it is still possible to find significant numbers of people who were given radium orally or intravenously. It is generally assumed that the Ra^{226} given these people was relatively free from mesothorium and radiothorium contamination.

There exist only a few scattered observations which pertain to the quantitative metabolism of radium in humans. These have been summarized by Silberstein[40] and by Aub *et al.*[2] Although it is possible today to find persons with appreciable radium burdens, there is usually no means of determining the original dosage, and other circumstances surrounding the administration often remain obscure. Therefore, it is especially significant when a group of subjects with a known history of radium administration is found.

In 1931, a selected group of patients in the Elgin State Hospital, Elgin, Illinois, mostly dementia praecox cases, were each given multiple intravenous injections of radium chloride (10 micrograms radium element per dose) at weekly intervals over periods ranging from two to six months. This study, reported by Schlundt, Nerancy and Morris,[37] is almost unique in that the dosages were recorded and the patients were measured for radium retention on two

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separate occasions within the first year. Nineteen of the original 32 patients were located in 1951 and studied for clinical symptoms and for radium content. In addition, several other persons who had received radium injections have been located in the Chicago area and likewise studied. This report deals with the results of these physical determinations and attempts to draw conclusions concerning the long term metabolism of radium in humans. The results of clinical studies of these patients will be described in another article.[21]

BASIS FOR MEASUREMENT OF RETAINED RADIUM

Radium 226 is a naturally radioactive element with a half-life of 1,620 years. Inspection of its decay pattern shows that in disintegrating it is converted to radon, a radioactive noble gas, having a half-life of 3.825 days. Radon is produced by radioactive decay of its parent at an essentially constant rate of 2.097×10^{-12} curies per second per microgram of radium.

Since the noble gases cannot participate in chemical reactions, a considerable fraction of the radon is removed from the site of production (bone) by the processes of diffusion and dissolution in body fluids. The work of Tobias *et al.*,[42] Behnke and Willmon,[4] and Lange and Evans[18] indicates that minor losses of radon from the body probably occur by way of the skin and intestinal tract. Practically all of the radon elimination from the body is by way of the lungs and, with proper instrumentation, this radon may readily be measured in the expired air. Thus, with any constant set of respiratory conditions maintained for a sufficient time, each 2.097×10^{-12} curies exhaled per second represents the contribution of 1 microgram of radium. The accuracy obtainable in estimating the quantity of radium that contributes to expired radon is limited almost entirely by the ability of the method of collection of expired air to obtain specimens representative of the rate of exhalation of radon averaged over periods of time large compared to its half-life. Unpublished work of the authors, in dogs injected with radium, shows that both the concentration of radon in the expired breath and the quantity expired per unit time may be altered appreciably by changes in respiratory activity. Thus, in practice, the deviations in individual determinations of radium, as represented by expired radon, may be considerable.

The fraction of radon retained in the body decays radioactively through several successive, short-lived, radioactive daughters. This decay process is accompanied by the emission of gamma rays which, by appropriate instrumentation, may be measured externally to the body.

The total radium content of a living subject, therefore, is determined as the sum of these two completely independent measurements.

DISCUSSION OF EARLY WORK OF SCHLUNDT *et al.*

The early determinations of radium retention in the Elgin Hospital patients were made using the best techniques and equipment available in 1931–1932. These measurements of expired radon and externally detectable gamma rays are described in the original paper of Schlundt, Nerancy and Morris.[37] Since approximately twenty years have elapsed between the early work of these authors and the recent measurements reported herein, it is well to examine the available information to determine the degree of over-all consistency and reliability. It may be stated at the outset that the authors have concluded that the early work of Schlundt *et al.* was essentially accurate, although it has been impossible to determine the error involved in individual measurements. In this evaluation, it should be indicated, considerable weight has been placed on Schlundt's reputation among his associates as an extremely thorough, careful worker with wide experience in working with radium. The following items appear to be worthy of individual consideration:

1. Was the original measurement of

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ampoule content correct?)

2. Did the patient receive the full content of the ampoule or was a significant percentage lost by adsorption onto the glass surfaces of the ampoule and syringe?
3. Were the radium preparations contaminated with mesothorium?
4. What degree of accuracy was attained in measurements of retained radium using the two complementary techniques for determination of retained and exhaled radon?

These questions will be covered separately.

From the files of the late H. H. Barker, a vice-president of the United States Radium Corporation, it was ascertained that the radium used for the Elgin Hospital patients was supplied by the U. S. Radium Corporation through an identified Chicago outlet. This radium was supplied in sealed glass ampoules, each of which was labelled to contain 10 micrograms of radium element (as the chloride) in 2 milliliters of sterile isotonic NaCl solution. Through the kindness of Dr. M. Williams of the Mayo Clinic and Mr. G. Ferlazzo of Memorial Hospital, New York City, it was possible to obtain seven such ampoules (originally prepared by the U. S. Radium Corporation) which had been retained unopened for about twenty-five years (Fig. 1). These ampoules were measured (without being opened) for radium content in a pressurized, gamma-ray ionization chamber which had been calibrated against National Bureau of Standards radium preparations. The results are presented in Table 1. It will be

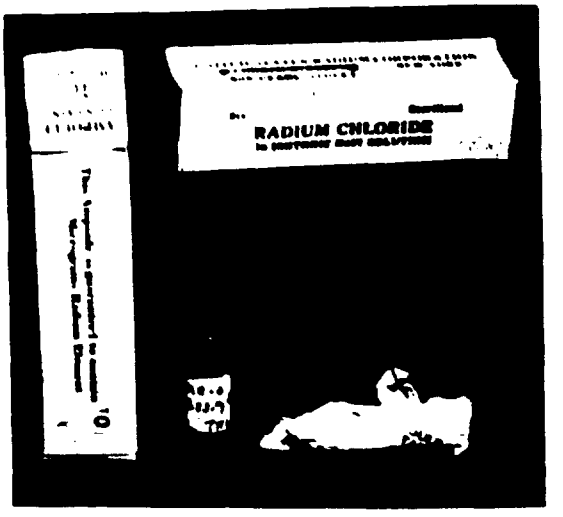

Fig. 1. Ampoule of $RaCl_2$ originally prepared about 1928 for intravenous injection. Label on ampoule was added by the authors.

TABLE I

MEASUREMENTS OF $RaCl_2$ AMPOULES PREPARED FOR INTRAVENOUS ADMINISTRATION ABOUT 1928

Ampoule (No.)	Total Ra Content (μgm.)	Per Cent of Measured Ampoule Content			MsTh, 1953* (per cent)
		Retained in ampoule	Retained in syringe	Delivered from syringe	
MC-4	9.16	1.96	2.62	95.20	
MC-5	8.83	27.41	4.64	66.02	.05 ± .03
MH-1	9.00	0.44	2.22	97.44	.05 ± .03
MH-2	8.99	1.00	3.56	95.33	
MH-3	18.15†	1.05	3.14	93.94	
MH-4	9.00	1.11	2.78	96.00	
MH-5	8.31	1.68	2.89	96.03	
Average	8.93	1.21‡	2.87‡	95.66‡	

* Per cent MsTh is calculated as $\frac{\mu cMsTh}{\mu cMsTh + \mu cRa} \times 100$.

† 20 μgm. ampoule—treated as two 10 μgm. ampoules in averaging.

‡ Mc-5 not figured in averages.

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noted that the radium content of these ampoules was close to 9 μgm. in every case.

The ampoules were then opened and the solutions withdrawn, with separate 2 ml. Ideal syringes fitted with B-D No. 22 1 inch needles, using techniques calculated to duplicate hospital methods and not to deliver quantitatively. The syringes were emptied into new Pyrex ampoules which were then sealed off as were the original empty ampoules. The syringes and needles were placed directly into glass tubes which were then sealed. After an appropriate period to allow radon equilibration the radium contents of the three parts were measured as before. The results (Table 1) indicate that, with one exception, after twenty-five years the radium salt was essentially quantitatively in solution and that *96 per cent* of the total radium was delivered from the syringe.

Since the quantities of radium in these ampoules were only 90 per cent of the stated content, it was particularly important to determine whether this discrepancy could be attributed to the decay of an initial mesothorium contaminant. The assay of residual mesothorium in two of these ampoules (Table 1) was accomplished through the kindness of Dr. C. E. Miller and Mr. R. E. Rowland, of the Radiological Physics Division of this Laboratory, who have devised an ingenious method of determining MsTh in the presence of large amounts of Ra by measuring the delayed coincidences of the ThC β particle and the ThC' α particle. This method will be published in detail elsewhere. The results of the measurements indicated that, in 1953, the MsTh content was no more than 0.05 per cent, a value which is so near the present limiting sensitivity of the instrument that it should only be regarded as an upper limit.

The half-life of mesothorium (6.7 years) is such that a given quantity of MsTh will be reduced to 7.5 per cent of its initial value in twenty-five years. Therefore, the initial MsTh contamination in these ampoules could not have exceeded 0.66 per cent, a negligible quantity.

Further evidence of the absence of MsTh contamination in the radium preparations used in the Elgin Hospital study is supplied by the fact that earlier publications by Schlundt *et al.*[35] described the detection of thoron, an isotope of Rn produced through decay of MsTh, in the expired air of persons containing MsTh. Since the apparatus was essentially the same in both studies it is probable that the presence of significant quantities of MsTh and its daughters would have been detected in the Elgin study.

Another such indication is that shipments of radium from the U. S. Radium Corporation to retail outlets, including the Chicago vendor of interest here, were accompanied by a certificate which stated, "The gamma radiation from this preparation is due entirely to radium and its derivatives and not to mesothorium or any of its disintegration products."

As mentioned above, it has been impossible to determine the error in individual determinations which may have been present in the early work of Schlundt, Nerancy and Morris.[37] However, certain observations which indicate the results were generally correct are presented in the following text. As stated in their original paper, the calibration of the Wulf-Hess electrometer used for determining the nonemanating radium fraction was based upon the results of Ives, Knowles and Britten[17] who used a duplicate instrument. These authors, in addition to working against known radium sources, checked their calibration against radon seeds implanted in a cadaver in proportion to skeletal mass. They also made observations of the rate of fall of their electrometer fiber produced by radium sources at fixed distances and determined that a radium source placed 37.4 cm. from the instrument produced the same reading as an equivalent amount of radium distributed in a cadaver under their conditions of measurement. Schlundt, Nerancy and Morris repeated these measurements of sources using their own instru-

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ment and determined the ratio of sensitivity of their instrument to that of Ives *et al.* to be 1.19. Their calibration constant of 180×10^{-6} div/sec/microgram Ra in the patient is to be compared to 151×10^{-6} obtained by Ives and to 85.7×10^{-6} reported by Schlundt, Barker and Flinn in 1929.[35] The latter value was obtained from postmortem measurements of the body of a woman who had worked as a dial painter. This value was not used by Schlundt in the Elgin study presumably because of the high probability of enough mesothorium in the cadaver to invalidate the result with respect to radium. As a commentary on the determination, it may be pointed out that at the time of the early measurements, nonexhaled radon represented a rather small fraction of the total radium and therefore relatively large errors would have been of small significance in the final value for total radium content.

The greater part of the total radon in Schlundt's measurements was found in the expired air. This exhaled radon was measured using a Lind electrometer with ionization chambers calibrated directly against radon from known radium solutions.

The largest source of error probably arose from the use of an assumed average respiratory volume of 7.5 liters per minute for all patients. Thus a concentration of $2.097 \times 10^{-12} \times 60/7.5 = 16.8 \times 10^{-12}$ C/Rn/liter was taken to represent 1.0 μgm. of Ra element in the patient. It is apparent that the actual mean radon concentration will be inversely proportional to the true minute volume. However, it is noteworthy that the average minute volume assumed in this early work is identical with the average measured in all patients in the current study. Furthermore, the spread in retention for the group was no greater in Schlundt's measurements than obtained by us after twenty years.

It should also be noted that the ratio of expired to nonexpired radon in Schlundt's measurements was quite constant at each of the two intervals where determinations were made. At the time of the first measurements the average percentage of the retained radium appearing as expired radon was 88 per cent and six months later was 84 per cent. The measurements made by the present authors showed this value to be about 70 per cent after twenty years. Since all experience,[40] as well as unpublished data (*vide infra*) of the present authors obtained from dogs in which this factor was specifically studied, shows that the maximum percentage exhalation of radon occurs at the earliest times after injection and decreases thereafter, it follows that the early values of Schlundt should have been in excess of later values, as is borne out by the combined data compiled in Table II.

This review of the early work with the Elgin Hospital patients reveals no reason to suspect any major source of error. Examinations of radium ampoules prepared for injection about 1928 indicate that in the Elgin study about 4 per cent of the intended dosage may have been lost in the syringe and ampoule and that the actual radium contents of the ampoules may have been about 10 per cent lower than the intended amount. However, these findings can be regarded as little more than indications and in view of lack of more detailed information about the early work, no correction for these possibilities has been applied.

MEASUREMENTS IN THE CURRENT STUDY

In an effort to reduce sampling errors caused by variations in respiratory activity, in the determination of expired radon, a method was devised in which all the radon expired in a period of twenty minutes was quantitatively adsorbed at low temperature on activated coconut charcoal. This technique affords relatively large quantities of radon so that instrumental sensitivity is not a problem and permits measurements of the total volume of gas expired during the sampling. The average minute volume determined in 57 patients was 7.5 liters per minute which is in excellent agreement with the value assumed by Schlundt *et al.*

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TABLE II

MEASUREMENTS OF RADIUM RETENTION IN ELGIN HOSPITAL PATIENTS

Patient	Sex	Age at injection	Injected dose μgm. Ra	Interval from last injection to 1st measurement	R1 First Measurement: % Injected dose as radon	% Injected dose as γ-rays	% Injected dose retained	Rn/(Rn+γ)	Retention μgm.	R2 6 Months after First Measurement: % Injected dose as radon	% Injected dose as γ-rays	% Injected dose retained	Rn/(Rn+γ)	Retention μgm.	R3 253 Months after First Measurement: % Injected dose as radon	% Injected dose as γ-rays	% Injected dose retained	Rn/(Rn+γ)	Retention μgm.	R4 258 Months after First Measurement: % Injected dose as radon	% Injected dose as γ-rays	% Injected dose retained	Rn/(Rn+γ)	Retention μgm.
				Days																				
A	F	22	150	201	4.80	0.67	5.47	0.88	8.2	1.67	0.60	2.27	0.74	3.4	0.69	0.38	1.07	0.64	1.61	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
B	M	27	150	201	3.60	0.40	4.00	0.90	6.0	1.87	0.20	2.07	0.90	3.1	0.26	[illegible]	0.33	[illegible]	0.50	—	—	—	—	—
C	F	63	150	201	2.27	0.20	2.47	0.92	3.7	0.94	0.12	1.06	0.87	1.6	0.22	0.06	0.28	0.79	0.42	—	—	—	—	—
D	F	51	150	201	8.33	0.93	9.26	0.90	13.9	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
E	M	29	160	194	7.82	0.81	8.63	0.91	13.8	2.56	0.88	3.44	0.74	5.5	—	[illegible]	—	—	—	—	—	—	—	—
F	F	56	160	194	2.31	0.56	2.87	0.80	4.6	—	0.44	—	—	—	—	—	—	—	—	—	—	—	—	—
G	F	48	160	194	1.81	0.44	2.25	0.80	3.6	0.00	0.19	—	—	—	—	—	—	—	—	—	—	—	—	—
H	—	—	160	194	2.12	0.25	2.37	0.89	3.8	1.12	0.05	1.17	0.95	1.9	—	—	—	—	—	—	—	—	—	—
I	F	28	180	180	3.28	0.44	3.72	0.88	6.7	1.00	0.06	1.06	0.94	1.9	0.32	0.11	0.43	[illegible]	[illegible]	0.24	0.11	0.35	0.69	0.63
J	F	31	200	166	2.95	0.15	3.10	0.95	6.2	2.05	0.05	2.10	0.98	4.2	0.33	0.16	0.49	[illegible]	[illegible]	0.33	0.12	0.45	[illegible]	[illegible]
K	F	22	200	166	—	0.25	—	—	—	—	—	—	—	—	0.35	0.11	0.46	[illegible]	[illegible]	0.35	0.11	0.46	[illegible]	0.93
L	F	25	260	124	4.62	0.88	5.50	0.84	14.3	1.27	0.69	1.96	0.65	5.1	1.73	0.83	2.56	0.68	6.65	1.74	[illegible]	2.61	[illegible]	6.8[illegible]
M	F	—	380	124	—	0.26	—	—	—	—	0.34	—	—	—	—	—	—	—	—	—	—	—	—	—
N	F	30	360	180	0.50	0.31	0.81	0.62	2.9	1.58	0.25	1.83	0.86	6.6	0.32	0.16	0.48	[illegible]	[illegible]	0.33	0.14	[illegible]	[illegible]	[illegible]
O	F	25	260	23	2.46	0.46	2.92	0.84	7.6	0.92	0.27	1.19	[illegible]	3.1	0.21	0.15	0.36	0.58	0.93	0.26	0.13	0.39	[illegible]	1.01
P	F	23	250	30	2.32	0.44	2.76	0.84	6.9	1.68	0.36	2.04	0.82	5.1	0.64	0.38	1.02	0.63	2.56	—	—	—	—	—
Q	M	33	450	20	3.58	0.35	3.93	0.91	17.7	—	0.29	—	—	—	0.13	0.05	0.18	[illegible]	0.81	0.29	0.05	0.34	0.85	1.54
R	F	32	410	13	—	0.27	—	—	—	—	—	—	—	—	0.56	0.31	0.87	0.64	3.57	0.45	0.30	[illegible]	0.62	3.09
S	F	51	70	60	—	0.71	—	—	—	—	—	—	—	—	0.50	[illegible]	[illegible]	0.65	0.54	0.62	0.29	0.91	0.68	0.64
T	F	18	110	30	7.56	0.62	8.18	0.92	9.0	4.36	0.46	4.82	0.90	5.3	0.65	0.25	0.90	[illegible]	0.99	[illegible]	0.29	0.99	[illegible]	1.09
U	F	28	90	30	—	0.56	—	—	—	—	0.67	—	—	—	0.43	0.21	0.64	0.67	0.58	0.40	0.24	0.64	0.63	0.58
V	M	23	100	30	6.20	0.30	6.50	0.95	6.5	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
W	M	—	90	30	9.56	1.22	10.78	0.89	9.7	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
X	—	—	90	30	4.33	0.33	4.66	0.93	4.2	—	—	—	—	—	—	—	—	—	—	—	—	—	—	—
Rose D.	F	22	200		4.70	0.85	5.55	0.86	11.1	—	—	—	—	—	0.63	[illegible]	0.91	0.69	1.82	—	—	—	—	—
Paul N.	M	23	110		—	—	—	—	—	—	—	—	—	—	0.35	[illegible]	0.42	0.83	0.46	[illegible]	[illegible]	[illegible]	0.81	[illegible]
Edith C.	F	23	260		—	—	—	—	—	—	—	—	—	—	0.19	0.12	0.31	0.61	[illegible]	—	—	—	—	—
Average					4.45*	0.51	5.00*	0.88*	—	1.75†	0.35	2.08	0.84	—	0.40‡	0.20‡	0.60‡	0.69	—	0.42‡	0.19‡	0.62‡	[illegible]	—

* Excluding N.
† Excluding G.
‡ Excluding L.

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TABLE III

COMPARISON OF BODY RADIUM CONTENT ESTIMATED FROM CONCENTRATIONS IN BONE AND FROM *in vivo* MEASUREMENTS

Patient No.	Body wt., kg.	Estimated wt. skeleton, kg.	Wt. bone specimen, gm.	Ra content of specimen, μgm.	Ra content of specimen μgm. $\times 10^4$/gm.	Estimated Ra content of skeleton, μgm.	Ra content estimated in vivo, μgm.	Source of bone specimen
104 (M.C.) Ra injections	67.5	6.8	22.0	.015	6.82	4.0	5.3	Fragments from acetabulum and head of femur
112 (M.K.) Ra injections	69	5.9	77.2	.038	4.92			Skull
			32.1	.005	1.56			Distal fibula
			72.9	.009	1.24			Tarsal bones (tumorous)
			51.2	.006	1.17			Proximal tibia
			38.9	.002	.52			Ankle bones
			272.3	.060	2.20	1.3	1.2	
118* See also Case 4, ref. 2 Drank Ra water	52	5.2	67.8	.048	7.08			Foot bones
			189.4	.120	6.34			Vertebrae
			204.8	.146	7.13			Femur
			150.3	.041	2.73			Ribs
			612.3	.355	5.80	3.0	10.5*	
302 (I.D.) Dial painter	57	5.7	34.2	.028	8.19			Distal femur
			79.6	.065	8.17			Proximal tibia
			40.3	.021	5.21			Distal tibia
			29.5	.015	5.08			Foot bones
			37.2	.017	4.57			Proximal fibula
			78.9	.035	4.44			Calcaneus
			299.7	.181	6.04	3.4	3.8	
313 (R.W.) Dial painter	43.6	4.4	72.0	.010	1.30			Fibula
			107.4	.014	1.39			Tibia
			179.4	.024	1.34	0.6	1.3	

* In vivo measurement in 1941 by Aub, Evans, Hemplemann and Martland.[8]

The adsorbed radon was removed from the charcoal by heating and flushed into one of a dual set of ionization chambers, connected to a Lindeman-Ryerson electrometer (Failla's design—purchased from the Cambridge Instrument Co., Grand Central Terminal, N. Y.). The instrument had been previously calibrated against radon from radium solutions furnished by the National Bureau of Standards. The standard deviation of repeated determinations of expired radon on single patients is estimated as ±14 per cent.[41]

The nonexhaled radon was measured to an accuracy of about 10 per cent through its gamma-ray emission using a calibrated, thallium activated, sodium iodide, crystal scintillation counter.[22]

RESULTS AND DISCUSSION

The 19 patients who were still available of the original 32 injected by Schlundt, *et al.* were remeasured for radium content in May, 1951, and again in July, 1953. This was 235 months, and 261 months respectively, on an average, after the last injection received by the patients in 1931. The measurements were made in the Veterans Building of the Elgin State Hospital using the methods just mentioned. The results are presented in Table II along with the earlier data obtained by Schlundt *et al.*[27] For convenience of the reader the code letters referring to the patients have been retained exactly as in the original manuscript of 1933.

Most of the patients were cooperative

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TABLE IV

MEASUREMENTS OF SMALL SAMPLES OF BONE FROM PATIENT 112 ILLUSTRATING NONUNIFORMITY OF RADIUM CONCENTRATION

Sample No.	Wet weight, gm.	Ra content μgm. $\times 10^{-4}$	Concentration, μgm. $\times 10^{-4}$/gm.	Sources of sample
5C2	.113	.124	1.1	Trabecular bone from head of humerus
9A6	.132	.198	1.5	Cortex of fibula
7C1	.087	.139	1.6	Cortical bone from tibia
8I3	.184	.369	2.0	Endosteal surface of femoral cortex
5C1	.124	.321	2.6	Cortical bone from proximal end of humerus
7I3	.151	.498	3.3	Trabecular bone from distal end of tibia
5C3	.075	.420	5.6	Superior segment of head of humerus
6R	.423	2.410	5.7	Parietal bone of skull
8D7	.131	.878	6.7	Trabecular bone from head of femur
9A8	.082	.779	9.5	Cortex of fibula
6Q	.407	3.948	9.7	Parietal bone of skull
8I2	.120	1.202	10.0	Cortex of right femur
8D6	.088	1.056	12.0	Cortical bone near head of femur

and free from apprehension during the collection of expired radon. With the exception of patient (O) who was combative, these people were generally unconcerned with the procedures and appeared to behave as well as or often better than normal patients. The error of the combined estimates, that is the error in the estimate of the total radium burden, probably does not exceed ± 20 per cent.

Since radium is contained almost quantitatively in the skeleton, these estimates of errors could be substantiated by measurements of bone specimens obtained from other cases of radium poisoning where *in vivo* measurements were made prior to surgery or autopsy. The fresh samples, sealed in glass tubes to prevent loss of radon, were measured in a pressurized gamma-ray ionization chamber. The concentration of radium per gram of fresh bone was multiplied by the estimated total skeletal weight (total skeletal weight was estimated as 10 per cent of the body weight[19]) to obtain the total radium burden. Although it is known that the radium concentration in bone is not uniform,[12,22] the use of large specimens of bone, as was ordinarily the case here, should give reasonably valid results. The data given in Table III show good agreement between radium burdens estimated from autopsy specimens and *in vivo* measurements. The lack of agreement between the results obtained from autopsy samples and the *in vivo* results reported by Aub *et al.*[2] in Patient 118 may be due to the fact that twelve years have elapsed since the *in vivo* determination.

Further evidence of the nonuniform distribution of radium in bone is given in Table IV which shows radium concentrations found, using the radon emanation method, in a number of small portions of bone taken from Patient 112 (M.K.). Areas of high and low concentration were selected using radioautographs of slabs of the bone[22] as a guide. The 10-fold range of concentration observed is substantially the same as that found by Dudley (see ref. 2) using densitometric measurements of radioautographs.

Norris and Evans[31] and Norris and Kisieleski[32] have shown that the retention and excretion of the alkaline earths, including radium, in rats and mice can be adequately represented as "power functions" (which plot as straight lines on log-log paper). Later, Hursh[11] demonstrated

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that excretion of radium from the dog could also be described in this fashion. Unpublished data of the authors, obtained from 2 adult dogs injected with radium, corroborate this finding of Hursh and also supply information pertaining to the behavior of radium fractions contributing to exhaled radon and to retained radon as functions of time after injection. These data are presented graphically in Figure 2 in order to allow comparisons with the human data and to substantiate the applicability of the method of mathematical analysis. As will be brought out in more detail later, if the rate of excretion with time is a power function having a slope, b, then the rate of change of retention may be calculated as a power function with a slope, $b+1$. It will be noted that the retention measured in the one dog which was sacrificed (at 63 days) agrees with the prediction from excretion measurements.

The observed values of measurements of gamma-ray activity of these dogs have been corrected to an equilibrium value during the first thirty days after injection of de-emanated radium on the assumption that the state of the radium parent is such that the growth of Rn follows the theoretical pattern. The results demonstrate that the rate of decrease of the γ-emitting fraction as measured is far less than that of total retention. This convergence of the curves of total retention and the gamma-emitting fraction demonstrates that the expired radon fraction, which is the difference between the two, is decreasing with time.

Measurements of expired radon in general tended to exceed the prediction of the quantity of radium which contributes to this measurement. However, this was not surprising since the dogs hyperventilated themselves appreciably during the collection of the samples. Serial sampling of expired radon as a function of respiratory activity under anesthesia indicated that hyperventilation causes the quantity of Rn exhaled per minute to increase while the concentration of Rn per liter decreases.

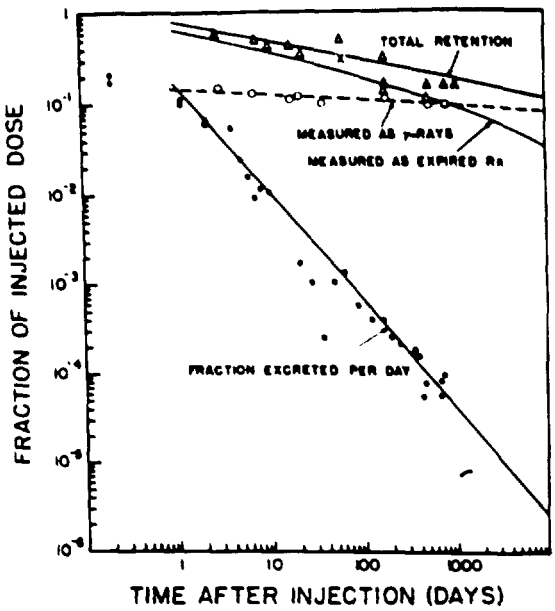

FIG. 2. Radium metabolism in intravenously injected dogs. ● = Measurements of total radium excreted per day $E_t = 0.1 t^{-1.21}$. N = Total retention measured in sacrificed dog. The curve of total retention vs. time is derived from excretion data $R_t = 0.80 t^{-.21}$.

Determinations of retained radium in the living animal:

1. ○ Measured as γ-rays.
2. △ Measured as expired Rn. The line drawn to represent the fraction appearing as expired Rn *vs.* time was derived as the difference between the curves of total retention and the γ-ray fraction.

Reductions in respiratory activity would presumably cause the opposite response.

Since the "power function" can be used to describe over-all radium metabolism in animals, an attempt was made to treat the data from humans in the same fashion. This treatment is presented with the realization that the function may have no particular significance insofar as the *precise* elucidation of metabolic behavior is concerned. Such might be better expressed as the sum of a large number of exponentials and, indeed, the data may be fitted by such a form. However, our inability to deal with the exponential form, both from the standpoint of lack of information and the computational difficulties encountered in

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TABLE V

CONSTANTS OF THE RETENTION FUNCTION OF RADIUM IN HUMANS

Patient	No. of injections	Single dose approximation		Continuous injection approximation	
		A	b	A	b
A	15	.411	−.41	.411‡	−.41‡
B	15	2.254	−.73	2.183	−.74
C	15	.617	−.61	.617‡	−.61‡
I	18	.642	−.58	.715	−.58
J	20	.756	−.57	.676	−.57
O	26	.532	−.56	.434	−.59
P	25	.104	−.26	.078	−.23
T	11	.798	−.50	.523	−.46
Average	18	.577 ± 23%*	−.53 ± .05†	.512 ± 38%*	−.52 ± .055†

* Geometric mean and associated per cent error.
† Arithmetic mean and associated standard error.
‡ Further approximations did not give a better fit than already obtained using the constants from the single dose approximation.

empirically analyzing such a mathematical model, caused us to resort to the "power function" representation which describes well the available information, requires simple mathematical manipulations, and allows the estimation of sample statistics.

The method of injection to which the Elgin group was subjected differed somewhat from that used in the animal experiments. The Elgin patients received multiple equal dosages at weekly intervals whereas the animals were given single injections. However, the information derived from experimental animals allows the constants associated with the retention pattern in humans resulting from a single intravenous injection of radium to be determined, provided the following assumptions are made:

(1) Each dose is handled in like metabolic fashion.
(2) Neither a single dose nor any combination of doses has an effect on the metabolism of other doses.
(3) The retention function associated with each injection is independently described by the relationship:

$$R_t^* = Aqt^b \qquad b<0,\ t\geq 1 \qquad (1)$$

where R_t^* is retention at t units of time after injection, q is the quantity injected, A is a constant which is equal to the fraction of q retained when t is equal to 1, and b is a negative constant.

Following these assumptions, if n repeated doses, q_i, are given at times t_i ($i=1, 2, 3, \cdots, n$) then the retention, R_t^*, at some time $t=t_n+\Delta t\geq 1$ will be:

$$R_t^* = A\sum_{i=1}^{n} q_i(t-t_i)^b. \qquad (2)$$

When all values of q_i are equal to q, expression (2) simplifies to

$$R_t^* = Aq\sum_{i=1}^{n} (t-t_i)^b. \qquad (3)$$

Equation (3) gives the retention at any time $t=t_n+\Delta t\geq 1$ after n equal doses injected at times t_i and describes exactly the retention of radium in the Elgin patients under the above assumptions. For purposes of comparison retention is usually expressed as a fraction, R_t, of the total injected dose. The equivalent expression is immediately obtained by dividing (3) by nq.

$$R_t = \frac{A}{n}\sum_{i=1}^{n} (t-t_i)^b \qquad (4)$$

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However, because of the computational difficulties associated with expressions (2), (3), and (4), the estimation of the retention constants, A and b, by the use of these equations is impractical.

Graphic examination of the behavior of Equation (4) demonstrates that after some period of time, depending upon the value of b, following the nth injection, the contribution from each equal injection to the total retention will be very nearly the same. Inspection of the data indicated that the most probable value of b lay between -0.6 and -0.4. Using these two values of b and with n equal to 18 (the average number of injections per patient) the behavior of R_t in Equation (4) with respect to time was determined graphically. This indicated that by 100 to 200 days after the last of eighteen consecutive weekly injections the fractional retention pattern is essentially that arising from the single injection of a quantity nq given at time $t=0$. Thereafter R_t may be closely approximated as

$$R_t' = At^b. \tag{5}$$

Since the majority of Schlundt's measurements were made later than 100 days after the last injection, the "single dose approximation" (Eq. 5) was applied to the analysis of the multiple dose data, using the method of least squares on the log transforms of both R_t and t (in days) to estimate the constants (A and b) of the retention function. From the Elgin group, 8 patients were selected for whom three consistent ($t_3>t_2>t_1$, $R_{t_1}>R_{t_2}>R_{t_3}$) measurements of retention were available, and the individual retention constants determined (Table v). Figure 3 illustrates graphically the behavior of Equation (4) using the mean values obtained for these constants ($n=18$, $b=-0.53$ and $A=0.58$).

Where the interval between successive injections is small relative to the interval from the last injection to the time of measurement, the discrepancy between the retention measured following a series of discrete injections and the retention that would be measured if the same amount of

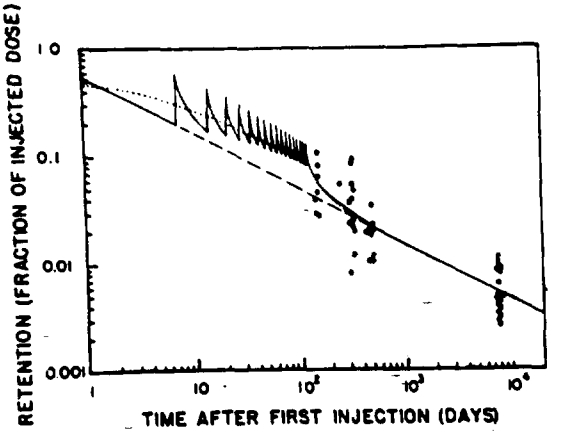

FIG. 3. Retention of radium in Elgin Hospital patients.

— — Single dose approximation $R_t' = 0.58t^{-.53}$

——— Summation of multiple injections

$$R_t'' = \frac{.58}{18}\sum_{i=1}^{18}[t-7(i-1)]^{-.53}$$

Eq. (4) using average constants estimated by the "single dose approximation."

– – – Continuous injection

$$R_t''' = \frac{.51}{18\times 7}\int_0^{18\times 7}(t-18\times 7)^{-.53}d\tau.$$

This continuous injection function is plotted with an adjustment in the time scale which places the times of the discrete injections at the means of the equivalent continuous injection periods.

material were administered at a uniform rate over the same period of time becomes negligibly small. Thus, the retention constants can also be estimated using the continuous injection model:

$$R_t''' = \frac{AC}{CT}\int_0^T (t-\tau)^b d\tau \qquad t \geq T$$

$$= \frac{A}{T(b+1)}\left[t^{b+1}-(t-T)^{b+1}\right] \tag{6}$$

Where A and b are constants of the retention function following a single injection, τ is the dummy integration variable with T being the total time of continuous injection (equivalent to the number of discrete injections times the interval between in-

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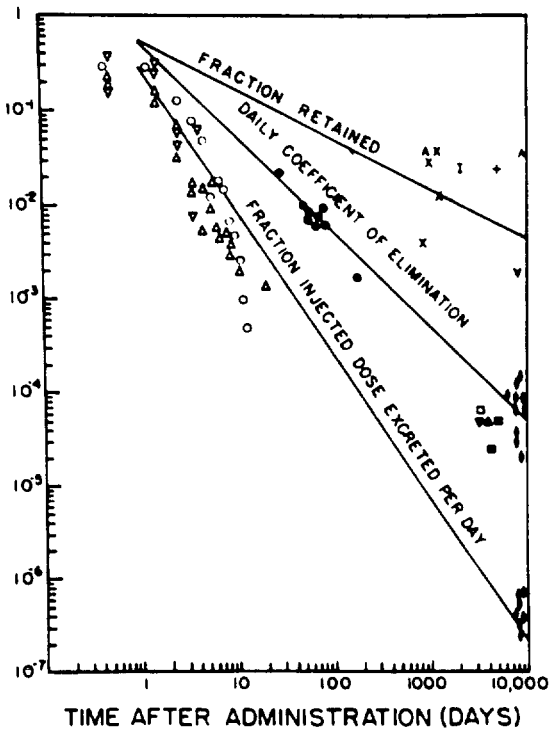

FIG. 4. The lines representing the coefficient of elimination (fraction of body burden excreted per day) and the fraction of the injected dose excreted per day are derived directly from the equation of retention (7). These plots are compared with existing data.

Retention (fraction of injected dose)

- — Current study—average of Elgin patients: $R_t = 0.54t^{-.52}$
- ∧ Current study—early measurement refers to Case VII of Barker and Schlundt[3]
- ∨ Current study—Case III of Barker and Schlundt[3]
- × Barker and Schlundt (oral and intravenous)[3]
- + Stevens (intravenous)[42]
- I Gettler and Norris (oral)[10]

Coefficient of elimination (fraction of body burden excreted per day)

- ♦ Current studies—all subjects
- ■ Schlundt and Failla (dial painters)[38]
- ▼ Aub, Evans, Gallagher and Tibbets (intravenous)[1]
- ▲ Aub, Evans, Gallagher and Tibbets (dial painter)[1]
- ● Aub, Evans, Gallagher and Tibbets ($RaCl_2$ inhalation)[1]
  Values calculated following Evans' assumption of γ-ray representing 55 per cent of the total in the first and last instances. Intermediate points determined by subtracting measured excretion values from retention at period 1.
- □ Craver and Schlundt[7]

Excretion (fraction of injected dose per day)

- ◇ Current studies—all subjects
- △ Seil, Viol and Gordon (intravenous)[38]
- ▽ Seil, Viol and Gordon (oral)[38]
- ○ Rajewsky and Muth (inhalation $RaCl_2$)[33]

jections) in the same units as t, and $C = nq/T$ is the rate of injection. By a method of successive least squares approximations, constants A and b can be estimated. This model can be generally applied under the assumptions made above and will give unbiased results at all times over its interval of definition; whereas, the "single dose approximation" will include a bias unless the times at which retention measurements are made are several months removed from the time of the last injection. This method gives estimates of A and b that are in close agreement with those obtained using the "single dose approximation" method and in cases of repeated or continuous administration provides a more tractable mathematical system of calculation. The constants found using this approach are compared in Table V and in Figure 3 with those obtained by the alternative method. The compatibility between individual retention values and the empirically derived retention function using the continuous injection approximation was found, by Chi-square, to be exceptionally good ($0.80 < P < 0.90$).

It may be noted that the two functions are plotted in Figure 3 for eighteen weekly injections, which is the average number given the 8 patients, the data from whom are used in the previous mathematical analyses. The average number of injections for all the Elgin patients is 19.8 and since the curve is only slightly displaced by somewhat increasing or decreasing this number it is permissible to plot all the available retention data from the Elgin group on this graph using t_{18} as being equivalent to t_n for each patient. This is done (Fig. 3)

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TABLE VI

RATE OF EXCRETION AND COEFFICIENT OF ELIMINATION OF RADIUM IN HUMANS

Patient	Date injected	Dose, μgm.	Date of measurement	Ra burden, μgm.	Excreta collection interval, days	Ra excreted per day, gm. $\times 10^{-12}$	Fraction injected dose excreted per day $\times 10^{-7}$	Fraction Ra burden excreted per day $\times 10^{-6}$	Per cent injected dose retained
Elgin Group A	1931	160	July, 1953	1.70	10.0	60.4	4.0	3.6	See Table II
Elgin Group J	1931	200	July, 1953	.93	9.8	132.0	6.6	14.2	See Table II
Elgin Group K	1931	200	July, 1953	.92	3.0	64.7	3.2	7.0	See Table II
Elgin Group N	1951	360	July, 1953	1.70	7.3	140.0	3.9	8.2	See Table II
Elgin Group S	1931	70	July, 1953	0.69	3.0	18.5	2.6	3.1	See Table II
Elgin Group U	1931	90	July, 1953	0.68	3.0	48.7	5.4	8.4	See Table II
101*	1927	250	Sept., 1951	0.60	-	—	-	—	0.20
103	ca. 1925	-	April, 1953	5.5	51.0	388.5	—	7.1	—
104†	1927	330	June, 1951	12.0	6.0	244.8	7.4	2.0	3.6
112	ca. 1925	-	Feb., 1948	1.1	11.0	175.8		16.0	-
116	1931	—	June, 1951	0.8	3.0	72.7		9.1	—

* Case III, Barker and Schlundt.[3]
† Case VII, Barker and Schlundt.[3]

using the time schedule originally published.[37]

The constants derived from the two methods of mathematical analysis are averaged to give a best estimate of the retention pattern of radium in humans as a function of time in days after a single intravenous injection.

$$R_t = 0.54t^{-.52} \qquad t > 1. \tag{7}$$

The use of the power function has the advantage that, given either the equation of retention vs. time or fraction injected dose excreted per day vs. time the other may be readily derived. In the instance of these data on humans, where the retention line has been derived experimentally, the equation of the line defining the fraction of the injected dose excreted per day as a function of time may be obtained by differentiating the equation of retention (5) which gives

$$\frac{dR_t}{dt} = b.At^{b-1} \tag{8}$$

or substituting the appropriate constants from Equation (7).

$$\frac{dR_t}{dt} = -0.28t^{-1.52} \qquad t > 1. \tag{9}$$

The retention and excretion functions are drawn in Figure 4 according to Equations (7) and (9) respectively along with previously published data for comparison.* Of particular interest are the actual excretion data from the Elgin patients (see Table VI) which are shown to be in good agreement with the prediction. Data from the analysis of excreta of patients other than the Elgin group have shown that no more than 3 per cent of the total radium excreted in long-standing cases is eliminated via the urine (see Table VII). This finding is substantially the same as that reported by Aub *et al.*[1] and by Rajewsky and Muth.[32] Therefore, only fecal specimens of the Elgin patients were analyzed.

TABLE VII

PARTITION OF EXCRETED RADIUM BETWEEN URINE AND FECES IN HUMANS

Patient	Collection interval, days	gm. Ra/day $\times 10^{-12}$ Urine	Feces	Total	Per cent in feces
103	51	5.5	383	388.5	98.6
104	6	3.8	241	244.8	98.4
112	11	3.8	172	175.8	97.8
116	3	1.7	71	72.7	97.7

* It should be noted that although Equation (9) is a daily rate equation, it cannot be used to calculate excretion in any one day at times close to the time of administration. This should be done by integration of (9), namely by using (7).

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The coefficient of elimination (fraction of the total body radium excreted per day) may be calculated by dividing Equation (8) by Equation (5).

$$\frac{\frac{dR_t}{dt}}{R_t} = \frac{b.At^{b-1}}{.At^b} = \frac{b}{t} = -0.52t^{-1}. \qquad (10)$$

From the way this equation is derived, the slope of the corresponding line is always -1 regardless of the slope of the retention line, the only variation being in the intercept. This line is also drawn in Figure 4 and corresponding data derived from other workers are plotted for comparison. One will note that good agreement is also obtained in this case. The data of Aub *et al.*[1] obtained from a man who had inhaled a quantity of radium chloride also follow this pattern closely, indicating that inhalation of a soluble salt is followed by rapid solution and removal from the lung as opposed to the behavior noted by Marinelli *et al.*[24] following inhalation of insoluble radium sulfate.

If a person receives uniform daily injections or continuous administration of radium chloride over a period of time, the radium burden at any time t in days while treatment is continuing may be calculated. For this purpose Equation (7) is multiplied by its differential element, dt, and integrated from one to t. To this the fractional retention at the end of one day must be added and the entire function multiplied by the daily dosage, C, which gives

$$R_t = C[1.12(t^{.48}-1)+0.54] \quad t \geq 1. \qquad (11)$$

This function would be particularly useful if applicable to situations where the subject ingests an approximately constant amount of radium daily, as is the case with the naturally occurring radium content of food and water. Although it is ordinarily considered that the retention of orally administered radium is less than with intravenous injection, there is little or no direct information to substantiate this belief in the case of humans. On the contrary, it may be seen by reference to Figure 4 that data obtained following oral administration as well as the single case of inhalation of soluble radium salts follow the pattern found for intravenous administration. The work of Hursh and Gates,[16] Hursh[15] and Shandley[29] indicates that with an estimated daily radium dosage in food and water of 1.0×10^{-12} gm. a human retains 1.18×10^{-10} gm. Ra at the end of sixty-seven years. Substituting these values for C and for t in Equation (11) one obtains a value of 1.43×10^{-10} gm. Ra which is in surprisingly good agreement with Hursh's results when all the uncertainties are considered. Unfortunately, this is the only instance where both the daily radium dosage from natural sources and the radium content of comparable unexposed individuals is known. However, the agreement obtained in the above comparison suggests that such ingested radium is metabolized to the same extent as with intravenous injection.

From the preceding discussion it is apparent that any concept of a well defined "biologic half-time" of radium in bone is untenable. Schlundt, Nerancy and Morris,[27] and later Hoecker,[11] approximated constants for radium excretion in the Elgin patients on the assumption that the function was of the form of a single exponential. Hoecker also pointed out the possibilities of better describing the data with the power function. Aub *et al.*[1] have also attempted to describe radium retention in humans as a single exponential function. It seems evident that this technique will allow approximations only over limited periods of time.

If the equivalent Ra values represented by γ-ray activity and expired radon in the Elgin patients are viewed separately, it is noted that the rate of decrease of the γ-ray fraction with time is considerably less than that of either expired radon or total retention. This is qualitatively identical to the pattern described above in dogs. However, man appears to retain a smaller part of the injected dose in the γ-ray fraction and to lose it somewhat more rapidly. The data are plotted in Figure 5 and serve to further

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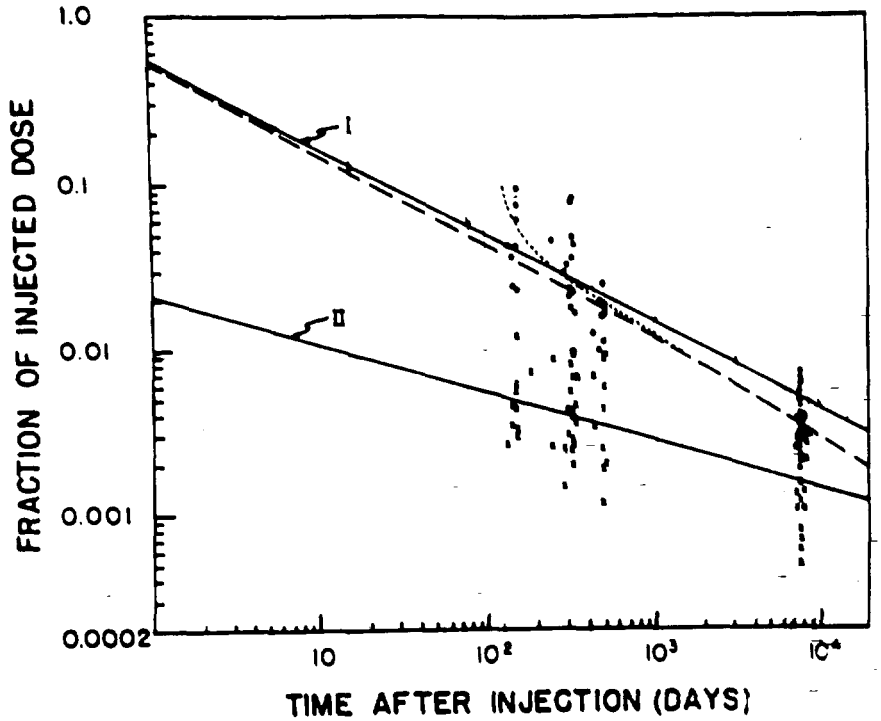

FIG. 5. Separate analysis of the fractions measured as expired Rn and as γ-rays in humans.
I Total retention following a single intravenous dose of radium $R_t = 0.54t^{-.48}$
II Fraction of single dose measured as γ-rays —individual measurements plotted as x, $\gamma_t = 0.021t^{-.28}$
- - - Fraction of single dose measured as expired Rn (Curve I–Curve II)
- - - - - Behavior of expired Rn fraction following the last of 18 injections of 10 μgm. Ra each at intervals of one week —individual measurements plotted as ●.

$$Rn_t = \frac{0.54}{60.48}[t^{.48} - (t-126)^{.48}] - \frac{.021}{89.71}[t^{.715} - (t-126)^{.715}]$$

illustrate the disporportionation of the two fractions as a function of time.

Since the γ-ray fraction in dogs was found to continue as a straight line function with time on the log-log plot while the expired Rn fraction did not, it is reasonable to assume that the same situation exists with respect to the human data. Therefore the equation of the γ-ray fraction has been derived using the "single dose approximation" method described earlier. Because of the small negative slope which exists in this case, the error in the measurements taken close to the last injection is small and the equation of the γ-ray fraction following a single intravenous injection is closely approximated as

$$\gamma_t = 0.021t^{-.28}. \qquad (12)$$

The fractional retention appearing as expired Rn after a single injection of radium, as indicated in Figure 5, is the difference between the single dose total retention and γ-ray functions

$$Rn_t = 0.54t^{-.48} - 0.021t^{-.28}. \qquad (13)$$

In order to best describe the results of measurements of the expired Rn fraction following multiple doses of radium in the Elgin patients the continuous injection approximation method has been used. Again the average number of injections (eighteen) has been used as n for all subjects. Using the continuous injection approximation, the fraction of the injected dose measured as expired radon may be calculated as

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$$Rn_t = \frac{0.54\int_0^{18\times 7}(t-\tau)^{-.92}d\tau - 0.021\int_0^{18\times 7}(t-\tau)^{-.25}d\tau}{18\times 7} \quad (14)$$

The behavior of this function with time after the end of the injection period is shown graphically in Figure 5 along with the actual measurements.

This continuing difference in behavior of these two fractions suggests that Ra may be metabolized in at least two distinctly different compartments at considerably different rates. It is of interest to speculate on the possible relationship between the more slowly metabolizing γ-ray component and the highly localized areas of high Ra concentration ("hot spots") which have been demonstrated in the bones of long-standing cases.[2,12,22] That the "hot spots" are mainly responsible for the γ-ray fraction is strongly suggested since they must also of necessity be metabolized at an extremely low rate or their identity would be lost. However, there exists no other evidence which relates to this hypothesis.

Inspection of Table II demonstrates that, in these long-standing cases of radium poisoning, an average of 70 per cent of the radon produced in the body is exhaled. All values necessary to these calculations were measured directly. This value of 70 per cent radon exhaled is considerably in excess of that of 45 per cent reported by Evans[9] and presently widely accepted as a basis for estimation of radium body burdens. Evans calculated total radon expired on the basis of an assumed respiratory minute volume and the radon content of 1 liter of expired air. It seems that Evans' use of an assumed breathing rate of 5 liters/min. for all patients[8] is largely responsible for this discrepancy. In the work reported here a total of 169 twenty minute breath collections were made from 19 men and 38 women under resting conditions. The resulting average value of 7.5 liters/min. is sufficient to account for the above difference in expired radon percentages. The wide deviation around the average of 7.5 l/min. (4.0 to 13.2 l/min.) encountered in measurements of minute volumes shows the inadvisability of using such an average value for accurate calculation of expired radon in individual cases.

The reported presence of MsTh, in many of Evans' early cases, may also have contributed to a lowered value for the fraction of radon expired. The short half-life (54.5 sec.) of thoron prevents its expiration to the same extent as radon and, in addition, there is more gamma radiation associated with 1 μc. of MsTh, than with 1 μc. of Ra. The magnitude of these possible discrepancies has been discussed in detail by Evans.[2]

SUMMARY AND CONCLUSION

The concept of a well defined biological half-time of radium in bone is inconsistent with the long term data presented and an alternative is offered. Previously published information,[14,31,32] which shows that the retention and excretion of radium in animals may be represented as power functions, has been extended to the analysis of comparable studies in humans. The data presented are compatible with this form as are existing data in the literature. The use of the power function enables the derivation of the equation of retention from that of the excretion function or vice versa.

Where persons are exposed to soluble radium salts at a more or less constant level over an extended period of time, the application of the power function may be extended to predict radium burdens with time or to estimate the retention pattern following cessation of exposure.

There is substantial agreement among students of the subject that the presence of 0.1 μgm. of radium "fixed," that is, not being rapidly excreted, in the body has not been observed to be accompanied by deleterious effects, and therefore this quantity is currently defined as the permissible burden for man.[30] However, the relationship of radium burden to time has not been positively introduced as a factor. The data

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presented indicate that the proper placement of the time of exposure in chronological time is of great importance in the prognosis of a given case. Since methods are available to determine both total radium burden and daily excretion of radium, it is now possible to use the daily coefficient of elimination as an index of elapsed time since exposure to a single equivalent dose of radium provided, of course, that soluble salts are known to have been involved and that allowance is made for the possibility of very recent exposures. Thus it is possible to estimate more certainly the course to be taken with regard to a specific individual.

The retention of intravenously injected radium in the human has been measured as 0.6 per cent of the original dose after twenty-two years. In this group of patients there was no noticeable effect of age or sex on the pattern observed; however, the group was largely composed of young, adult females and the numbers of males and old adults were so small as to make the observation inconclusive.

The behavior of the expired and retained radon fractions with time have been studied and described and the possible relationship of the retained radon fraction to "hot spots" is discussed.

The data include measurements of rate of radium excretion, concentrations in bone and comparisons of estimates of body radium burdens from *in vivo* determinations and from measurements of autopsy or biopsy specimens.

An average of 70 per cent of the total radon produced in long-standing cases of radium retention is exhaled.

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REFERENCES

1. Aub, J. C., Evans, R. D., Gallagher, D. M., and Tibbets, Dorothy M. Effects of treatment on radium and calcium metabolism in human body. *Ann. Int. Med.*, 1938, *11*, 1143-1463.
2. Aub, J. C., Evans, R. D., Hempelmann, L. H., and Martland, H. S. Late effects of internally-deposited radioactive materials in man. *Medicine*, 1952, *31*, 221-329.
3. Barker, H. H., and Schlundt, H. Detection, estimation and elimination of radium in living persons given radium chloride internally. II. Am. J. Roentgenol. & Rad. Therapy, 1930, *24*, 418-423.
4. Behnke, A. R., and Willmon, T. L. Gaseous nitrogen and helium elimination from body during rest and exercise. *Am. J. Physiol.*, 1941, *131*, 619-626.
5. Blum, T. Osteomyelitis of mandible and maxilla. *J. Am. Dental Assoc.*, 1924, *11*, 802-805.
6. Castle, W. B., Drinker, K. R., and Drinker, C. K. Necrosis of jaw in workers employed in applying luminous paint containing radium. *J. Indust. Hyg.*, 1925, *7*, 371-382.
7. Craver, L. F., and Schlundt, H. Parathyroid extract and viosterol treatment of radium poisoning. *J.A.M.A.*, 1935, *105*, 959-960.
8. Evans, R. D. Protection of radium dial workers and radiologists from injury by radium. *J. Indust. Hyg. & Toxicol.*, 1943, *25*, 253-269.
9. Evans, R. D. Radium poisoning: II. Quantitative determination of radium content and radium elimination rate of living persons. Am. J. Roentgenol. & Rad. Therapy, 1937, *37*, 368-378.
10. Gettler, A. O., and Norris, C. Poisoning from drinking radium water. *J.A.M.A.*, 1933, *100*, 400-402.
11. Hoecker, F. E. Significance of absorbed radium as indicated by coefficient of elimination. *J. Indust. Hyg. & Toxicol.*, 1944, *26*, 289-295.
12. Hoecker, F. E., and Roofe, P. G. Studies of radium in human bone. *Radiology*, 1951, *56*, 89-98.
13. Hoffman, F. L. Radium (mesothorium) necrosis. *J.A.M.A.*, 1925, *85*, 961-965.
14. Hursh, J. B. Excretion of radium by dogs after single intravenous injection. Quarterly Tech

1133583

Report, University of Rochester, AEC Project, January 1–March 31, 1952, UR, 205, 6–10.

15. Hursh, J. B. Radium content of public water supplies. University of Rochester, AEC Project, UR 257 (1953)

16. Hursh, J. B., and Gates, A. A. Body radium content of individuals with no known occupational exposure. *Nucleonics*, 1950, *7*, No. 1, 46–59.

17. Ives, J. E., Knowles, F. L., and Britten, R. H. Health aspects of radium dial painting. III. Measurements of radioactivity in workers. *J. Indust. Hyg.*, 1933, *15*, 433–446.

18. Lange, K., and Evans, R. D. Absorption of radon through skin and its exhalation through lungs. *Radiology*, 1947, *48*, 514–516.

19. Lisco, H. The standard man. Quarterly Report, Biological and Medical Division, Argonne National Laboratory, ANL 4253, 96–101, November, 1948 to February, 1949.

20. Looney, W. B., Editor. Radium Toxicity Program. Progress report of clinical studies on twenty-four patients. ANL Report 4666 (1951).

21. Looney, W. B., Hasterlik, R. J., Brues, A. M. and Skirmont, E. Clinical investigation of chronic effects of radium salts administered therapeutically (1915–1931). To be published in Am. J. Roentgenol., Rad. Therapy & Nuclear Med., June, 1955.

22. Looney, W. B., and Woodruff, Lois A. Investigation of radium deposition in human skeleton by gross and detailed autoradiography. *A.M.A. Arch. Path.*, 1953, *56*, 1–12.

23. Marinelli, L. D., Miller, C. E., and Gustafson, P. F. Quantitative determination of gamma-ray emitting elements in living persons. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., April, 1955, *73*, 661–671.

24. Marinelli, L. D., Norris, W. P., Gustafson, P. F., and Speckman, T. W. Transport of radium sulfate from lung and its elimination from human body following single accidental exposures. *Radiology*, 1953, *61*, 903–915.

25. Martland, H. S. Histopathology of certain anemias due to radioactivity. *Proc. New York Pathol. Soc.*, N. S., 1926, *26*, 65–72.

26. Martland, H. S. Occupational poisoning in manufacture of luminous watch dials. *J.A.M.A.*, 1929, *92*, 466–473; 552–559.

27. Martland, H. S. Occurrence of malignancy in radioactive persons. *Am. J. Cancer*, 1931, *15*, 2435–2516.

28. Martland, H. S., Conlon, P., and Knef, J. P. Some unrecognized dangers in use and handling of radioactive substances. *J.A.M.A.*, 1925, *85*, 1769–1776.

29. Martland, H. S., and Humphries, R. E. Osteogenic sarcoma in dial painters using luminous paint. *Arch. Path.*, 1929, *7*, 406–417.

30. Maximum permissible amounts of radioisotopes in human body and maximum permissible concentrations in air and water. National Bureau of Standards, Handbook 52 (1953).

31. Norris, W. P., and Evans, H. B. Studies of metabolism and toxic action of injected radium. CH-3852, AECD-1965, 1946.

32. Norris, W. P., and Kisieleski, W. E. Comparative metabolism of radium, strontium and calcium. *Cold Spring Harbor Symposia on Quantitative Biology*, 1948, *13*, 164–172.

33. Rajewsky, B., and Muth, H. Untersuchungen zum Problem der Radiumvergiftung; die Ausscheidung radioaktiver Substanz aus dem menschlichen Körper (bei zwei Radiumvergiftungsfällen gewonnene Untersuchungsergebnisse). *Strahlentherapie*, 1952, *88*, 261–275.

34. Reitter, G. S., and Martland, H. S. Leucopenic anemia of regenerative type due to exposure to radium and mesothorium. Am. J. Roentgenol. & Rad. Therapy, 1926, *16*, 161–167.

35. Schlundt, H., Barker, H. H., and Flinn, F. B. Detection and estimation of radium and mesothorium in living persons. I. Am. J. Roentgenol. & Rad. Therapy, 1929, *21*, 345–354.

36. Schlundt, H., and Failla, G. Detection and estimation of radium in living persons. III. Normal elimination of radium. Am. J. Roentgenol. & Rad. Therapy, 1931, *26*, 265–271.

37. Schlundt, H., Nerancy, J. T., and Morris, J. P. Detection and estimation of radium in living persons. IV. Retention of soluble radium salts administered intravenously. Am. J. Roentgenol. & Rad. Therapy, 1933, *30*, 515–522.

38. Seil, H. A., Viol, C. H., and Gordon, M. A. Elimination of soluble radium salts taken intravenously and per os. *Radium*, 1915, *5*, 40–44.

39. Shandley, P. D. Radium content of common foods. University of Rochester AEC Project, UR 255 (1953).

40. Silberstein, H. E. Radium poisoning; survey of literature dealing with toxicity and metabolism of absorbed radium. AEC Document, 2122, 1945.

41. Stehney, A. F., Norris, W. P., Lucas, H. F., and Johnston, W. H. Method for measuring rate of elimination of radon in breath. Am. J. Roentgenol., Rad. Therapy & Nuclear Med., May, 1955, *73*, 774–784.

42. Stevens, R. H. Radium poisoning. *Radiology* 1942, *39*, 39–47; 739.

43. Tobias, C. A., Jones, H. B., Lawrence, J. H. and Hamilton, J. G. Uptake and elimination of krypton and other inert gases by human body *J. Clin. Investigation*, 1949, *28*, 1375–1385.

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