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RADIUM-INDUCED MALIGNANT TUMORS IN MAN

ABSTRACT: *The incidence of radium-induced malignant tumors and blood dyscrasias was related to current or preterminal radium burden measurements and to retrospective estimates of maximum radium burdens for a series of 293 persons, most of whom acquired radium burdens in the period, 1918 to 1933. The 46 malignant diseases included 23 bone sarcomas, 16 neoplasms of the skull (principally mastoid and paranasal air cell carcinomas), and 7 leukemias and aplastic anemias. Retrospective estimates of maximum radium burdens were made by application of the appropriate power function for ingestion or for multiple injections. The power function parameters used here ($a = 0.30$ and $b = -0.44$) were recently derived by an analysis of data from long-term studies on 8 patients for whom suitable data are available. The lowest estimated maximum radium burden for the bone sarcoma cases was 6.72 μCi, and that for carcinoma of the maxilla was 1.23 μCi. The comparable value for radium-attributed leukemias and other blood dyscrasias was over 50 μCi. Based on the estimated maximum initial burden, these data imply at least a 12-fold margin of safety in the maximum permissible level for internally deposited radium.*

INTRODUCTION

For many years we have been engaged in an investigation of the long-term effects of radium deposition in man. For the present symposium we have been asked to review and interpret our data as they bear on the subject of radium-induced malignant tumors. As a result of this

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emphasis on oncogenesis, this contribution will be highly selective and will not attempt to cover many other aspects of the consequences of radium deposition in skeletal tissues viewed after a considerable lapse of time.

POPULATION AVAILABLE FOR STUDY

Although the largest group of cases that we have studied was exposed occupationally, the cases have been drawn from two principal sources: industrial and iatrogenic. Industrial exposure occurred mainly in the dial painting industry although we have also studied several chemists who worked at extraction and purification of radium. The principal route of entry into the body in the dial painters and chemists was ingestion, along with a smaller possibility of inhalation. In the latter case, most of the inhaled particles would have passed through the gastro-intestinal tract by the clearing action of the tracheobronchial cilia. We have acquired the names of approximately 250 individuals who worked at radium dial painting in Illinois before 1930. Of these persons who were exposed to radium occupationally, we have studied 185 by whole-body gamma-ray spectroscopy and by skeletal radiography. We have examined only a few of the 200 or so persons who started to work after 1930, since all those that have been measured have small radium burdens.

The iatrogenic group of cases resulted from the administration of radium orally or by intravenous or intramuscular injections up to 1933 for treatment of a variety of diseases. These ailments included, among others, general malaise and fatigue, myocarditis, arthritis, poliomyelitis, venereal disease, and mental disorders.[1, 2] In some cases in our series, including children, radium was given orally as a tonic. Many of the patients were unaware that they had acquired radium, and it was only as a result of the suspicions of knowledgeable physicians that they were discovered actually to bear a radium burden. One series of at least 41 patients was treated in this way from 1931 to 1933 in a state mental hospital not far from Chicago.[2] We have studied or have other pertinent knowledge of 36 of these cases found by a deliberate search of records. In addition, we have accumulated another series of 36 patients who received radium from personal physicians. Many of these cases have come to our attention because of pathological changes that they developed, and they represent a very small sample out of the several thousand persons presumed to have been so treated by their doctors.

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THEORETICAL CONSIDERATIONS

If these studies are to shed any light on the problem of maximum permissible body burdens of radium, and if the malignant tumor experience is to be used as the principal criterion for evaluating operational safety, then a suitable method of expressing radium burden must be selected for this purpose. Whole-body counting techniques involving gamma-ray spectroscopy have made possible the rather exact measurement of radium in the human body down to levels approaching 0.001 μCi. However, delight in these recent determinations should not obscure the fact that they have been made 25 to 45 years after the radium deposit was acquired. During this period the radium burden has followed a pattern of decreasing retention that has been shown to be mathematically describable in fairly simple terms by a power function.[4, 5] Experiments with large populations of mice have led to the suggestion that the initial, or maximum, burden may be more important in evaluating tumor production by internally deposited radionuclides than any other index or measurement.[6] For this reason we have attempted in this paper and elsewhere[7, 8] to evaluate the disease experience of our patients in terms of a retrospective estimate of maximum radium burden.

The calculations of these estimates have been based on the power function and its applications to the varying modes of intake of radium. The single exponential function may provide a better description for radium retention over the more recent portion of the time span than does the power function, but it cannot be used to estimate the initial or maximum body burden except in the case of a single injection.[7] Any estimate of initial body burden computed on the basis of sums of exponentials presupposes a knowledge of the parameters of early exponential curves, a knowledge that is in fact non-existent.

After a single intravenous injection, retention of radium according to the power function proposed by Norris *et al.*[4, 5] is given by

$$R_{inj}(t) = a\,t^{b}, \quad (t \geqq 1) \qquad (1)$$

where t = time after administration, a is a constant that provides the intercept at unit time, and b has a negative value and is the slope of the straight line given by the function on a double-log grid. Norris *et al.* proposed power function parameters of $a = 0.54$ and $b = -0.52$ for radium retention, and these values for a and b have been widely used. More recently,[7] we have re-examined the question after further investigation involving several additional radium measurements of the same state mental hospital patients that Norris had studied. On the basis of our more recent analysis we have arrived at somewhat different mean

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power function values: $a = 0.30$, $b = -0.44$. This average power function was based on an arithmetic mean of the slopes and a geometric mean of the intercepts of individually determined, best-fitting power functions for 8 patients for whom appropriate data were available.[7] In this series, the patient who held on to radium most tenaciously had a power function given by $a = 0.18$, $b = -0.22$, while the patient who lost radium most rapidly had values of $a = 0.89$, $b = -0.63$.

Where radium is acquired orally, as in the case of the dial painters, the amount of radium retained at t days after cessation of unit daily absorption during F days can be shown to be given by

$$R_{oral}(F, t) = \frac{a}{b+1} \left[(t+F)^{b+1} - t^{b+1}\right]. \qquad (2)$$

Fig. 1 illustrates the pattern of radium retention after cessation of ingestion given by Equation (2) and the new power function parameters for a number of selected ingestion periods. When $F = 1$ day, the retention curve after 90 days becomes identical with the familiar power function straight line on a log-log plot that holds for a single intravenous injection. As the ingestion period becomes longer, the earlier portion of the retention curve becomes flatter. At longer times after the end of the ingestion period, the slopes of the curves begin to approach that for a single injection.

The experimental support for this mathematical formulation was reported at the Second International Congress on Radiation Research.[9] The power function parameters for retention, after a single intravenous injection in mice, were shown to hold for retention after radium feeding periods of varying length. This correspondence of data supports the assumption that ingestion over a period of days can be considered to be the equivalent of the integral of a series of daily intravenous injections over the same period. In this paper this assumption, which was verified experimentally with mice, will be applied to man in order to evaluate the human experience that involved two basic routes of administration.

The point of maximum retention, which occurs at the end of the feeding period, F, is given by

$$R_{oral}(F, 0) = \frac{a}{b+1} F^{b+1} \qquad (3)$$

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In this equation the end of the ingestion period marks the beginning of the time period after cessation of administration, i.e., $t = 0$. The notation used here differs slightly from that of Norris[5] but the mathematical formulation is the same.

For each case where radium was acquired orally, we computed a ratio, Q, in which the radium burden at the end of the ingestion period was divided by the radium at time, t, after cessation of ingestion:

$$Q = \frac{R_{oral}(F, 0)}{R_{oral}(F, t)} \tag{4}$$

This quotient represents the ratio of the maximum radium burden to any measured burden at time t thereafter and hence provides the factor by

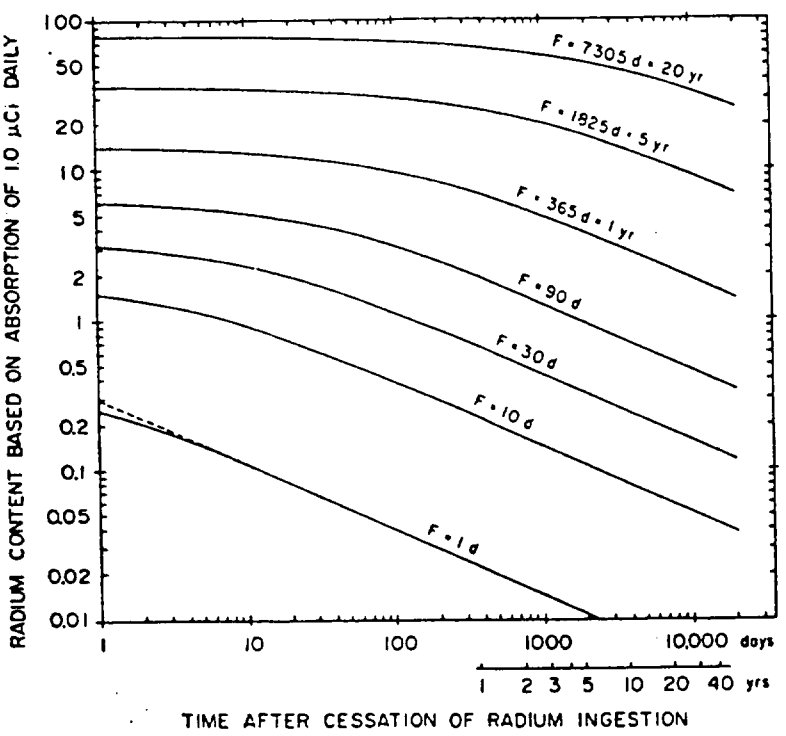

Figure 1. Log-log plot of radium retention after cessation of oral ingestion for ingestion periods (F) of selected lengths of time. Daily absorption of 1.0 μCi is arbitrarily assumed. Power function parameters: $a = 0.30$, $b = -0.44$.

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which the maximum burden was greater than the subsequently measured amount. For any individual measurement the maximum burden can then be estimated from the magnitude of Q and the whole-body radium measurement:

$$\text{Estimated maximum} = Q \times (\text{measured radium burden}), \quad (5)$$

Sample retention values for a selected number of F periods and t intervals after cessation of ingestion are presented in *Table 1*. These computations are based on the parameters of the new mean power function, $a = 0.30$ and $b = -0.44$, and on the assumption that 1.0 μCi was absorbed into the body each day. The second column for each ingestion period gives the Q ratios, which are dimension-free values. Extensive tables such as these were also used to generate the curves shown in *Fig. 1*.

For the radium dial painters whose work history was known, the length of the ingestion period, F, was computed in days on the assumption that ingestion occurred throughout the period at the same rate because of consistency in personal work habits. This computation does not correct for absence from work on weekends, holidays, and vacations but is nevertheless a reasonable approximation. In the cases of those dial painters whose work history straddled January 1, 1926, we have ignored any work period subsequent to that date on the assumption that the bulk of the ingestion occurred before the practice of pointing the brushes between the lips was discontinued.

In the cases where radium was acquired medically by multiple injections, another approach was used to compute the maximum burden. Since these injections were typically given at weekly intervals, computer programs were devised to sum individual power function retention curves at 7-day intervals for n number of injections. A typical curve is given by *Fig.* 2 which shows the step-like increase in body burden with each succeeding standard 10 μCi injection as well as the changing shape of the retention curve with each successive injection when plotted on a log-log grid. This figure also depicts the retention of radium after a series of 15 weekly injections when such retention is described by the new average power function parameters. For cases where the number of injections is known, or can be surmised with reasonable certainty from the known practices of the physicians involved, the maximum body burden can be estimated on the basis of the number of injections and the power function parameters. *Table 2* illustrates the retention values computed for selected time periods after weekly injections of 10 μCi radium for a selected number of injection periods. The radium burden obviously reaches a maximum with the final 10 μCi injection in any series of injections. The para-

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Table 1. Values of retained radium (R) and ratio (Q) computed for t days after cessation of periods of ingestion F days in length.*

Days after cessation of ingestion	Length of ingestion period (F)									
	1 day		30 days		183 days		365 days		1825 days	
	R	Q	R	Q	R	Q	R	Q	R	Q
0	0.536	1.00	3.598	1.00	9.906	1.00	14.58	1.00	35.91	1.00
1	0.254	2.11	3.129	1.15	9.401	1.05	14.07	1.04	35.39	1.01
2	0.201	2.66	2.941	1.22	9.177	1.08	13.84	1.05	35.14	1.02
3	0.173	3.09	2.804	1.28	9.006	1.10	13.66	1.07	34.95	1.03
7	0.124	4.33	2.454	1.47	8.524	1.16	13.14	1.11	34.40	1.04
30	0.0667	8.03	1.707	2.11	7.187	1.38	11.64	1.25	32.64	1.10
100	0.0394	13.58	1.118	3.22	5.583	1.77	9.64	1.51	29.94	1.20
350	0.0228	23.52	0.671	5.36	3.783	2.62	7.01	2.08	25.38	1.42
1,000	0.0144	37.32	0.428	8.41	2.530	3.92	4.88	2.99	20.23	1.78
3,500	0.0083	64.71	0.248	14.52	1.497	6.62	2.95	4.94	13.70	2.62
10,000	0.0052	102.76	0.156	23.02	0.950	10.42	1.89	7.72	9.16	3.92
15,000	0.0044	122.76	0.131	27.52	0.796	12.44	1.58	9.21	7.76	4.63
20,000	0.0038	139.36	0.115	31.22	0.702	14.11	1.40	10.44	6.88	5.22

* Daily absorption of 1.0 μCi assumed. Power function parameters $a = 0.30$, $b = -0.44$.

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Table 2. Values of retained radium computed for t days after n weekly injections of 10 μCi.*

Days after last injection	*No. of weekly injections*							
	1	*5*	*10*	*15*	*20*	*25*	*30*	*40*
0	10.000	13.691	16.435	18.579	20.415	22.052	23.548	26.237
1	3.000	6.564	9.282	11.415	13.244	14.876	16.369	19.053
2	2.211	5.664	8.357	10.479	12.301	13.929	15.418	18.097
3	1.850	5.204	7.873	9.984	11.799	13.423	14.908	17.582
7	1.274	4.319	6.897	8.966	10.756	12.362	13.833	16.489
30	0.671	2.886	5.090	6.961	8.623	10.136	11.538	14.091
100	0.395	1.871	3.532	5.046	6.447	7.760	9.000	11.306
350	0.227	1.120	2.196	3.232	4.234	5.205	6.147	7.957
1,000	0.143	0.713	1.416	2.109	2.792	3.466	4.132	5.437
3,500	0.082	0.412	0.824	1.233	1.641	2.047	2.451	3.254
10,000	0.052	0.260	0.520	0.780	1.039	1.298	1.557	2.072
15,000	0.043	0.217	0.435	0.653	0.870	1.087	1.304	1.737
20,000	0.038	0.192	0.384	0.575	0.767	0.958	1.150	1.532

* Power function parameters $a = 0.30$, $b = -0.44$.

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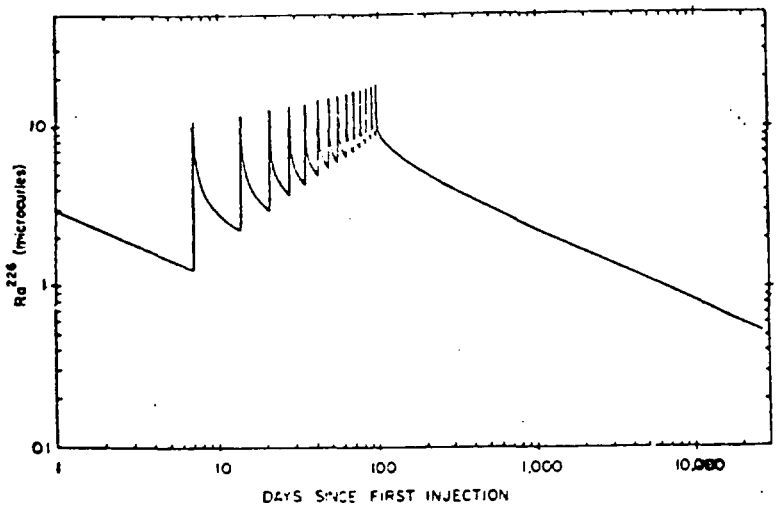

Figure 2. Log-log plot of radium body burden during and after 15 weekly injections of 10 μCi each calculated in accordance with a newly derived power function, $R = 0.30\ t^{-0.44}$.

meters for the average power function ($a = 0.30$, $b = -0.44$) were used for all the retrospective estimates reported here, except as otherwise noted.

MALIGNANT TUMORS IN DIAL PAINTERS

The malignant tumor experience among the dial painters up to September, 1967, is presented in *Tables 3* through *6*. These tables identify the patients by code number and, where known, give the year of birth, work period, pathological diagnosis, date of death, the most recent radium body burden, and the estimated maximum burden based on the mean power function with $a = 0.30$ and $b = -0.44$. In all, 41 patients developed 44 malignant tumors or fatal blood dyscrasias.

Table 3 lists 13 cases of malignant tumors primarily in skeletal tissues. Radium burden data are known for 8 of these cases. While the current or preterminal radium burdens range from 0.81 to 7.61 μCi, the estimated maximum burdens range from 6.72 to 63.44 μCi. Five cases were not studied and the information for these persons is largely derived from death certificates. Case 03–665 may actually have had lymphosarcoma rather than a bone sarcoma, and the location of the primary tumor is not known for case 03-661.

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Table 3. Malignant tumors in radium dial painters as a result of occupational exposure. A. *Tumors principally of skeletal tissues.*

Case No.	Year of Birth	Work period	Diagnosis (year of diagnosis)	Living (1967) or dead	Radium body burden (μCi) Current or preterminal	Radium body burden (μCi) Est. maximum $a = 0.30$ $b = -0.44$
03–455	1906	7/22– 8/23	Fibrosarcoma, Lt. radius (1935)	L	0.81	6.72
03–402*	1905	7/23– 7/26	Fibrosarcoma, Lt. femur (1954)	L	1.06	6.99
03–649†	1906	10/24–10/50	Fibrosarcoma, Rt. ischium (1954)	D	1.30	8.89
03–619	1903	8/22– 4/23	Fibrosarcoma, Lt. femur (1962)	D	1.50	16.14
03–401	1900	6/23– 4/25	Fibrosarcoma, Lt. leg (1963)	D	2.29	15.38
03–671	1906	7/22– 9/22	Fibrosarcoma, Lt. femur (1953)	D	3.82	66.49
03–584	—	—	Osteogenic sarcoma, Rt. pelvis (1958)	D	6.00	—
03–648‡*	1903	9/21– 9/22	Fibrosarcomas, Lt. femur and Rt. humerus (1956)	D	7.61	63.64
03–660	1907	—	Spindle-cell sarcoma, neck (1936)	D	Not studied	—
03–661	1906	—	Generalized sarcoma (1934)	D	Not studied	—
03–665	1909	—	Sarcoma, retroperitoneal lymph glands (1930)	D	Not studied	—
03–680	1906	—	Osteogenic sarcoma, Lt. humerus (1946)	D	Not studied	—
03–800	1909	—	Osteogenic sarcoma, Lt. femur (1945)	D	Not studied	—

* Each of these two cases also had malignant tumor of mastoid; see *Table 4.*
† Case 03–649 also listed as 01–023 (M.I.T. series).
‡ Case 03–648 also listed as 01–013 (M.I.T. series).

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Table 4 lists a series of tumors that are mostly cancers of epithelial or mesenchymal origin developing in an unusual set of locations: the mastoid air cells of the temporal bone of the skull, the paranasal sinuses, or at the apices of the teeth. Malignant tumors in these locations are extremely unusual and it is noteworthy that in this series of 8 patients, deaths from these tumors have all occurred since 1953 and 6 of them were after 1960. The late appearance of these tumors is in contrast to the situation with malignant tumors of bone, which have occurred in this series from 1935 to 1963. Current or preterminal radium body burdens for the patients in *Table 4* range from 0.13 to 7.61 μCi and the estimated maximum burdens range from 1.23 to 63.64 μCi.

The situation with leukemias and other serious blood dyscrasias is less clear. Only two of the patients listed in *Table 5* have had quantitative determinations of radium burden. Case 03–487 had chronic lymphatic leukemia, a disease not usually attributed to the presence of radionuclides that deposit principally in skeletal tissue. The estimated maximum for case 03–657 is based on a whole-body determination of radium burden by Prof. Robley D. Evans at the Massachusetts Institute of Technology in 1936,[10] and it is included here because this patient worked as a dial painter in the group that we have been studying. Information for the other cases again is largely derived from hospital records, death certificates, or examination of the original blood smears, and no radium burden data are available. Two hundred and fifty women of this series painted watch dials in the 1920's. The elapsed time since ingestion of radium is 40 years. The natural incidence of myeloid leukemia in the general population is approximately one case per 16,000 subject years. In this instance, namely 10,000 subject years, the probability of seeing at least one case of myeloid leukemia in any group of 250 women observed for 40 years is high.

Finally, the malignant tumors that are *not* directly attributable at the present time to occupational exposure or to radium deposition are listed in *Table 6*. Current or preterminal body burdens in this series range from <0.001 to 0.90 μCi while the corresponding estimated maximum radium burdens range from 0.20 to 7.29 μCi.

MALIGNANT TUMORS AFTER MEDICAL ADMINISTRATION OF RADIUM

State hospital patients

This group of cases derives from a study carried out by Schlundt and his colleagues[3,4] in 1931–33 in which a group of psychotic patients at

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Table 4. Malignant tumors in radium dial painters as a result of occupational exposure. B. *Tumors principally of mastoids and paranasal sinuses.*

Case No.	Year of Birth	Work period	Diagnosis (year of diagnosis)	Living (1967) or dead	Radium body burden (μCi) Current or preterminal	Radium body burden (μCi) Est. maximum a = 0.30 b = — 0.44
03–685	1902	10/21– 1/23	Carcinoma, maxilla (1962)	L	0.13	1.23
03–417	1909	7/24– 9/25	Carcinoma, Rt. maxilla (1962)	D	0.62	5.72
03–402*	1905	7/23– 7/26	Carcinoma, Rt. mastoid (1964)	L	1.06	6.99
03–407	1905	6/23– 6/46	Carcinoma, Rt. mastoid (1959)	D	1.40	7.67
03–648†*	1903	9/21– 9/22	Mixed carcinosarcoma, Rt. mastoid (1955)	D	7.61	63.64
03–675	1896	—	Rhabdomyosarcoma, Rt. maxilla (1960)	D	Not studied	—
03–772	1904	—	Carcinoma, Lt. mastoid (1953)	D	Not studied	—
03–785	1903	—	Carcinoma, Rt. mastoid (1955)	D	Not studied	—

* Each of these two cases also had a malignant tumor of bone; see *Table 3.*

† Case 03–648 also listed as 01–013 (M.I.T. series).

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Table 5. Blood dyscrasias in radium dial painters. C. *Leukemias and aplastic anemias.*

Case No.	Year of Birth	Work period	Diagnosis (year of diagnosis)	Living (1967) or dead	Radium body burden (μCi) Current or preterminal	Est. maximum $a = 0.30$ $b = -0.44$
03-487	1907	7/24- 7/37	Chronic lymphatic leukemia (1964)	D	0.37	2.57
03-657*	1906	7/22- 7/36	Splenic leukemia (1939)	D	18.00	55.64
03-659†	1908	—	Splenic leukemia (1934)	D	Not studied	—
03-662	1901	—	Aplastic anemia (1946)	D	Not studied	—
03-658	1907	—	Aplastic anemia (1938)	D	Not studied	—

* Case 03-657 also listed as 01-002 (M.I.T. series). Terminal diagnosis was taken from death certificate. Body burden determination by R. D. Evans.[10]

† Case 03-659 died in 1938. The original blood slide made on 11-28-34 was located and the diagnosis of chronic myeloid leukemia (formerly called "splenic leukemia") was confirmed from examination of this slide.

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Table 12. Range of estimated maximum radium burdens computed by various power function parameters.

Type of tumor	*No. of cases*	$a = 0.30$, $b = -0.44$	$a = 0.54$, $b = -0.52$	$a = 0.18$, $b = -0.22$	$a = 0.89$, $b = -0.63$
Osteo- and other sarcomas probably arising in skeletal tissues	12	6.72 – 66.49	10.11 – 117.36	2.28 – 35.84	17.35 – 262.96
Malignant tumors of the skull	11	1.23 – 63.64	1.91 – 98.32	0.42 – 35.84	3.58 – 184.30
Leukemias and other blood dyscrasias	4	2.57* – 101.42	3.85* – 160.84	0.94* – 70.66	6.92* – 203.87

* Case of chronic lymphatic leukemia.

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Table 13. Incidence of radium-induced malignant tumors and blood dyscrasias on basis of current and preterminal radium body burdens (September, 1967).

Current or preterminal burden	*Range of estimated maximum burdens*	*No. of persons*	*Bone tumors*	*Other cancers*	*Leukemias and other blood dyscrasias*	*Total*	*Incidence*
0.01 – 0.0316	0.019 – 0.48	61	0	0	0	0	0.000
0.032 – 0.099	0.066 – 17.34	30	0	0	0	0	0.000
0.10 – 0.316	0.11 – 17.34	34	0	1	0	1	0.029
0.32 – 0.99	1.92 – 24.93	37	4	3	1*	7	0.189
1.00 – 3.16	6.29 – 65.74	36	9	6	0	15	0.417
3.2 – 9.99	15.95 – 66.49	15	5	2	0	7	0.467
10.0 – 31.62	52.48 – 101.42	5	0	0	3	3	0.600
	Total	218	18	12	3	33	

* Case of chronic lymphatic leukemia not included in the radium-induced tumor incidence rate.

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The incidence of radium-induced malignant tumors in the population studied is given in *Tables 13* and *14*. The data for the 156 dial painters and the 26 state hospital patients are only slightly biased since most of these cases were acquired as a result of systematic search. The medical treatment cases frequently came to our attention because of serious symptoms and to that extent they do bias the incidence data. This bias is mostly at the higher body burden levels.

The data in *Table 13*, which are arranged in increasing blocks of current or preterminal radium burdens, are plotted as a dose-response curve on a semi-log grid in *Fig. 3*. Except for the 0.42 incidence between 1.0 and 3.2 μCi, the other points above 0.1 μCi can be connected by a straight line or perhaps somewhat better by a slightly S-shaped curve. In either case the points above 3.2 μCi are based on rather small numbers of cases and are probably not very dependable, especially since the higher radium burdens in some cases are the consequence of measurements made 15 to 30 years ago whereas the majority of cases were studied in the past 10 years.

More important for the establishment of a dose-response curve is the rearrangement of the 205 suitable cases in terms of blocks of increasing estimated maximum radium burdens (*Table 14*). Twelve fewer cases are listed here than in *Table 13* because retrospective estimates of maximum burden could not be made for these dozen patients who nevertheless did have current or preterminal radium measurements. These data

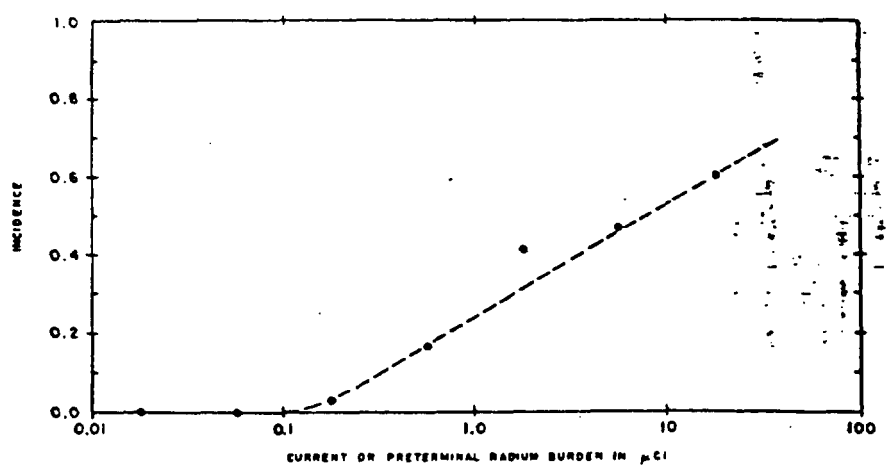

Figure 3. Incidence of radium-induced malignant tumors and blood dyscrasias in the ANL-ARCH series plotted against current or preterminal radium burdens in μCi, September, 1967.

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Table 14. Incidence of radium-induced malignant tumors and blood dyscrasias on basis of estimated maximum radium body burdens (September, 1967).

Estimated maximum burdens	*No. of persons*	*Bone tumors*	*Other cancers*	*Leukemias and other blood dyscrasias*	*Total*	*Incidence*
0.01 – 0.0316	6	0	0	0	0	0.000
0.032 – 0.099	16	0	0	0	0	0.000
0.10 – 0.316	37	0	0	0	0	0.000
0.32 – 0.99	35	0	0	0	0	0.000
1.00 – 3.16	33	0	1	1*	1	0.030
3.2 – 9.99	24	3	3	0	6	0.250
10.0 – 31.62	47	7	6	0	13	0.277
32.0 – 99.9	6	2	1	2	5	0.833
100.0 – 316.2	1	0	0	1	1	1.000
Total	205	12	11	3	26	

* Case of chronic lymphatic leukemia not included in the radium-induced tumor incidence rate.

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provide the dose-response curve shown on a semi-log plot in *Fig. 4* where an S-shaped nature is more clearly evident and where a straight line is more difficult to justify.

The data presented and discussed here have certain implications for the establishment of maximum permissible levels. Briefly, no person that we have studied whose maximum radium burden has been estimated to have been below 1.2 μCi has developed a malignant tumor reasonably ascribable to radium deposition. This approach in terms of estimated maximum burdens is much more rational than that which bases maximum permisible levels on the relationship of pathological changes to current measurements, which are high shortly after administration of the radium and which decline steadily thereafter. The 1.2 μCi value given above and in *Table 11* implies that on the average, based on the estimated peak radium burden, there is at least a 12 fold margin of safety in the currently accepted maximum permissible level of 0.1 μCi for pure ^{226}Ra and its daughters. A peak burden of 0.1 μCi would be expected to decline throughout the life of the bearer at a rate that depends on the route of administration, the amount incorporated, the time period during which the burden was acquired, and the particular bone turnover rate of the individual.

Finally, no attempt has been made here to interpret the data in terms of delivered dose. The present state of knowledge of tumor induction does not permit the delineation of the precise volume of tissue that needs to be

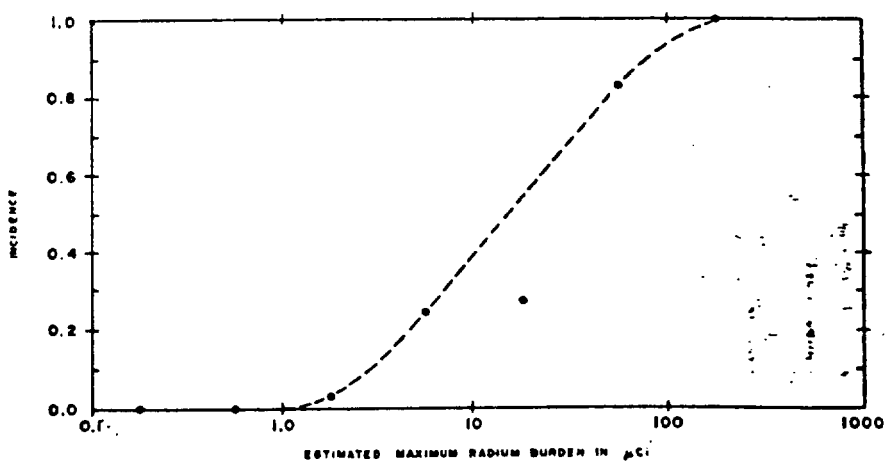

Figure 4. Incidence of radium-induced malignant tumors and blood dyscrasias in the ANL-ARCH series plotted against estimated maximum radium burdens in μCi, September, 1967.

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considered as irradiated and as the site of malignant transformation. Another difficulty is in the establishment of the time span required for the induction of the malignant tumor, i.e., from the administration of the radiation to the onset of irreversible neoplastic change. This period of time, which is the real latent period and which has up to now defied even rough definition, is far more important in radiation carcinogenesis than the apparent latent period to the time of detection of the tumor or to time of death as a result of the tumor. Until these many factors involved in dosimetry and in the instigation of malignant change are resolved, the practice of computing any type of cumulative radiation dose that results in neoplasia is probably misleading and does little to illuminate the problem of radiation oncogenesis.

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DIALOGUE

WILLIAM D. SHARPE: I was struck by the rather high incidence of the central nervous system malignancies in Table 6. I wonder if these might not also be related to the radiation?

ASHER J. FINKEL: We too were struck by the fact that there were two gliomas and one acoustic neuroma. At this point there is no reason to ascribe these tumors to radium, but they are certainly not excludable.

ROBIN MOLE: Do you get irradiation of the nervous tissue from the bones of the skull?

ASHER J. FINKEL: Quite likely. Whether it is enough to instigate tumors, I don't know. If in the next few years we see several more cases of glioma of the brain, I think we would have to start considering this particular pathological entity as perhaps attributable to radium.

HERTA SPENCER: Since the main pathway of excretion of radium is via the intestine, is there a possibility of inducing carcinomas of the colon?

ASHER J. FINKEL: We had one carcinoma of the stomach, two carcinomas of the colon, and one carcinoma of the rectum (Table 6). It may very well be that these also should be considered attributable to radium. This is one reason we have listed all these miscellaneous tumors in a separate table.

CHARLES W. MAYS: I would like to express my very sincere thanks to the M.I.T. team and the Argonne team for presenting at this symposium such a tremendous wealth of new numerical data. I was particularly pleased to see this paper's detailed tabulation of *all* tumors, regardless of whether or not they are currently believed to be radiation-induced.

The induction of bone sarcomas and the head carcinomas is relatively easy to establish because of their extremely low natural incidence in the

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general population contrasted against their high occurrence among the heavily exposed radium cases. It is much more difficult to assign a cause to the malignancies which have a higher natural incidence, such as carcinomas of the digestive tract and neoplasms of hematopoietic tissue.

ROBERT J. HASTERLIK: Some very careful semantic considerations went into the headings on the tables. Some list "tumors as a result of occupational exposure," while others list "tumors not attributed to occupational exposure." We reserve the right to change our opinion. I agree with the others who have commented that we must think very seriously concerning the relationship of radium burdens to the possible induction of the various tumors.

CONSTANTINE J. MALETSKOS: Dr. Finkel, you find effects at lower current and initial burdens than have been observed in the M.I.T. series. How does this affect the interpretation of a practical threshold?

ASHER J. FINKEL: We have a case of carcinoma of the maxilla in a person whose current radium burden is about 0.13 μCi ^{226}Ra. Although this finding bothers some people, I am not disturbed by it because I don't think the current burden means that much. I think the estimated maximum burden (in this case about 1.2 μCi) means more and we are safe.

ROBLEY D. EVANS: There is a 500 rad average accumulation in that particular patient even without any bizarre distribution of radioactivity.

CHARLES W. MAYS: I hope these studies will continue long enough so that when we predict the effect of other emitters such as ^{224}Ra, ^{239}Pu, and ^{241}Am in man, we can do so with detailed information on the complete effects of radium throughout the entire human life-span.

ROBIN MOLE: I would like to second everything Dr. Mays has said about the importance of these studies. I hope they will go on and expand.

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