RADIUM-INDUCED MALIGNANT TUMORS IN MAN*

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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 ($\underline{a}$ = 0.30 and $\underline{b}$ = -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 twelvefold 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 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.

We have a photograph of a group of radium dial painters taken in 1925 in a "radium studio" in a town that lies within 100 miles of Chicago. Within a rather large room there are 6 rows of young women seated at individual school-type desks with 9 to 12 desks per row. Of the 67 persons in the photograph, 14 have not been identified and are not known, and 9 have been identified but have not been studied. We are fairly certain that we

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know the names of 9 of these 14 unidentified persons, but the names have not been matched with the faces. The remaining 44 women have either been studied by us within the past 10 years or are otherwise known to be well or to have had a specific disease. Among these 44 cases, there are 16 who are no longer alive, and 7 of these 16 had malignant diseases attributable to radium, and 5 had malignancies presumably unrelated to radium. Among the 28 persons who are still alive in September 1967, there is one woman who has had two different malignant tumors attributable to radium. For the population represented in the 1925 photograph, then, there are 8 known cases among 67, or 11.9%, who have developed malignant tumors ascribable to radium.

By way of contrast, we have another photograph taken in a second dial painting company in the same town in 1935, ten years later. Here there are 32 young women, 7 of whom were also in the 1925 picture. We have studied 20 of these dial painters, and of the 12 that were not studied we have been unable to identify 6. Of these 20 that were studied, 15 are still alive and are in reasonably good health, and 5 have died, all of malignant tumors. Among these 5 deaths there are 3 cases with malignant disease attributable to radium. However, 2 of these cases were also present in the 1925 picture and the third person was known to have started work in 1924. When the latter 3 cases are deleted, we have for the new faces a known incidence of 0/17 = 0% malignancies ascribable to radium.

The reasons for this striking difference may be many, but the 10-year average age difference is not the principal one. In the group that appeared exclusively in the 1935 picture, current or preterminal body burdens of radium range from <0.001 to 0.020 μCi for those who started to work after 1926. The comparable range is 0.028 to 18.0 μCi for those women in the 1935 photograph who started to work before 1926. The principal cause for this difference is the fact that tipping or pointing the radium-laden brush between the lips was discontinued as an acceptable practice on or about January 1, 1926 as far as we have been able to ascertain. As a result of this change radium was acquired internally only to a very slight extent after this date. The largest body burden that we have seen in a dial painter who started to work after 1930 is 0.033 μCi in a woman who worked from July 1943 through July 1951. Twelve dial painters whose employment in the second plant began in the 1930's and 1940's had radium burdens ranging from <0.001 to 0.033 μCi when they were measured in the Argonne National Laboratory whole-body counter in 1957-1959. Because of the low radium burdens in this more recently employed group, we have concentrated our attention largely on those persons who worked before 1930.

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 gastrointestinal tract by the clearing action of the tracheobronchial cilia.

Some idea of the size of the industrial population available for study can be obtained from the biennial issues of the city directory for the town in Illinois where radium dial painting principally occurred. Since these directories noted occupations it was a simple matter to compile lists of employees of radium dial "studios." There were 72 employees in 1924, 75 in 1926, 76 in 1928 and 36 in 1930. In addition to these city directory lists, we have 24 additional names derived from a photograph of employees taken in front of the factory building in 1924. Other towns where radium dial painting took place have been similarly investigated. Lists such as these along with photographs have enabled us to identify and trace former dial painters and to arrive at an estimate of the total population at risk. By these means, 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.[3] 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.

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

TABLE 2

Values of retained radium computed for $\underline{t}$ days after $\underline{n}$ weekly injections of 10 μCi*

Days after last injection	Number 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	1.350	5.204	7.873	9.384	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: $\underline{a}$ = 0.30, $\underline{b}$ = -0.44.

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 $\underline{a}$ = 0.30 and $\underline{b}$ = -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

TABLE 3

Malignant tumors in radium dial painters as a result of occupational exposure.

Tumors principally of skeletal tissues

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

[redacted]

current or preterminal radium burdens range from 0.81 to 7.61 μCi, the estimated maximum burdens range from 6.72 to 66.49 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.

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.

TABLE 4

Malignant tumors in radium dial painters as a result of occupational exposure.

Tumors principally of mastoids and paranasal sinuses

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

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, and was present in both the 1925 and 1935 pictures referred to at the beginning of this paper. 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.

TABLE 5

Blood dyscrasias in radium dial painters.

Leukemias and aplastic anemias

Case No.	Year of birth	Work period	Diagnosis and 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
[redacted] 03-487	1907	7/24-7/37	Chronic lymphatic leukemia 1964	D	0.37	2.57
[redacted] 03-657*	1906	7/22-7/36	Splenic leukemia 1939	D	18.00	55.64
[redacted] 03-659†	1908	-	Splenic leukemia 1934	D	Not studied	-
[redacted] 03-662	1901	-	Aplastic anemia 1946	D	Not studied	-
[redacted] 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. 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.

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.

TABLE 6

Tumors in radium dial painters not attributed to occupational exposure

Case No.	Year of birth	Work period	Diagnosis and year of death	Living (1967) or dead	Radium body burden, μCi: Current or preterminal	Radium body burden, μCi: Est. maximum a = 0.30 b = -0.44
[redacted] 03-476	1895	10/27-11/27	Carcinoma of uterus	L	< 0.001	0.020
[redacted] 03-682	1907	-	Carcinoma of breast	L	< 0.001	-
[redacted] 03-403	1915	3/35-9/43	Carcinoma of ovary 1964	D	0.008	0.019
[redacted] 03-507	1907	6/23-8/23	Acoustic neuroma 1962	D	0.012	0.26
[redacted] 03-420	1906	9/22-10/26	Carcinoma of colon 1960	D	0.018	0.088
[redacted] 03-547	1907	7/23-8/25	Carcinoma of colon 1962	D	0.019	0.12
[redacted] 03-456	1921	7/43-7/51	Carcinoma of breast 1965	D	0.033	0.066
[redacted] 03-627	1905	7/24-7/28	Carcinoma of breast 1966	D	0.072	0.52
[redacted] 03-489	1911	10/26-3/28	Carcinoma of stomach 1964	D	0.12	0.84
[redacted] 03-408	1908	8/24-4/26	Glioblastoma 1959	D	0.16	1.13
[redacted] 03-499	1906	6/24-7/25	Carcinoma of thyroid	L	0.23	2.04
[redacted] 09-003	1892	-	Carcinoma of lung* 1963	D	0.43	-
[redacted] 03-586	1908	1/26-8/27	Carcinoma of breast	L	0.90	7.29
[redacted] 03-654	1905	-	Glioma of brain 1954	D	Not studied	-
[redacted] 03-667	1877	-	Carcinoma of rectum 1927	D	Not studied	-
[redacted] 03-815	1904	-	Carcinoma of breast 1955	D	Not studied	-

*Case 09-003 (radium chemist), who was the only male in this series, had two independent primary malignant lung tumors; the only male in Tables 3 through 6.

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 in 1931-1933 in which a group of psychotic patients at one of the state hospitals in Illinois was given weekly injections of 10 μCi of radium.[3,4] As far as we can ascertain from somewhat discrepant records, the number of injections for 30 patients ranged from 7 to 45. We have been unable to find injection data for an additional 11 patients. Most of the patients received radium when they were young adults: 25 of 33 known cases were younger than age 34, while 8 cases formed an older group with ages ranging from 47 to 63. The median age for the 33 younger cases was 27 years. Twelve patients are still alive and have been measured for radium burden and studied by periodic skeletal radiography within the past few years. In addition, 7 of the 9 patients who have died since 1955 have been similarly studied.

The mortality experience for the group of 41 patients is presented in Table 7. The details of 4 cases of malignant tumors ascribable to radium are given in Table 8. Preterminal radium burdens varied from 0.85 to 3.09 μCi, while the maximum burdens computed with the average power function parameters used in this paper ranged from 16.90 to 26.49 μCi. Similar ranges were found for all categories of mortality experience in this group. This finding suggests that there may be a minimum burden for the development of radium-induced malignant tumors but that burdens above an apparent threshold value do not guarantee the development of such tumors. It is interesting that 3 of the 4 tumors were malignancies of the skull and that, despite the large amounts of radium injected, these tumors did not develop until the last 10 years. The 3 malignant tumors that were presumably unrelated to radium were carcinomas of the bladder in 2 cases and a carcinoma of the stomach.

TABLE 7

Mortality among state hospital patients who received radium injections in 1931-1933

	Total No. cases			Range of body burdens, μCi		
Clinical data (1967)	Males	Females	No. studied	Current or preterminal	Est. maximum $\underline{a}$ = 0.30 $\underline{b}$ = -0.44	Not studied
Malignant tumors due to radium	2	2	4	0.85-3.09	16.90-26.49	0
Malignant tumors not attributed to radium	0	3	2	0.63-1.04	14.90-24.93	1
Dead from nonmalignant disease	7	6	8	0.42-9.70	15.95-25.73	5
Dead from unknown causes	5	4	2	1.90-4.20	16.44-18.97	7
Living	3	9	12	0.44-1.40	15.95-27.77	0
Total	17	24	28			13

TABLE 8

Malignant tumors attributed to radium in state hospital patients

Case No.	Sex	Year of birth	No. of injections	Diagnosis	Year of diagnosis and death	Radium body burden, μCi	
						Preterminal	Est. maximum*
[redacted] 03-105	M	1904	16	Cancer (type not known) ethmoid or sphenoid sinus	1957	0.85†	13.67
[redacted] 03-141	M	1906	11	Carcinoma, left mastoid	1963	0.87	16.90
[redacted] 03-126	F	1911	20	Carcinoma, sphenoid sinus	1965	1.50‡	20.42
[redacted] 03-118	F	1898	41	Osteogenic sarcoma, right tibia	1955	3.09	26.49

*Estimated maximum based on average power function and number of injections.
†Computed value on basis of number of injections and elapsed time. The whole-body measurement was 2.59 μCi in 1951.
‡Corrected for missing leg by adding 15% of measured burden.

Radium Treatments by Private Physicians

A total of 37 miscellaneous patients who acquired radium from their personal physicians has come to our attention and study. Among these 37 persons, 5 males and 11 females have developed malignant tumors or blood dyscrasias that may be attributed to the presence of radium in their bodies. Since these cases were acquired principally because of the symptoms that they presented and not as a result of an epidemiological survey, the data are biased in favor of deaths from malignant tumors ascribable to radium.

The pertinent data for the 16 patients with malignancies are given in Table 9. There are 9 cases of malignant bone tumors, 5 cases of carcinoma (4 of which involve mastoids and sinuses), 1 of aplastic anemia and 1 of panmyelosis. Preterminal radium burdens ranged from 0.60 to 10.7 μCi. Estimation of the maximum radium burdens was more difficult for this series of cases and involved a variety of computations. Where the administration was oral (cases 03-208 and 03-212), the computation was based on Eq. (4) and was the same as that used for the dial painters. Where the radium was given by injection and where the number of injections was known or could be reasonably assumed, the maximum burden was estimated by the method used for the state hospital patients. The last column in Table 9 gives the number of injections assumed for each calculation and parenthetically includes the value expected by these computations for the year of the preterminal measurement (cf. Table 2).

Where estimates can be made, the maximum radium burdens range from 13.69 to 29.46 μCi for the bone tumor cases and from 17.34 to 22.05 μCi for the carcinomas of the mastoids and sinuses. Much higher estimates are obtained for the two cases of blood dyscrasia; 52.48 to 101.42 μCi. Unfortunately, comparable estimates cannot be made at the present time for the cases of blood dyscrasia among the dial painters.

TABLE 9

Malignancies and blood dyscrasias attributable to radium in other medical cases

	Case No.	Sex	Diagnosis and year of diagnosis	Living (1967) or year of death	Ra administration		Last radium measurement		Estimated maximum burden	
					Year	Route	Year	μCi	μCi	Method of estimation
[redacted]	03-226	F	Osteogenic sarcoma, left femur 1959	1961	1922	Injections	1961	0.60	17.77	Assume 13 injections (→0.58 in 1961)*
[redacted]	03-227	F	Osteogenic sarcoma, right tibia 1949	1952	?	Not known	1951	0.56	-	-
[redacted]	03-234	F	Fibrosarcoma, right femur 1964	1965	?	Not known	1965	0.92	-	-
[redacted]	03-209	M	Fibrosarcoma, right scapula 1958	1960	1925-1936	Not known	1951	1.00	-	-
[redacted]	03-212	F	Fibrosarcoma, right tarsal scaphoid 1951	1951	1929	Oral	1951	1.30	29.46	Assume 25 days' ingestion (Q = 22.658)
[redacted]	03-210	M	Osteogenic sarcoma, left calcaneus 1956	1958	1926	"A few" injections	1958	1.35	13.69	Assume 5 injections (→0.29 in 1958)*
									22.05	Assume 25 injections (→1.21 in 1958)*
[redacted]	03-201	F	Osteogenic sarcoma, right humerus 1962	1963	?	Not known	1962	2.99	-	-
[redacted]	03-215	M	Fibrosarcoma, right ulna 1957	L	1920-30	Not known	1961	3.45	-	-
[redacted]	03-213	F	Fibrosarcoma, lumbosacral spine 1954	1955	1925-26	Several injections	1952	6.57	14.32	Assume 6 weekly injections (→0.31 in 1952)*
									20.17	Assume 6 daily injections (→0.31 in 1952)*
[redacted]	03-221	M	Carcinoma of oral cavity 1962	1963	1924	Injections	1957	0.62	17.77	Assume 13 injections (→0.62 in 1957)*
[redacted]	03-235	F	Carcinoma, sphenoid sinus 1965	L	?	Not known	1965	1.15	20.42	Assume 20 injections in 1925 (→1.00 in 1965)*
									22.05	Assume 25 injections in 1925 (→1.24 in 1965)*
[redacted]	03-214	F	Carcinoma, left mastoid 1959	1966	?	Not known	1964	1.23	-	-
[redacted]	03-232	F	Carcinoma, left mastoid 1956	1957	1917	Not known	1956	4.70	17.34	Assume 12 injections (→0.52 in 1956)*
[redacted]	03-240	F	Carcinoma, left mastoid 1952	1955	1920-1930	Not known	-	-	-	-
[redacted]	03-208†	F	Panmyelosis 1951	1953	1918	Oral	1941	10.5	75.21	Assume 12 months' ingestion (Q = 7.162)
									101.42	Assume 6 months' ingestion (Q = 9.659)
[redacted]	03-226	M	Aplastic anemia 1949	1953	1924	40 injections, 20 μCi weekly	1951	10.7	52.48	On basis of 40 injections, 20 μCi weekly (→4.28 in 1951)*

*Values in parentheses preceded by arrow are computed estimates of recent body burdens based on the stated assumptions and the mean power function. In some cases the correspondence between the computed and the observed burdens is very close; in other cases there is a large discrepancy.
†Case 03-208 also listed as 01-004 (M.I.T. series). Body burden determination by R. Evans.[10]

External Radiation Dose to Dial Painters

Apart from the radiation delivered to potential tumor-forming cells from radium deposited in the skeleton, some consideration should be given to the external irradiation that the dial painters might have received. In order to evaluate the magnitude of this dose, we investigated the work practices of the major dial painting plant in our territory. The physical arrangement of the desks used by the dial painters was reconstructed from photographs taken in 1922-1925 within the "radium art studios." The distances between desks have been estimated from a measurement of the width of windows, heat registers, floor boards, etc. that are shown in the photographs and that still exist in these rooms. Each dial painter sat at a wood school desk, which had a drawer under the seat that pulled out to the right, and these desks were arranged in rows from the front to the back of the room. The front edge of each desk was usually very close to the back rest of the desk in front of it so that the painters were about 80 cm apart, midline to midline. The rows were about 1 meter apart from center to center.

In order to ensure that the employees placed about the same amount of material on each of the dials painted during the day, the management issued only enough material at any one time to paint a single tray of dials. Although the radium-phosphor ratio of the material varied with the size of the dial, the number of dials in the tray and the amount of material placed on the dial also varied in such a manner that about the same amount of radium was used to paint a single tray of dials of any size. The tray of dials was placed on the open drawer adjacent to the girl's right hip and the container of radium was placed on the desk. She painted one dial at a time on the desk before her and then returned the finished dial to the tray. During the dial painting operations, the full quantity of radium was gradually transferred from the desk top to the tray alongside the right hip of the employee.

We have been reliably assured that no mesothorium or radiothorium was mixed with the radium in the companies whose employees we have studied. In fact, we have been told that the radium dial company guaranteed to the watch manufacturers that the dials contained only pure radium. To comply with this guarantee no mesothorium or even reclaimed radium was used. Of all of our cases studied by total-body counting only 2 showed evidence of contamination with ^{228}Ra (MsTh). We have ascertained that between 20 and 40 μCi of ^{226}Ra were given to each girl for one tray of dials. If we assume the most serious situation in which 40 μCi of radium were always present on the desk, and that the ^{226}Ra was in equilibrium with its daughters (which, in fact, it would not be since a significant fraction of the radon would have escaped), and that the 40 μCi of radium were located 25 cm from the anterior chest of the dial painter, then this quantity would yield an air dose to the front surface of the body of 0.6 mR/hr and about 0.3 mR/hr at the center of the chest. The 40 μCi of radium located about 35 cm behind the employee would yield a dose of about 0.3 mR/hr to her back and 0.2 mR/hr to the midline of the body. The dishes of ^{226}Ra located on the two desks immediately across the aisle and the two across the aisle diagonally behind the dial painter would give her a surface dose on each side of about 0.04 mR/hr and a midline dose of about 0.12 mR/hr (0.03 $\times$ 4 dishes). The radium sources on the desk in front of the worker and on the desks across the aisles one seat forward are ignored here since they were shielded by the persons seated at those desks.

The dial painters who worked surrounded by other painters, then, received as a maximum a front surface dose of about 0.6 mR/hr, a back surface dose of about 0.3 mR/hr, and a midline dose of about 0.62 mR/hr. If the painters worked 48 hr/week, 50 weeks/yr, they received a maximum of about 1.5 R/yr, a value considerably below the 5 R/yr currently accepted as permissible. If each painter had 100 μCi on her desk, the external radiation dose would not have exceeded 4 R/yr or 80 R in 20 yr.

[redacted]

In these calculations, the beta-ray dose has been ignored. The fact that the gamma-ray dose was based on an equilibrium mixture of ^{226}Ra, RaB and RaC rather than the appropriate mixture should more than compensate for the omission of the beta-ray dose. This reconstruction of the external dose under the work conditions of our dial painters suggests that in this series of cases the external radiation can be safely ignored as an oncogenic agent.

Discussion

The principal interest in the malignant tumor experience in the radium cases that we have been examining lies in the implications that the data may have for radiation carcinogenesis, for oncogenic dose-response curves, and for the problem of maximum permissible levels for internally deposited bone-seeking radionuclides. By relating the occurrence of a malignant tumor to an estimate of the maximum burden in each case, we have sought to avoid problems resulting from biological variability in time of appearance of tumors and variations in body burdens that result from vagaries in the time of measurement.

The results of the computations set forth in Tables 1 through 9 are summarized in Table 10 in which the estimated maximum burdens range from 6.72 to 66.49 μCi for the bone sarcoma cases, from 1.23 to 63.64 μCi for the radium-induced skull carcinoma cases, and 52.48 to 101.42 μCi for the leukemias and other blood dyscrasias (excluding the one case of chronic lymphatic leukemia, a disease which at present is not considered to be radiation-induced in man). That these estimates are lower than the values

TABLE 10

Summary of data on malignant tumors and blood dyscrasias attributable to radium deposition

Type of tumor	No. of cases	No. studied	Source of radium	Range of measured preterminal radium burdens, μCi	Range of estimated maximum burdens,* μCi
Osteo- and other sarcomas, probably arising in skeletal tissues	13	8	Occupational	0.81-7.61	6.72-66.49
	1	1	State hospital	3.09	26.49
	9	9	Other medical	0.60-6.57	13.69-29.44
Malignant tumors of the skull	8	5	Occupational	0.13-7.61	1.23-63.64
	3	3	State hospital	0.85-1.50	16.90-20.42
	5	4	Other medical	0.62-4.70	17.34-22.05
Leukemias and other blood dyscrasias	5	2	Occupational	0.37†-18.00	2.57†-55.64
	0	0	State hospital	-	-
	2	2	Other medical	10.50-10.70	52.48-101.42
Total	46	34			

*Based on power function parameters $\underline{a}$ = 0.30, $\underline{b}$ = -0.44.
†Case of chronic lymphatic leukemia.

yielded by Norris' parameters can be seen in Table 11, which gives comparable estimates based on other power function parameters. The retrospective estimates based on Norris' parameters are somewhat larger, but both sets are much smaller than the rather extravagant values computed by Hems[11] who lumped all the cases together and assumed that orally acquired burdens in the dial painters can be treated as if the radium had been received as a single intravenous injection 36 years earlier. Table 11 also gives the range of maximum burdens computed with the parameters for the patient in our state hospital series who retained radium most avidly (a = 0.18, b = -0.22) and with the parameters for the patient who lost radium most rapidly (a = 0.89, b = -0.63). These computations are included in order to emphasize the range of metabolic disparities that exists among the state hospital patients we have studied and that undoubtedly existed among the dial painters and other patients. While we have relied principally on the parameters of an average power function, the range of possible departures from this average function should also be kept in mind.

TABLE 11

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.

The incidence of radium-induced malignant tumors in the population studied is given in Tables 12 and 13. The data for the 156 dial painters and

TABLE 12

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.

[redacted]

TABLE 13

Incidence of radium-induced malignant tumors and blood dyscrasias on basis of estimated maximum radium body burdens

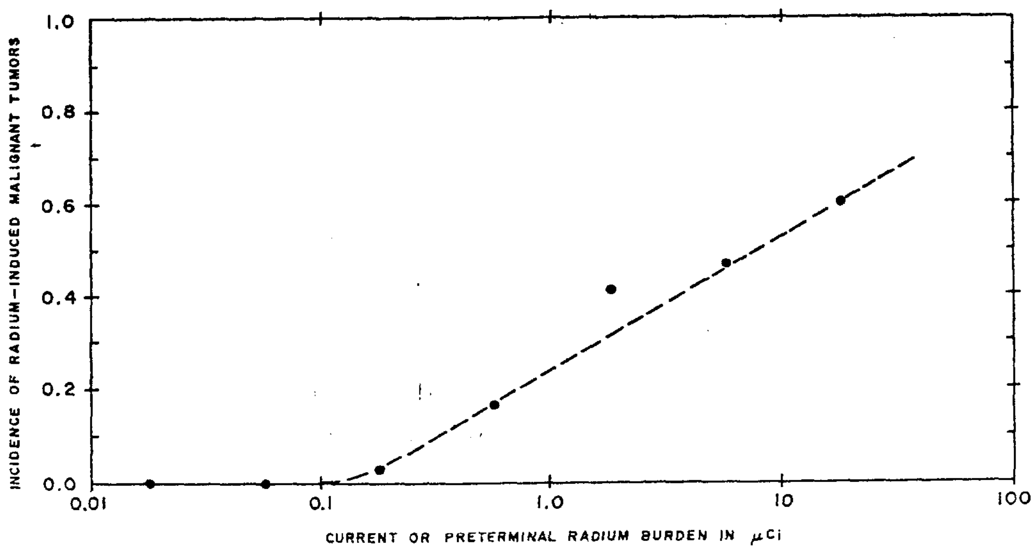
(September 1967)

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.

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 12, which are arranged in increasing blocks of current or preterminal radium burdens, are plotted as a dose-response curve on a semilog grid in Figure 3. Except for the 0.42 incidence between

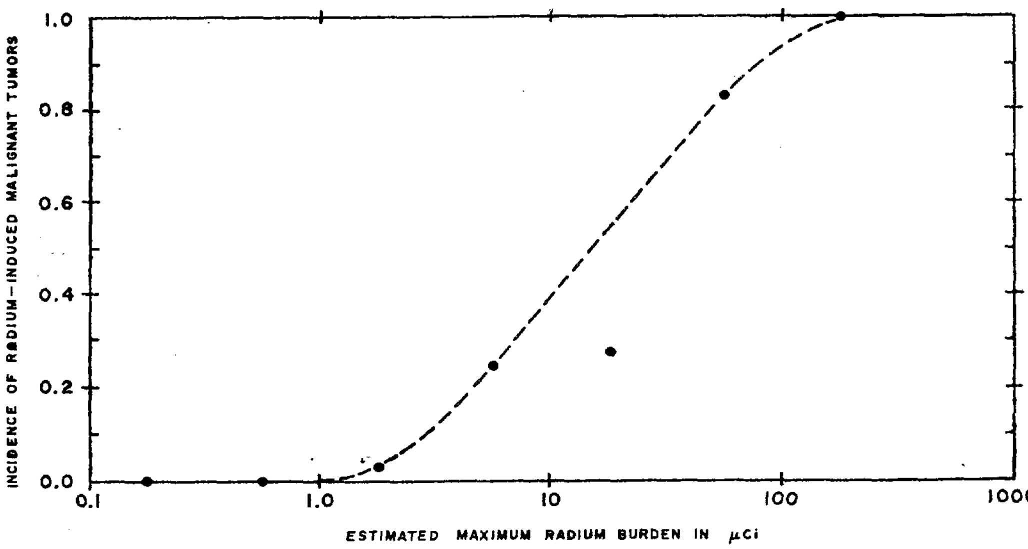


194-121

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

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 13). Twelve fewer cases are listed here than in Table 12 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 provide the dose-response curve shown on a semilog plot in Figure 4 where an S-shaped nature is more clearly evident and where a straight line is more difficult to justify.



194-120

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

The data presented and discussed here have certain implications for the establishment of maximum permissible levels. Briefly, no person whom 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 permissible 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 10 implies that, on the average, based on the estimated peak radium burden there is at least a twelvefold 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 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.

Appendix

Two additional tables are appended to the preceding paper since its presentation at the Sun Valley Symposium on Delayed Effects of Bone-Seeking Radionuclides in September 1967. Table 14 lists the additional cases of malignant tumors that have been uncovered by a search of records

TABLE 14

Additional tumor cases: dial painters

	Case No.	Year of birth	Year of death	Worked with Ra	Type of tumor	Radium burden
[redacted]	03-429	1908	L	1923-27	Osteosarcoma, right third metacarpal, 1967	1.7 μCi (1966)
[redacted]	03-749	1902	1949	1922	Carcinoma of stomach	NS*
[redacted]	03-760	1907	1946	1925	Probable mastoid carcinoma	NS
[redacted]	03-768	1906	1964	1924-25	Astrocytoma	NS
[redacted]	03-779	1905	1942	1922	Sarcoma, probable fibrosarcoma, thigh	NS
[redacted]	03-806	1896	1956	1924	Probable sarcoma, left femur	NS
[redacted]	03-848	1903	1958	1918	Probable sarcoma, right femur	NS

*Not studied.

since September 1967, along with a new case of osteosarcoma involving the right third metacarpal that developed late in 1967 in one of the radium dial painters whom we have been following.

Table 15 is a preliminary analysis of the known malignant tumor experience of dial painters who worked with radium before 1930 in the Chicago area. The tumors are listed by general type, and the expected number of tumors has been computed from crude U.S. rates for white females in 1959 for specific tumor groups. While analysis of these data will have to be accomplished by use of more refined demographic techniques, the preliminary results indicate that the incidence of osteosarcomas and fibrosarcomas, of carcinomas of the mastoids and paranasal sinuses, and possibly also of central nervous system tumors is significantly greater in this group of dial painters than in the general population.

TABLE 15

Known malignant tumor experience of dial painters who worked with radium before 1930

Type of tumor	Observed tumors	Expected tumors*	Ratio O/E
Osteosarcomas and fibrosarcomas	17	0.07	243
Carcinomas of mastoids, sinuses, etc.	9	0.02	450
Central nervous system tumors	4	0.2	20
Gastrointestinal tract tumors	5	3.8	1.3
Carcinomas of breast	4	2.1	1.9
Carcinoma of lung	1	0.2	5.0

*Based on (1) known work population of approximately 200, average elapsed time about 40 years: 200 × 40 years = 8000 man years; (2) crude U.S. rates for white females in 1959 for specific tumor groups.