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SOME DOSE-RESPONSE RELATIONSHIPS FOR TUMOR INCIDENCE IN RADIUM PATIENTS

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A population of 777 radium cases for whom the total dose received has been calculated was obtained by combining the MIT and the ANL-ACRH studies. Within this population a total of 71 malignancies were considered to be radiation induced: 51 sarcomas and 20 carcinomas. Dose-response functions of the form Incidence = KDe^{-D/D_0} and $I = KD^2e^{-D/D_0}$ are examined and found to provide reasonable fits to the data over most of the dose range.

The object of this review is to consider dose-response relationships that could be used to describe data on the radium cases that have been studied in this country during the past 40 years. The end points used are those malignancies which have been assumed to be radiation induced, i.e., the bone sarcomas and some carcinomas, primarily of the paranasal sinuses and the mastoid air cells.

Such an analysis is now possible, for we have, for the first time, dose calculations for all of the radium cases. The raw data, including the dose calculations for all of the cases studied at the Massachusetts Institute of Technology (MIT) by Professor R. D. Evans and his colleagues, have been transferred to the Center for Human Radiobiology here in the Radiological Physics Division of the Argonne National Laboratory. To these MIT cases we have added the data from the cases studied by Miller, Hasterlik, and Finkel.[1] This has been possible, even though no dose calculations were included in their detailed report, through the efforts of one of us (ATK) and Mary Margaret Shanahan of the MIT group, who have calculated the doses for all of the cases listed in the above-mentioned report.

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Our concern is with the low-dose cases, and we have tried to find formulations compatible with the large number of these cases in which malignancies have not (as yet) developed. R. D. Evans and his colleagues[2]

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have postulated a threshold concept to fit their data, and there is no doubt that it does fit well. On the other hand, we have examined continuous functions to see how well they might fit the data. It should be understood that we have attempted to fit response functions to the observed data, not to specify safety criteria which seek a linear relationship such that the observed incidence at any dose is less than that predicted.

We have so far identified 777 cases from the two series for which detectable levels of radium were found. In this group a total of 71 malignancies have been identified which are considered to be radiation induced: 51 sarcomas and 20 carcinomas. We have included all of the cases for which we have data, rather than attempt to select a group which could be considered epidemiologically suitable. We thus include cases found as a consequence of their symptoms, with the full realization that this may have a tendency to enhance the observed incidence of malignancies.

It is of interest, and quite important to bear in mind, that approximately 580 of these 777 cases are still living. The age distribution of the living cases is shown in Figure 1. The age at death of the remainder is shown in Figure 2. Since such a large fraction of the population is still living, it is entirely possible that the tumor incidence may change in future years. This fact emphasizes the importance of a continuous long-term

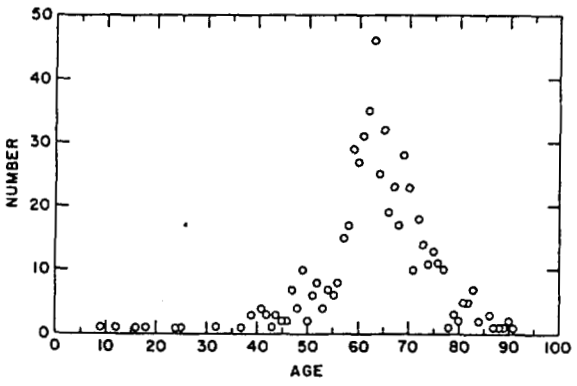

FIG. 1.--The age distribution of the living members of the population under study in 1969.

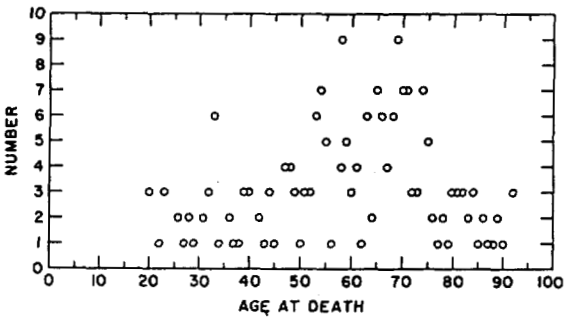

FIG. 2.--The distribution of the dead members of the population as of 1969 according to age at death.

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follow-up of this population.

It is also of interest to note that there exists a remarkably consistent distribution of malignancies within the two independent studies. The malignancies and total number of cases considered in the report are shown in Table 1 and identified as to source.

TABLE 1. Distribution of Malignancies within Two Independent Studies

Location Studied	Cases	Sarcomas	Carcinomas
MIT	474	33	10
ANL-ACRH	316	20	11
Total[a]	777	51	20

[a] There are some cases that have been studied and reported on by both groups so that the total number of cases and malignancies is less than the sums from the independent studies.

The unit of dose employed for this analysis is the total number of rads accumulated by the skeleton from acquisition of radioactive material to death, or to diagnosis of a malignancy, or if neither of these events had occurred, to January 1, 1969. The validity and/or shortcomings of using the average skeletal dose calculated from a uniform distribution of radioactivity in the skeleton will be discussed later. The calculation requires evaluation of the expression

$$D = \int_0^T R(t)\,dt,$$

where R(t) is the average skeletal dose rate at any time, and D is the dose accumulated in time T. The calculation includes the contribution of ^{228}Ra and daughters as well as ^{226}Ra and daughters. This is identical to the "cumulative rads" as employed by Evans.[3]

We have considered dose-response functions of the following forms:

(1) Incidence = KD

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(2) Incidence $= K_1 D e^{-D/D_1}$

(3) Incidence $= K_2 D^2 e^{-D/D_2}$.

As will be shown, the linear expression [Eq. (1)] does not fit all the data, and as is often the case, can only be employed in the low-dose region where no malignancies have been observed. We will make an attempt to define an upper limit (i.e., the linear equation with the largest slope that is not contradicted by the data) that could be used in this region. We have included an exponential term in Eqs. (2) and (3) for, as will be shown below, tumor incidence drops in the highest dose levels, where life expectancy spans were relatively short.

For our analysis we listed all of the cases in order of decreasing dose and then separated the cases into dose ranges. The results are shown in Table 2.

TABLE 2. Analysis of Cases in Order of Decreasing Dose

Dose Range, Rads	Median Dose, Rads	No. of Cases	All Assumed Radiogenic Tumors	Incidence, %
$2\text{-}5 \times 10^4$	2.32×10^4	16	4	25.0
$1\text{-}2 \times 10^4$	1.44×10^4	25	16	64.0
$5\text{-}10 \times 10^3$	6.90×10^3	42	20	47.6
$2\text{-}5 \times 10^3$	4.13×10^3	72	22	30.6
$1\text{-}2 \times 10^3$	1.36×10^3	42	9	21.4
$5\text{-}10 \times 10^2$	7.40×10^2	42	0	0
$2\text{-}5 \times 10^2$	2.82×10^2	79	0	0
$1\text{-}2 \times 10^2$	1.38×10^2	83	0	0
$5\text{-}10 \times 10$	6.50×10^1	88	0	0
$2\text{-}5 \times 10$	3.12×10^1	139	0	0
$1\text{-}2 \times 10$	1.49×10^1	73	0	0
1-10	5.20	74	0	0
0.2-1	0.45	6	0	0
Total		781	71	

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In this tabulation it will be noted that we appear to have four cases more than the 777 we selected for analysis. This occurs because four cases have developed two independent tumors, in each case a carcinoma and a sarcoma. In some instances these tumors appeared many years apart. We calculated the doses to the time of tumor appearance and have listed each tumor separately. For example, Case 01-179 had an osteogenic sarcoma 19 years after radium injections and subsequently developed a carcinoma 42 years after the radium injections. Both tumors are considered to be a consequence of the radium burden. The doses for these two tumors are of the order of 3700 rads and 6100 rads, respectively. Therefore, this case appears twice, once in a range of 5000 to 10,000 rads (with a carcinoma) and once in the range of 2000 to 5000 rads (with a sarcoma).

The data are plotted on linear coordinates in Figure 3 as total tumor incidence vs. the median dose in rads. Along the top of this graph the extent of each dose range is indicated by the length of the solid bar. In the fraction appearing under the bar, the number of tumors is given as the numerator and the number of cases in the range as the denominator. It will be noted that this graph with linear coordinates has forced us to put about three-quarters of our cases in the lowest range, with zero tumor incidence.

A far better graphical representation of these low-dose cases occurs when we use semilogarithmic coordinates as in Figure 4.

On these graphs it will be noted that error bars have been placed on the tumor incidence points, including the points with zero incidence. Where there are tumors, the error bar is obtained from $\pm[\text{ number of tumors}]^{1/2}/[\text{number of cases}]$. In those ranges where no tumors have appeared, the error bar extends upward to indicate the value of the incidence had there been one tumor in that range. The reason for this choice is as follows: We ask, "At what incidence would an error bar extend exactly down to zero incidence?" It can easily be seen that, had there been one tumor in a given range, the error bar would extend down exactly to zero since $[1 - \sqrt{1}]/[\text{number of cases}] = 0$. Therefore, we have drawn our error bar up to this

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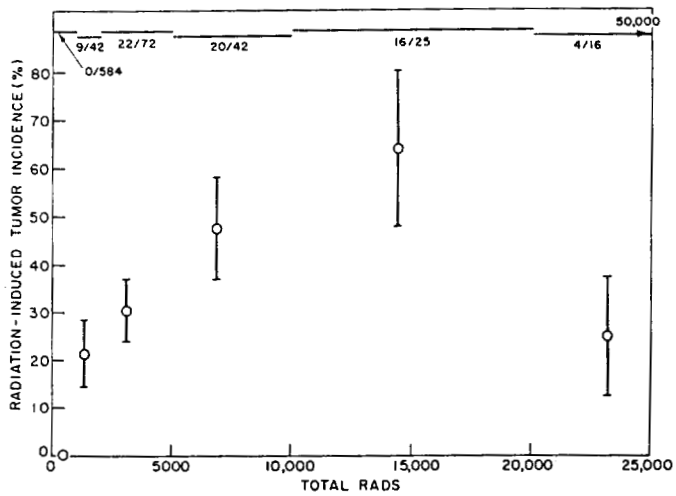

FIG. 3.--Percent tumor incidence as a function of the median value of total skeletal rads from Table 2 plotted on linear coordinates. The zero tumor incidence cases have all been combined in one dose range in this presentation. See text for discussion of dose ranges, error bars, etc.

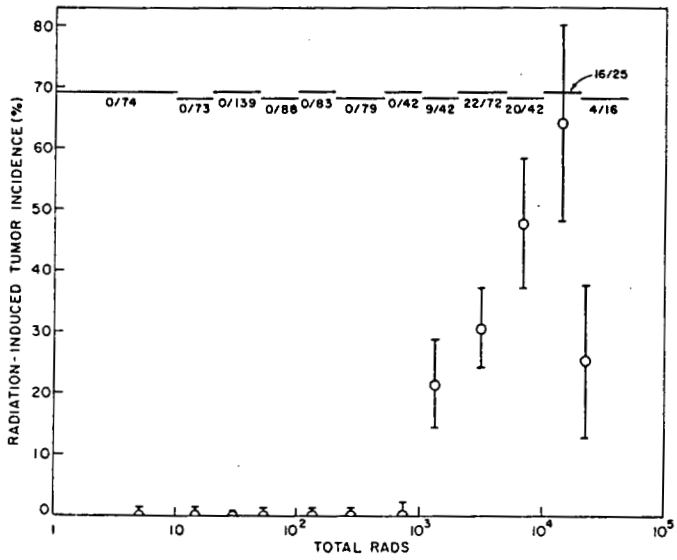

FIG. 4.--Semilogarithmic presentation of the data in Table 2. Percent total tumor incidence on a linear scale is plotted against the median value of total skeletal rads on a logarithmic scale. See text for further explanation.

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incidence level for each of the ranges in which no tumors have been observed. [A more rigorous method of drawing error bars when zero incidence is observed is given by J. H. Marshall elsewhere in this publication.]

By means of a least squares fit[4] we have determined the constants for equations of the form

$$(2)\quad I = K_1 D e^{-D/D_1}$$

and

$$(3)\quad I = K_2 D^2 e^{-D/D_2},$$

where I is the fractional incidence and D is the total dose in rads delivered to the skeleton from exposure to diagnosis of a tumor.

The actual values of the parameters in these two equations are

(2) $I = 1.15 \times 10^{-4} D\, e^{-D/1.25 \times 10^4}$

(3) $I = 5.24 \times 10^{-8} D^2\, e^{-D/4.85 \times 10^3}$.

How well do these equations fit the data? As can be seen from Figure 5, in the region above 1000 rads where tumors have been observed, both equations appear adequate. However, below 1000 rads the linear equation predicts many more tumors than have been observed.

We can ask the question, "What would be the probability of observing no tumors if the hypothesis under consideration were true?" The binomial distribution provides us with the mechanism to answer this question, and we tabulate in Table 3 probabilities of seeing zero tumors, using each of our two equations for the seven dose ranges between 1 and 1000 rads.

It is evident that Eq. (2), the linear-exponential form, predicts significantly more tumors in these dose ranges, and therefore that this is a highly unlikely fit to the actual tumor incidence data in this region. In fact, when we combine the probabilities for these listed ranges, we find the overall probability of seeing no tumors when a total of 8.49 is predicted is of the order of 0.0002.

Equation (3), the dose-squared exponential form, is seen to fit this region of zero incidence far better, with a total probability of the order of 0.23 for seeing zero

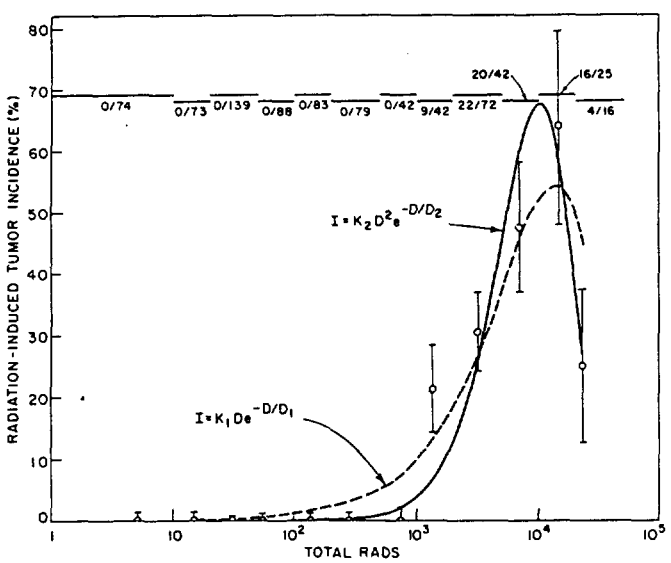

FIG. 5.--Least square fits of the functions $K_1 D e^{-D/D_1}$ and $K_2 D^2 e^{-D/D_2}$ superimposed on Figure 4.

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TABLE 3. Probabilities of Seeing Zero Tumors, Calculated with Two Different Equations

Range, rads	Tumors Observed	Eq. (2) $I = K_1 D e^{-D/D_1}$		Eq. (3) $I = K_2 D^2 e^{-D/D_2}$	
		Tumors Predicted	Probability P_0	Tumors Predicted	Probability P_0
$5\text{-}10 \times 10^2$	0/42	3.37	0.030	1.03	0.351
$2\text{-}5 \times 10^2$	0/79	2.50	0.079	0.31	0.733
$1\text{-}2 \times 10^2$	0/83	1.30	0.269	0.08	0.923
$5\text{-}10 \times 10^1$	0/88	0.65	0.519	0.02	0.981
$2\text{-}5 \times 10^1$	0/139	0.50	0.608	0.01	0.993
$1\text{-}2 \times 10^1$	0/73	0.13	0.882	0	1.0
1-10	0/74	0.04	0.957	0	1.0
	Total	8.49		1.45	

tumors when 1.45 are predicted. On the other hand, the incidence predicted for the dose range of 1000 to 2000 rads is much lower than the observed value; 9 tumors were observed in that range, whereas 3.07 are predicted. Nine or more tumors would have only 0.005 probability of occurrence by chance if the predicted incidence were correct. As previously observed by Evans et al. in their analysis of MIT data,[2] it appears that the combination of zero incidence in the lower dose levels and a rapid increase for doses in excess of 1000 rads is not well represented by smooth functions.

While we are still considering tumor incidence in terms of total malignancies, it is in order to examine a simple linear expression. It is evident from both Figures 3 and 4 that we cannot fit the data with a simple linear incidence-dose relationship. In fact, examination of Figure 3 shows that we could put a different line through each of the five data points and the origin. If we did this, the maximum slope would be obtained by using the incidence in the lowest dose range in which tumors have been seen,

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whereas the minimum slope would result from using the incidence in the highest dose range. It would perhaps be most logical to find the straight line that would predict the same total number of tumors for this population as we have observed, over the range of doses involved.

We have chosen, however, to determine an acceptable linear expression for the range in which no tumors have been observed. Table 2 indicates that no tumors were observed in the lowest eight dosage classes containing 584 cases. The best fit would be given by a prediction of zero incidence in this range. However, it is quite possible that a linear incidence of tumor induction is valid over this dose range, but that the limited population is too small to demonstrate its effect. We would, therefore, like to extract from these data a reasonable upper limit to the slope of a line with a zero intercept at zero dose.

Our approach was to find a slope with an acceptable probability of being too small. This was done by testing linear equations by the procedure previously employed in obtaining the probability data of Table 3. The product of the binomial probabilities of observing zero tumors in each dosage range was interpreted as the probability that the true relationship between incidence and dose was expressed by the equation being tested. The equation which provided a combined probability of 0.10 for observing zero tumors in the eight lowest dosage ranges was

$$I = 3 \times 10^{-5} D,$$

where I is the fractional incidence and D is total number of rads delivered to the entire skeleton from exposure to diagnosis of a tumor. It should be carefully noted that the dose is the average skeletal dose--a quantity easily calculated but not necessarily relevant. We will discuss this point below.

Let us now turn our attention to the two tumor types--the sarcomas and the carcinomas--for it may be that we should consider dose-response functions for the two types separately. Figure 6 (linear coordinates) and Figure 7 (semilog coordinates) show the incidence of the sarcomas and the

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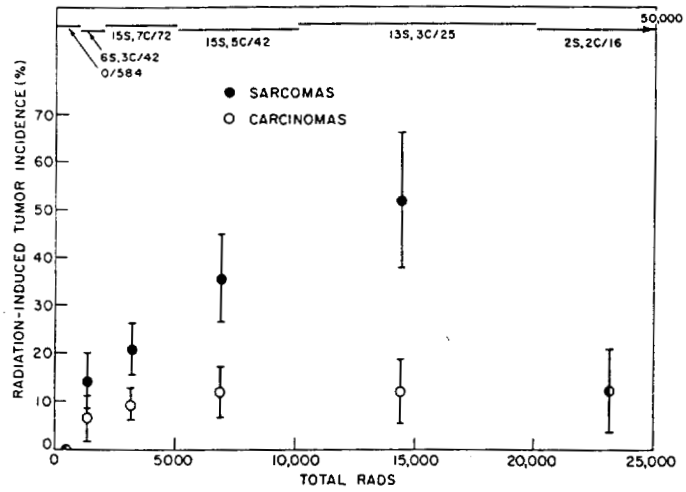

FIG. 6.--The percent incidence of sarcomas and carcinomas plotted separately against the median value of the total skeletal dose in rads in linear coordinates.

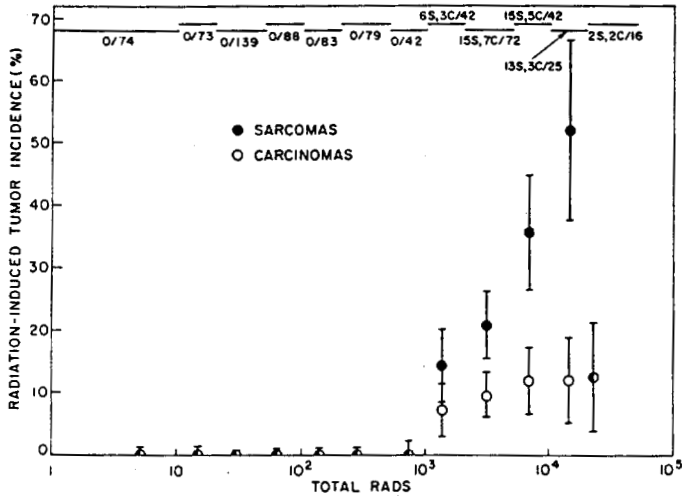

FIG. 7.--The percent incidence of sarcomas and carcinomas plotted separately on a linear scale against the median of the total skeletal dose in rads on a logarithmic scale.

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carcinomas separately, using the same format as previously employed. Turning first to a simple linear hypothesis, we see immediately that, again, these data are not well represented by this kind of function. Indeed, the best we can do is define a linear slope for the region where no tumors are observed. This is, of course, for each tumor type, the same slope that we determined above for the sum of the two tumor types, for we are working with the same total population and the same incidence--zero.

The sarcoma data by themselves can be fitted with equations of the form previously used. The parameters for the least-squares fits are

(2) $I = 8.12 \times 10^{-5} D e^{-D/1.28 \times 10^4}$

(3) $I = 3.90 \times 10^{-8} D^2 e^{-D/4.85 \times 10^3}$

Again, due to the wide discrepancy between the predictions of the linear dose-exponential equation and the zero incidence levels immediately below 1000 rads, the dose squared exponential expression provides a better fit. The incidence predicted for the dose range of 1000 to 2000 rads is more compatible with the observed incidence (probability of 0.03) than was the case for the total tumor data. This expression is shown fitted to the sarcoma data in Figure 8.

The carcinoma incidence appears best fit by a threshold hypothesis, with zero incidence below 1000 rads and a fairly constant incidence above this level. However, quite an acceptable fit was obtained with the linear dose-exponential equation; the parameters are

(2) $I = 3.1 \times 10^{-5} D e^{-D/1.24 \times 10^4}$.

The fit of this expression to the carcinoma data is shown in Figure 8.

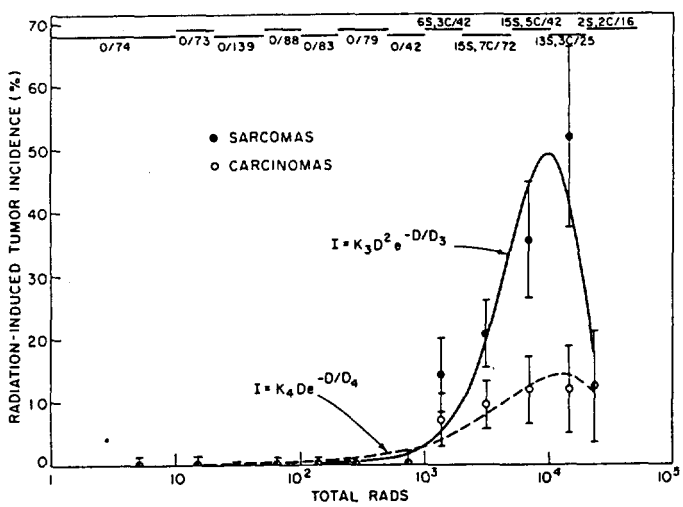

FIG. 8.--A least squares fit of the function $K_3D^2e^{-D/D3}$ superimposed on the sarcoma data of Figure 7 and a least squares fit of the function $K_4De^{-D/D4}$ superimposed on the carcinoma data of Figure 7.

Discussion

We are concerned with the interpretations that may be placed upon calculated doses, particularly in relation to the evaluation of the risk associated with low doses of various types of radiation. For example, we have come to the conclusion that, in the low dose range, a linear tumor incidence equation of the form

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$$I = 3 \times 10^{-5} D,$$

where I is the fractional incidence and D is the total skeletal dose in rads, is a reasonable upper limit, considering the absence of observed tumors in the 584 radium patients. This expression may be rewritten as a tumor incidence of 0.3% per hundred rads.

This expression has been derived on the basis of there being only a 10% probability that a linear tumor incidence for these data could be this large. Nevertheless, since it has been proposed that the leukemia risk for man lies in the range 0.2 to 0.5% per hundred rads mean dose to the bone marrow,[5] one might be tempted to speculate that the similarity in magnitude of these risks was an indication of a fundamental consistency between dose and malignancy.

We doubt that this is true. For example, the data presented here are valid for ^{226}Ra and ^{228}Ra, but cannot even be extrapolated to cover the effects of ^{224}Ra in man. This is demonstrated by the recent study of Spiess and Mays[6] on the toxicity of ^{224}Ra. They point out that the lowest dose known to produce a sarcoma in their ^{224}Ra series is 90 rads, while the lowest comparable dose in our ^{226}Ra series is 1160 rads. It thus would appear that ^{224}Ra is about 13 times as effective, rad for rad, as ^{226}Ra in producing bone sarcomas in man.

This is the case when the comparison is based on average rads to the skeleton. It is obvious, however, that it is not the energy deposited in bone mineral that gives rise to bone sarcomas, but more likely the energy deposited in certain cells in bone. Spiess and Mays[6] point out that if one calculates the dose delivered to a soft tissue layer 10μ thick adjacent to bone surfaces instead of calculating the average skeletal dose, then the lowest ^{224}Ra sarcoma dose would be increased to 810 rads, while the lowest ^{226}Ra sarcoma dose would be reduced to 760 rads. Thus the 13-fold difference in dose disappears, and the ^{224}Ra and ^{226}Ra doses required to produce a sarcoma become almost identical.

The point we wish to emphasize is that the data we have presented

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for ^{226}Ra and ^{228}Ra, based as they are on average skeletal dose, cannot be readily used to describe the toxicity of any other form of radiation. This is not to imply that results following exposure to one form of radiation cannot be used to estimate risks from a different type of radiation. Indeed, it is our expectation that they can, as is demonstrated by the agreement of ^{224}Ra and ^{226}Ra results when the relevant dosimetric basis is used. However, a thorough understanding of micro- and macrodosimetry appears to be required, as well as an understanding of the effects of the type of radiation involved, the dose rate, and the repair processes.

We use the average skeletal dose in our evaluation of the dose-response characteristics of radium in man with full knowledge of its shortcomings. The magnitude is relatively easy to calculate, and we feel relatively secure in comparing the doses received by various individuals in these terms. We are aware that it does not represent the actual dose received by the cells at risk, but then we really do not know where the cells at risk reside, nor how to determine the dose they receive in each of our cases. We caution those who would tend to generalize, that when average skeletal doses are used for bone-seeking radionuclides, a "rad" of ^{226}Ra α energy is not biologically equivalent to a "rad" of ^{224}Ra α energy, and both of these may differ from a "rad" of ^{239}Pu α energy or ^{90}Sr β energy. Meaningful dose comparisons can only be made when the appropriate targets have been identified and the energy distributions within these targets determined.

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Conclusions

We have examined dose-response relationships which may be used to describe the total tumor invidence vs. total skeletal dose for a large group of radium patients, and conclude that a dose-squared exponential expression of the form

$$I = KD^2 e^{-D/D_0}$$

is contradicted only by the tumor incidence observed in one of our 13 dose

ranges. Such an expression can also be used to describe the incidence of bone sarcomas for this group of cases. The radiation-induced carcinomas, however, seem to be better fitted by an expression of the form

$$I = KDe^{-D/D_0},$$

but the fact that these malignancies appear later than the sarcomas, and that as yet they are relatively few in number, may caution us not to place too much significance on this result.

A total risk of malginancies of the order of 0.3% per hundred rads can be considered as an upper limit for the dose range below 1000 rads where no malignancies have been observed.

It should be kept in mind that if the natural incidence of sarcoma is of the order of 10^{-5} per man per year, then, based on a 40-year observation period, we would predict $40 \times 800 \times 10^{-5}$ naturally occurring sarcomas in our series, i.e., 0.3. Since we can only observe sarcomas as integers, it is reasonable to calculate the probabilities of having zero, one, or two natural sarcomas. These probabilities are, respectively, 73%, 23%, and 3.7%. Since we have no means at present for differentiating between a natural and a radiation-induced sarcoma, we will have to consider every sarcoma found, regardless of the dose level, as possibly being radiation induced.

This paper, originally prepared for oral presentation at the IVth International Congress of Radiation Research, Evian, France, has drawn on the work of many individuals. We have depended heavily on Mary Margaret Shanahan for interpretation of the MIT data and dose calculations, and on Dr. Harvey Schultz for retrieval of information from our files. The least squares fits were obtained with the help of Dr. John Rundo.

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Appendix

The preceding paper has examined dose-response curves which are based on a sample of 777 radium cases in which a total of 71 malignancies were considered to be radium induced. For completeness, we tabulate here the cases with malignancies which we have included.

We request that these lists be considered preliminary and subject to change. With the extremely short time that the Center for Human Radiobiology has been in existence, there has been little or no time for verification on our part of the cases listed in Table 4.

TABLE 4. Malignancies in the ANL-ACRH Series

Case Number	Reference	Tumors Considered to be Radiation Induced	
		Sarcomas	Carcinomas
03-105	7		x
03-110	1	x	x
03-126	7		x
03-141	7		x
03-214	7		x
03-232	7		x
03-235	7		x
03-402	7	x	x
03-407	7		x
03-417	7		x
*03-648	7	x	x
03-118	7	x	
03-201	7	x	
03-209	7	x	
03-210	7	x	
03-212	7	x	
03-213	7	x	
03-215	7	x	
03-216	7	x	
03-227	7	x	
03-234	7	x	
03-401	7	x	
03-429	8	x	
03-455	1	x	
03-584	7	x	
03-619	7	x	
*03-649	7	x	
03-671	7	x	
Total		20	11

*These cases also appear in the MIT series.

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TABLE 5. Malignancies in the MIT Series

Case No.	Tumors considered radiation induced		Case No.	Tumors considered radiation induced	
	Sarcomas	Carcinomas		Sarcomas	Carcinomas
01-006		x	01-024	x	
01-008		x	01-025	x	
*01-013	x	x	01-026	x	
01-014		x	01-031	x	
01-022		x	01-032	x	
01-145		x	01-033	x	
01-149		x	01-046	x	
01-171		x	01-059	x	
01-179	x	x	01-073	x	
01-573		x	01-079	x	
00-003	x		01-099	x	
00-004	x		01-105	x	
00-005	x		01-112	x	
00-006	x		01-172	x	
00-007	x		01-239	x	
00-027	x		01-268	x	
00-028	x		01-389	x	
01-007	x		01-439	x	
01-009	x		01-520	x	
01-011	x		05-215	x	
*01-023	x		Total	33	10

*These cases also appear in the ANL-ACRH Series.

A few comments regarding the selection of these cases is in order. First, since it is clearly stated in Reference 8 that Case 03-685 is not to be considered as having a malignant lesion, we have not included it. However, we have included a case the principal investigators of the ANL-ACRH studies did not include in their lists of malignancies. This is Case 03-110, which was suspected of having both a sarcoma of the left first metacarpal and a possible mastoid carcinoma.[1] We have included both of these suspected malignancies, for we would rather err on the conservative side (i.e., attributing a malignancy to radiation) than to leave out malignancies which might well be considered by some to be due to radiation.

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To our knowledge, no published list of MIT malignancies exists, although all have been published in the MIT Annual Progress Reports. We have, therefore, compiled the data in Table 5 from the records in our possession. Errors of omission or commission which may be present in this compilation are not to be attributed to the MIT investigators; they are clearly the responsibility of the new Center for Human Radiobiology.

References

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