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EDITOR-IN-CHIEF: R. J. M. FRY

Volume 115, 1988

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RADIATION RESEARCH 115, 238–257 (1988)

An Epidemiological Assessment of Lens Opacifications That Impaired Vision in Patients Injected with Radium-224[1]

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CHMELEVSKY, D., MAYS, C. W., SPIESS, H., STEFANI, F. H., AND KELLERER, A. M. An Epidemiological Assessment of Lens Opacifications That Impaired Vision in Patients Injected with Radium-224. *Radiat. Res.* **115**, 238–257 (1988).

The incidence of lens opacifications that impaired vision (cataract) was analyzed among 831 patients who were injected with known dosages of ^{224}Ra in Germany shortly after World War II. The dependence of the incidence on dosage, i.e., injected activity per unit body weight, and on time after treatment was determined. The observations are equally consistent with proportionality of the incidence of cataract to the square of dosage or with a linear dependence beyond a threshold of 0.5 MBq/kg. The possibility of a linear dependence without threshold was strongly rejected ($P < 0.001$). The analysis of temporal dependences yielded a component that was correlated with the injected amount of ^{224}Ra and a component that was uncorrelated. The former

[1] Work performed under Euratom contracts BI-6-D-0083-D (B), BI-6-F-111-D, and BI-D-461-D (B), and U.S. Department of Energy contract DE-ACO2-76 EV-00119.

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was inferred by a maximum likelihood analysis to increase approximately as the square of the time after treatment. The component unrelated to the treatment was found to increase steeply with age and to become dominant within the collective of patients between age 50 and 60. The relative magnitudes of the two components were such that a fraction of 55 to 60% of the total of 58 cataracts had to be ascribed to the dose-related incidence. Impaired vision due to cataract was diagnosed before age 54 in 25 cases. In terms of injected activity per unit body weight no dependence of the sensitivity on age was found; specifically there was no indication of a faster occurrence of the treatment-related cataracts in patients treated at older ages. © 1988 Academic Press, Inc.

I. INTRODUCTION

The lens of the eye has long been recognized to be particularly sensitive to ionizing radiations. The history of experimental studies and clinical observations began within a few years of Röntgen's discovery of X rays. A bilateral anterior polar cataract in a guinea pig exposed to soft X rays was reported (although not ascribed to the exposure) in 1897 (*1*). In 1905 Treutler stated (*2*): "In an employee of an X-ray laboratory in Hamburg I noticed a bilateral posterior polar cataract. According to the statement of the patient he had good vision bilaterally before he was employed as an X-ray worker, while his visual acuity at the time of the examination was 6/60."

Dependences of the frequency of cataracts on absorbed dose and on radiation quality have been determined in various animal studies (*3–7*). Radiation-induced cataracts were reported among the survivors of the atomic bomb explosions in Hiroshima and Nagasaki (*8–10*) and for cyclotron workers (*11*). Of particular importance have been the observations of Merriam and Focht on radiotherapy patients (*12, 13*). In 1969 Spiess (*14*) reported an increased incidence of cataracts in the follow-up study of patients injected with ^{224}Ra. Enhanced frequencies of cataracts were also reported for dial painters who ingested large activities of ^{224}Ra (*15*). Additional studies dealt with the possible induction of cataracts by other internal emitters (*16*), with cataracts among leukemia patients exposed to high-dose whole-body irradiations (*17*), and with cataracts among radiation workers (*18*). A recent report includes a comprehensive review of radiation-induced cataracts in man (*19*).

The Spiess group of more than 800 patients exposed to ^{224}Ra has been subject to a careful follow-up. The resulting data are a unique source of information on the deleterious effects of a short-lived α-emitter (*20*). The completeness of the follow-up was achieved through the collaboration, over more than 30 years, among the patients, their doctors, and H. Spiess. Contact is still kept with nearly 400 surviving patients. Of particular importance has been the analysis of the dose and time dependence of the incidence of bone sarcomas (*21, 22*). The follow-up has also demonstrated other severe late radiation effects, such as growth retardation (*23*), tooth breakage (*24*), and kidney diseases (*25*). A summary of observations on cataracts, together with clinical case descriptions, has been given recently (*26*), and a strong correlation ($P < 0.001$) was shown between the frequency of cataracts and the injected activity.

It is the objective of the present report to quantify these results further and to deduce the dose and time dependences that underlie the observed correlation. Dosages are expressed in terms of the injected activity of ^{224}Ra relative to the body weight of the patients.[3] It is not possible at present to convert the activity divided by body

[3] The term "dosage" and the symbol A are used for the activity divided by the body weight to avoid confusion with absorbed dose, D.

weight into absorbed dose in the lens epithelium of the eye. But information from animal studies (*27*) may, in the future, permit a conversion of the injected dosages into values of absorbed dose.

II. METHODS

From 1945 to about 1952 repeated intravenous injections of ^{224}Ra were given to German children and adults, mainly for the intended treatment of tuberculosis and ankylosing spondylitis. In 1952 Spiess began a follow-up of these patients, initially by personal contact, hospital examination, and letters. Since 1964 their health status has been evaluated at about 3-year intervals by questionnaires mailed to the patients and with help from their physicians. Details of the procedures have been given earlier (*25*).

Initially, there was no reason to assume that injected ^{224}Ra might cause cataracts,[4] and the early questionnaires did not specifically deal with vision. However, by 1967 six patients had reported cataracts, and Spiess began to suspect that some might be radiation induced (*14*). Thus, beginning in 1969, the questionnaires inquired about problems with vision and the identity of the patient's ophthalmologist. It is, accordingly, possible that a few cases might have been missed among those patients who died prior to 1969.

Subsequently, an increasing number of patients reported lens opacification that impaired vision. Most of these were diagnosed when the patients experienced vision problems and consulted their ophthalmologists. The large majority of patients with lens opacification in one eye also developed an opacification in the other eye within a few years. Thus we tabulate the number of patients with cataract, rather than the total number of cataracts.

The classical radiation effect on the lens is a posterior subcapsular cataract, thought to be induced by damage to the actively proliferating germinal epithelial cells on the anterior aspect of the lens equator. The damaged epithelial cells produce defective lens fibers which accumulate at the posterior pole of the lens, creating a cataract, as first described in humans by Treutler in 1905 (*2*). Until recently there have been, in this collective of patients, no sequential ophthalmologic examinations to identify "subclinical" lens damages and observe their eventual progression. Such examinations have been initiated for the younger patients who are now in their forties. Thus it may be possible, in the years to come, to distinguish clinically in some cases between radiation-induced cataracts and other forms of cataracts.

Among 25 lens opacifications diagnosed before age 54 we have written confirmation by the patient's ophthalmologist or a record of cataract extraction for all but 4. For the total of 58 reported diagnoses we have such confirmation or the documentation of cataract extraction in 42 cases. In Germany cataract extractions are always preceded by a detailed ophthalmological examination, and they are only exceptionally performed at a visual acuity above 0.1 (20/200). For 11 cases an additional slit-lamp examination and documentation was performed at the Munich University Eye Hospital by one of us (F.H.S.). It was then found in most cases that the cataracts were located on the posterior pole of the lens and appeared as a plaque of conglomerated irregular granules interspersed with vacuoles (*26*).

A list of the patients with cataracts is given in the appendix.

As pointed out earlier (*26*), no evidence was found that enhanced cataract rates were caused by the trace amounts of eosin and colloidal platinum that accompanied most of the ^{224}Ra injections, although an influence of this admixture cannot be entirely excluded.[5] There is also no indication that males and females have different sensitivity to cataract induction. Consequently male and female patients were combined in the present analysis.

Enhanced cataract frequencies have been reported in ankylosing spondylitis patients, and a marked association with tuberculosis had been assumed in the past, although it is now considered less likely (*28*). Possible associations with the original disease do not interfere with the subsequent analysis which is concerned with correlations to injected activity, not with overall rates in the tuberculosis and ankylosing spon-

---

[4] Ophthalmologists term any opacity of the lens a cataract; the term therefore includes small opacities not interfering with vision. However, in the present report it is used to designate a lens opacification sufficiently progressed to impair vision.

[5] It has been pointed out in the earlier study (*26*) that no enhanced cataract rates were observed following tatooing of the cornea with platinum salt, or following the use in the United States in the 1930s of substantially larger doses of eosin (Rose Bengal) for liver-function tests in about a million patients.

TABLE I

Synopsis of Data through 1986

	Number of		Mean age*			Mean dosage[a] (MBq/kg)
	Patients	Cataracts	At first injection	At last follow-up	At cataract	
All adults	627	44	38.7 (10.8)	61.1 (11.7)	59.5 (12.7)	0.551 (0.397)
Spondylitis	365	24	41.3 (9.5)	63.1 (10.0)	62.6 (11.5)	0.379 (0.265)
Tuberculosis	218	19	33.5 (10.6)	58.0 (13.1)	56.2 (13.3)	0.858 (0.598)
Other	44	1	43.1 (12.6)	60.5 (13.5)	48.0 (—)	0.457 (0.333)
Male adults	468	33	39.3 (10.2)	61.5 (11.1)	58.9 (12.3)	0.489 (0.401)
Spondylitis	344	22	41.2 (9.4)	62.9 (10.1)	62.2 (11.8)	0.376 (0.265)
Tuberculosis	104	11	32.7 (9.7)	57.1 (12.6)	52.4 (10.5)	0.858 (0.535)
Other	20	0	40.6 (10.8)	58.8 (13.6)	— (—)	0.509 (0.372)
Female adults	159	11	37.0 (12.4)	60.1 (13.1)	61.1 (13.7)	0.734 (0.589)
Spondylitis	21	2	42.5 (10.7)	64.9 (8.5)	66.5 (6.5)	0.429 (0.259)
Tuberculosis	114	8	34.2 (11.2)	58.8 (13.5)	61.4 (14.8)	0.858 (0.632)
Other	24	1	45.3 (13.5)	62.0 (13.3)	48.0 (—)	0.414 (0.290)
Juveniles	204	14	11.6 (5.3)	37.7 (12.6)	33.1 (9.9)	1.036 (0.807)
Boys	105	5	11.6 (5.3)	38.8 (12.2)	31.0 (5.1)	1.095 (0.887)
Girls	99	9	11.7 (5.3)	36.5 (12.9)	34.3 (11.5)	0.973 (0.707)

Note. Number of patients included in analysis = 831. Number of patients with cataract = 58 (two before treatment: one within 1 year after treatment). Thirty-eight patients excluded from analysis because of missing dose information: 30 without follow-up.

[a] Mean and standard deviation.

dylitis patients. The correlation with dosage is not a correlation with the severity of original disease, because dosages varied substantially between different clinics and decreased markedly in consecutive years of the period when the ^{224}Ra treatment was practiced.

The principal purpose of the present analysis is to provide the dosage and time association of the incidence of cataracts and to compare the dependence for ^{224}Ra with those for X and γ rays. As pointed out, most lens opacifications were registered when they had developed far enough to impair vision. It was decided, therefore, to utilize, as far as possible, a uniform criterion and to record each cataract at a stage when it interfered with vision. A few lens opacifications which happened to be discovered at an early stage were accordingly assigned the later dates that corresponded to impaired vision.

The somewhat loose criteria of impaired vision that had to be used in this study might suggest that in some cases cataracts have been misdiagnosed, and that some acuity deficits might have been due to macular and other retinal defects. However, this is unlikely because there has been, in almost all cases, confirmation by an ophthalmologist of well-progressed cataracts. The major source of uncertainty appears to be merely the variability of the times to diagnosis which depended on the patient's perception of impaired vision.

III. SYNOPSIS OF THE DATA

Table I represents essential aspects of the data. The categorization is largely identical to the one in earlier reports (*14, 20, 25*).

Adults treated for bone tuberculosis were, on average, somewhat younger and received about twice the dosage as adults treated for ankylosing spondylitis. The juveniles were mostly treated for tuberculosis and received the highest dosages.

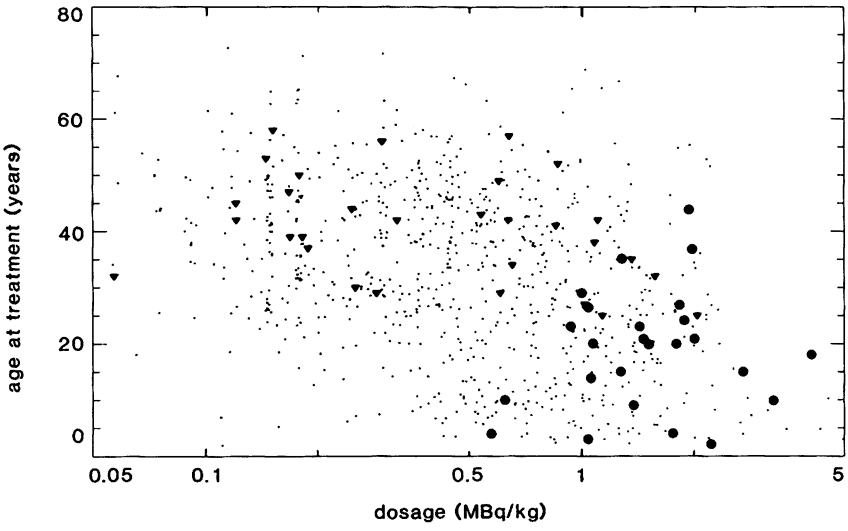

FIG. 1. Diagram of ages at injection and dosages, i.e., injected ^{224}Ra activities divided by body weight. Each patient is represented by a point. Patients who subsequently developed a cataract are represented by a solid dot (cataract before age 54) or by a triangle (diagnosis at age 54 or later).

The subsequent analysis includes 831 patients of known dosage with follow-up times exceeding 1 year. Cataract diagnoses of more than 1 year after treatment were reported in 55 cases, among them 25 before age 54. Factors such as sex, duration of treatment, or cause of treatment have not been included in the present analysis, since we found no indication of an influence of these factors.

In Fig. 1 each patient is plotted by the dosage received and the age at treatment. Patients who subsequently developed a cataract before age 54 are marked by a heavy dot. Patients who developed a cataract at a later age are marked by a triangle.

Figure 2 gives the information in more detail. The abscissa specifies the dosage, and the vertical lines connect the age at treatment to the age at diagnosis for those patients who developed cataracts. Over a wide range of dosages there were a substantial number of cataracts at higher ages; the early cataracts (before age 54), however, occurred predominantly at higher dosages.

A quantitative assessment of the frequency of patients with cataracts needs to be related to the number of patients at risk in the different dosage and age classes. To avoid the confusion of too many lines, for each patient without a known cataract the vertical line from treatment to the end of observation is replaced by a series of points with, on average, one point for each 5 years of observation. In this way one can judge the number of patients with cataracts and their age at injection and age at diagnosis in relation to the total number of patients at risk. This comparison demonstrates even more clearly that cataracts at ages above roughly 55 tend to be distributed nearly uniformly among patients in the entire dosage range while the early cataracts occurred predominantly in patients with higher dosages.

On a first, exploratory level the analysis will be restricted to a follow-up of the patients through age 53. The division line is somewhat arbitrary in view of the limited data for general populations (*29–35*) and the unknown influence of the original dis-

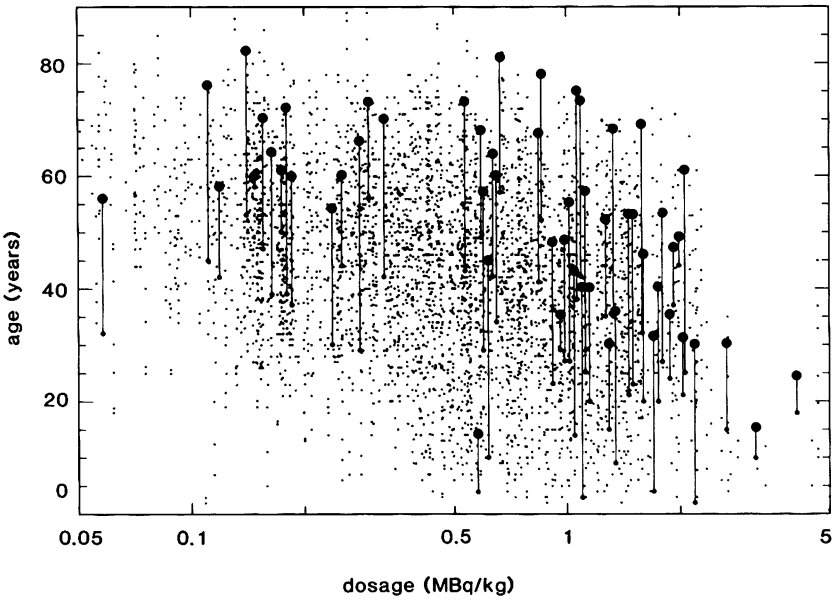

FIG. 2. The 55 patients with cataracts more than 1 year after injection are represented by vertical lines from their age at injection to age at diagnosis. The 773 patients without known cataracts are represented each by a vertical chain of points from age at injection to death or end of observation, with one point on the average per 5 years at risk. The point density in the resulting scatter diagram indicates the relative number of patients at risk at a specified age and dosage.

eases. However, it will be seen that the numerical results are substantially in line with a more general analysis that utilizes no cutoff but is, of necessity, more complex.

Figure 3 affords a visualization of the distribution of early (prior to age 54) cataracts in dosage, age at treatment, and time from treatment to diagnosis. The representation is largely analogous to that in Fig. 2. The abscissa is again the dosage. The ordinate is a temporal scale relative to the time of injection. Each patient with an early cataract is represented by a vertical line. The upper part of the line gives the time from injection to diagnosis; the total length of the line is the age of the patient at diagnosis of his cataract.

One point is plotted in the lower part of the diagram for each patient (heavier dots for the patients with cataract) to indicate the distribution of ages at treatment. In the upper part of the diagram the same method is used as in Fig. 2, i.e., each line for a patient without a reported cataract is replaced by a series of points, with one point on the average for each 5 years of follow-up through age 53.

IV. ANALYSIS IN TERMS OF DOSAGE CLASSES

The simplest analysis consists of forming several dosage classes and determining for these classes the fraction of patients who developed a cataract up to a specified time after injection. Figure 4 permits a synopsis of the data for this type of analysis. Ages at injection and times to diagnosis are given as heavy dots for those patients who developed a cataract; they are superimposed on the distribution of points which

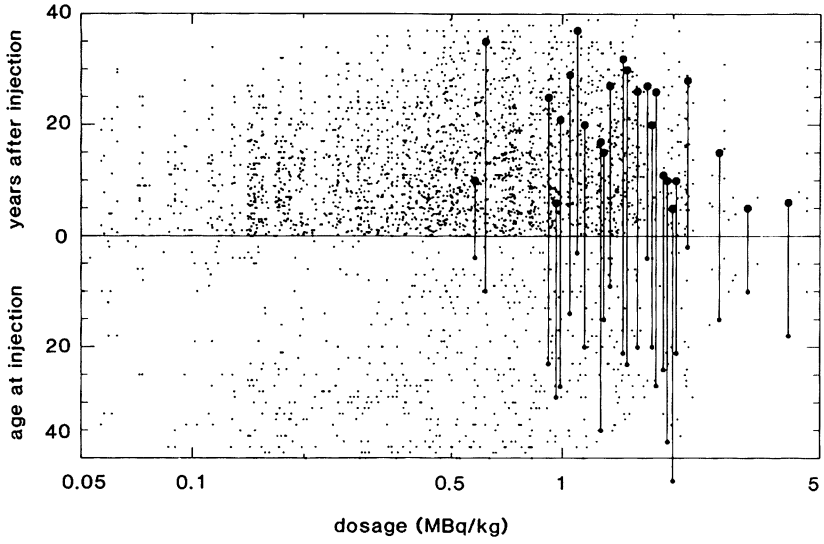

FIG. 3. The 25 patients with cataracts before age 54 are represented by vertical lines from their years of birth (relative to the year of injection) to the year of diagnosis. The locations of the light and heavy dots represent the distributions of age at injection and of time to diagnosis within the range of dosages, respectively. The light points on the lower half of the diagram give the age at ^{224}Ra injection for the patients without early cataracts. The scatter diagram in the upper part is analogous to that in Fig. 2. It gives one point per 5 years at risk up to age 54 for each patient without early cataract.

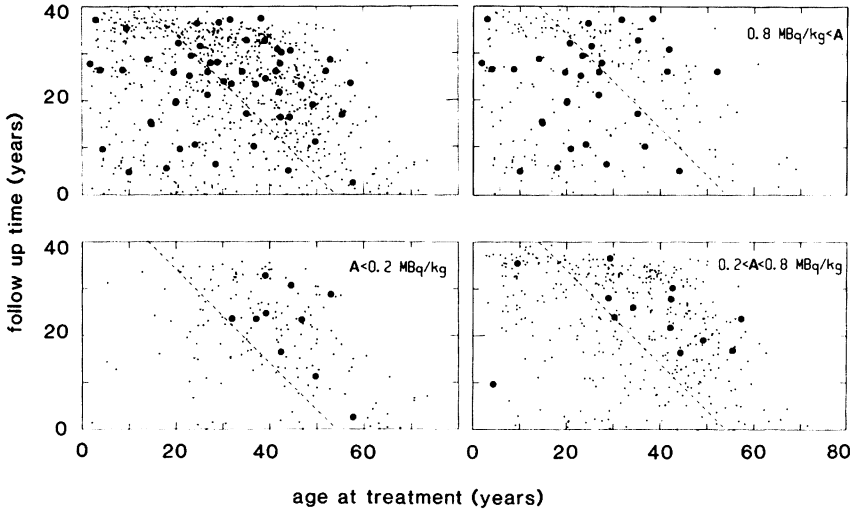

FIG. 4. Diagram of ages at injection versus time from injection to cataract (heavy dots) or last year of observation, up to 1986 (light points), for patients without reported cataracts. Each patient is represented by a single point. The broken lines indicate the cut-off at 54 years of age. Left upper panel, all dosages. Other panels, specified ranges of dosage.

give the age at injection and the total duration of follow-up (to 1986) for those patients who have not developed a cataract. The broken lines are inserted to separate the early opacifications from those that occurred later. It is evident that the early cataracts, i.e., those before the age of 54 (heavy dots below the broken line), occurred predominantly in the group of patients treated with higher dosages. The number of early cataracts in relation to the average dosages in each class not only shows the strong correlation to dosage, but indicates, even in this simple representation, that the correlation is not a proportionality, but a threshold-like dependence. This will be quantified in the subsequent analysis.

To obtain dependences on time after treatment in the different dosage classes, one needs methods that correct for competing risks, i.e., for the fact that some patients are lost from observation during the follow-up. The use of crude estimates could lead to results which are biased by differences of the follow-up times in the different dosage classes. Therefore, one uses for the analysis, the sum-limit estimate which has, in the same collective of patients, been used also for the analysis of bone sarcoma rates (*21*), and which is largely equivalent to the familiar Kaplan–Meier, or product–limit, estimate (*36, 37*). The method has been explained earlier (*38, 39*). The estimated cumulative rates, $\hat{R}(t)$, (cumulative-hazard rates) are obtained from the formula for the sum-limit estimate

$$\hat{R}(t) = \sum_{t_i \leqslant t} \frac{1}{N_i} \tag{1}$$

where t_i are the times after treatment when a cataract was diagnosed, and N_i is the number of patients with a follow-up time of not less than t_i. Patients were removed from the analysis at age 54. The summation includes cataracts diagnosed within the follow-up time t.

In view of the limited number of patients and of early cataracts, the cumulative rates after treatment are derived only for three different dosage ranges, as shown in Fig. 5. There were no early cataracts at dosages below 0.2 MBq/kg. The diagram confirms that the estimated cumulative rates increase with dosages in a nonlinear fashion.

For the patients injected as juveniles (Fig. 5, lower panel) there is no indication of systematically higher cumulative rates than for all patients (Fig. 5, upper panel). Nor is there a recognizable change of the temporal distribution with dosage; the earlier occurrence of some cataracts at the higher dose levels may merely reflect the overall increased frequencies. The data are consistent with a cumulative incidence that does not depend on age at treatment and that exhibits the same time course, apart from a dose-dependent factor. These conclusions will next be substantiated by an analysis that avoids the arbitrary separation into dosage classes.

V. ANALYSIS IN TERMS OF THE PROPORTIONAL HAZARDS MODEL

The results of the comparatively simple analysis in the preceding section are consistent with a proportional hazards model. Such a model postulates that rate factors into dependences on time after treatment and dosage,

$$R(t, A) = R(t)(aA + A^2)e^{-cA}, \tag{2}$$

where t is the time after treatment, and A is the value of the dosage expressed in

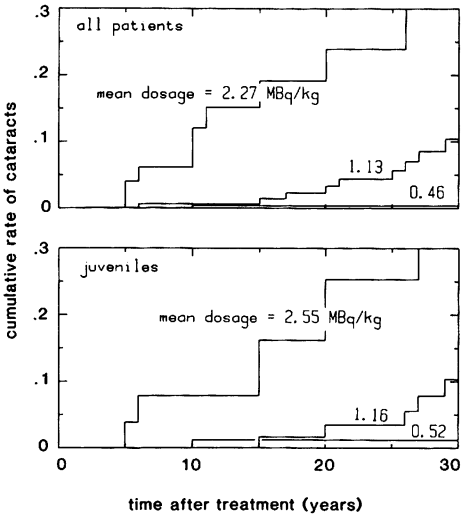

FIG. 5. Cumulative rates of cataracts versus time after injection. The curves are obtained from the sum limit estimate (Eq. (1)). The three relations correspond to the dosage ranges 0.2 to 0.8 MBq/kg, 0.8 to 1.6 MBq/kg, and 1.6 MBq/kg and beyond. The numbers of patients (and the numbers of cataracts before age 54) are 386 (2), 176 (12), and 56 (11) for the three groups in the upper panel, and 89 (2), 76 (6), and 30 (6) for the lower panel. Patients are included in the computations up to age 54.

MBq/kg. Suitable scaling of the so-called baseline function, $R(t)$, can make the coefficient with the linear or the quadratic term in dosage equal to unity. Since the quadratic term will be seen to be dominant, its coefficient is set equal to unity.

The model of Eq. (2) avoids the arbitrary separation into dosage classes. $R(t)$ can be any increasing dependence on time; it is determined by a maximum likelihood fit to the data. The dosage-dependent term is the familiar linear–quadratic dependence, with additional exponential term to account for possible deviations from the linear–quadratic dependence at larger doses. As far as the dosage dependence is concerned, the maximum likelihood fit determines merely the two parameters a and c. At this stage of the analysis patients were still considered only through age 53.

The baseline function and the parameters a and c are derived by maximizing the partial likelihood corresponding to Eq. (2). The maximum likelihood solution is obtained by a suitable modification of the algorithm of Cox (*36*). If, as stated, the dosage is expressed in MBq/kg, the optimum likelihood is achieved with $c = 0.35$ and a negative coefficient $a = -0.444$. Although negative values of $R(t, A)$ are, of course, meaningless, the solution is admissible because no early cataracts were observed at dosages less than a. The dosage dependence corresponding to the estimated parameters a and c is represented in Fig. 6 (dotted curve). The cumulative rate for a dosage 1 MBq/kg is given in the lower panel of Fig. 7. The estimated dosage dependence is, except for the highest dosages, quite close to a dose-squared dependence. The maximum likelihood solution of this simpler model,

$$R(t, A) = R(t)A^2, \tag{3}$$

is represented in Fig. 6 (solid line) and in the top panel of Fig. 7. The estimated

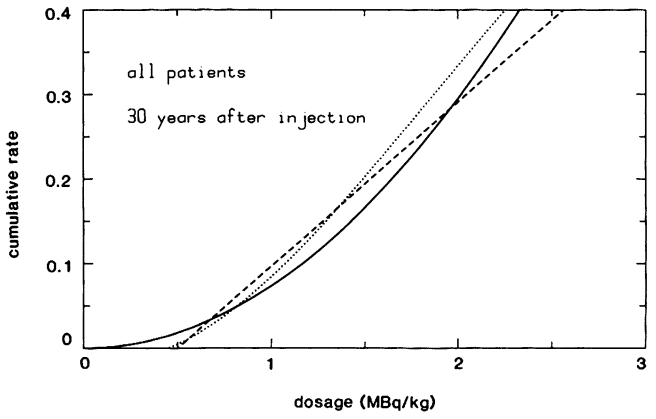

FIG. 6. Cumulative rate of cataracts 30 years after injection according to the proportional hazards models with nonparametric time dependence and three different dosage dependences. Solid curve, dose-squared model (Eq. (3)); straight line, linear model with threshold (Eq. (5)); dotted curve, linear–quadratic model (Eq. (2)). For numerical values of the parameters see Table II.

coefficients and the likelihood values for the two models are given in Table II. The more general model of Eq. (2) must evidently result in a somewhat better likelihood. However, the difference in likelihoods is too small to reject the simpler dose-squared

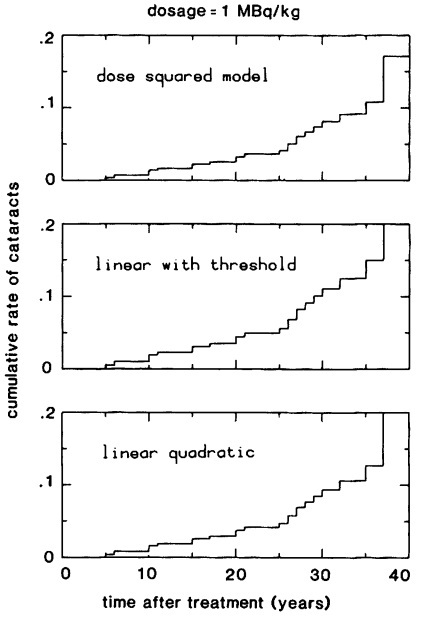

FIG. 7. Cumulative rate of cataract versus time after injection with a dosage $A = 1$ MBq/kg, according to the proportional hazards model with the three different dosage dependences: upper panel, dose-squared model (Eq. (3)); middle panel, linear model with threshold (Eq. (5)); lower panel, linear–quadratic model (Eq. (2)).

TABLE II

Analysis in Terms of Proportional Hazards Models

Age at treatment (years)	*Number of patients (of patients with cataracts)*	*Values of log-likelihood, L, and parameters*			
		$f(A) = A^2$	$f(A) = (aA + A^2) \times \exp(-cA)$	*Threshold (see Eq. (5))*	$f(A) = A^p$
<21	204 (14)	$L = -57.1$	$L = -56.6$ $a = -0.351$ $c = 0.292$	$L = -56.9$ $A_T = 0.455$	$L = -57.1$ $p = 1.9$
All ages	763 (25)	$L = -117.4$	$L = -115.71$ $a = -0.444$ $c = 0.351$	$L = -116.2$ $A_T = 0.5$	$L = -117.4$ $p = 2.1$

Note. Follow-up up to age 54; $R(t, A) = R(t) \cdot f(A)$; t, time after injection; A, dosage in MBq/kg.

model. This is also supported by computations in terms of a model that postulates a dependence on dosage with an unspecified exponent, p:

$$R(t, A) = R(t)A^p. \tag{4}$$

The value of p resulting from the maximum likelihood analysis is very close to 2 (see Table II).

One can go a step further and ask whether the data are equally consistent with a linear dependence beyond a dosage threshold, A_T. Such a threshold dependence has been fitted by Schull and Otake to the observations in the atomic bomb survivors (*40, 41*). The dependence has the form

$$R(t, A) = \begin{cases} 0 & \text{for} \quad A \leq A_T \\ R(t)(A - A_T) & \text{for} \quad A > A_T. \end{cases} \tag{5}$$

The same numerical methods are utilized as with Eqs. (2)–(4) to obtain the maximum likelihood solution. The result is represented by the dashed line in Fig. 6 and the middle panel of Fig. 7. The inferred dosage threshold is $A_T = 0.5$ MBq/kg. At twice the threshold, i.e., at dosage $A = 1$ MBq/kg, the estimated cumulative rate 30 years after injection lies between 0.08 and 0.1. This agrees roughly with the value estimated by Schull and Otake (*40, 41*) at twice their assumed threshold dose. The likelihood achieved with the threshold model is somewhat superior to the likelihood achieved with the dose-squared model. This is to be expected since the threshold model has one more free parameter than the dose-squared model. The difference in the values of the likelihood is not sufficient to reject the dose-squared model in favor of the threshold model. Both models afford an adequate representation of the data.

To detect a possible age dependence of the response, additional computations were performed that were restricted to the patients below age 21 at treatment. However, as seen in Table II, substantially the same results were obtained, i.e., no age dependence is recognizable in the data. Figure 8 gives the dose dependences for the juve-

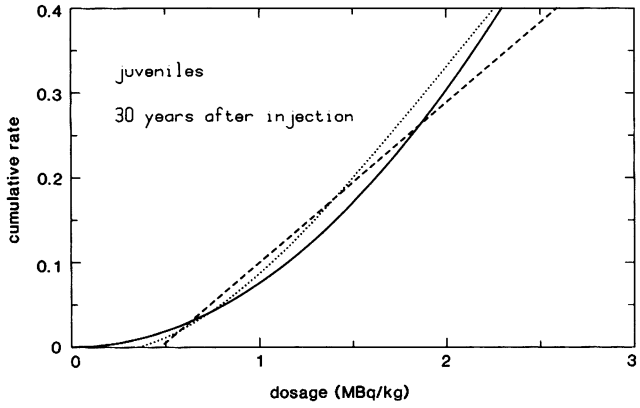

FIG. 8. Cumulative rate of cataract 30 years after injection for patients less than 21 years at injection. The relations are derived according to the proportional hazards model with nonparametric time dependence and three different dosage dependences: solid curve, dose-squared model (Eq. (3)); straight line, linear model with threshold (Eq. (5)); dotted curve, linear–quadratic model (Eq. (2)).

niles. Figure 9 gives, in separate panels for juveniles and all patients, the temporal dependence of the cumulative rate, $R(t)$, resulting from the dose-squared model of Eq. (3). The absence of a dependence on age at treatment appears to be in general agreement with earlier conclusions by Schull and Otake (*40, 41*). However, such agreement depends on the uncertain assumption that absorbed doses to the lens of juveniles and adults are equal at equal injected activity per unit body weight.

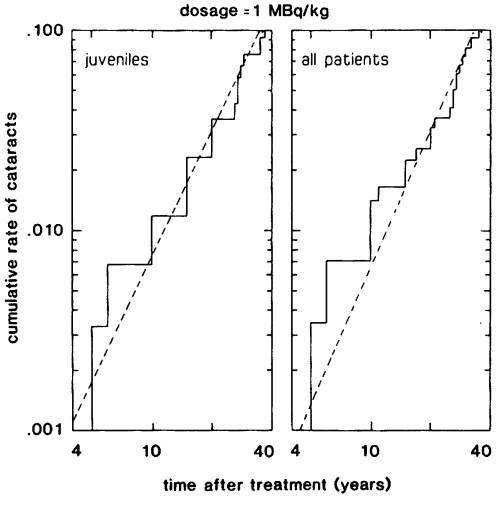

FIG. 9. Cumulative rate of cataracts resulting from the proportional hazards model with dose-squared dependence (Eq. (3)) and for an assumed dosage of 1 MBq/kg. The dependence in the right panel (semilog plot) is identical to the dependence in the upper panel of Fig. 7 (linear plot). The dashed lines are given for comparison. They result from the analysis of all cataracts (see Eq. (6)).

VI. MAXIMUM LIKELIHOOD SOLUTION WITH INCLUSION OF ALL OPACIFICATIONS

An analysis including all cataracts needs to account also for spontaneous cataracts, including those that occur at higher age and may or may be not associated with the original disease. In the literature data are given either for the frequency of cataract surgery (*29, 32, 34*) or for prevalences determined in slit-lamp examinations of population samples at specified ages (*33, 35*). Cataracts detectable by slit-lamp are more numerous than those severe enough to require surgery. The frequencies of age-related, or disease-related, cataracts in the ^{224}Ra patients must be expected to lie somewhere between. In view of this uncertainty a model was employed that assumes merely that lens opacifications unrelated to the ^{224}Ra treatment increase with some power of age,

$$R(t, A) = [c_1 t]^{p_1} A^2 + [c_2(t + \tau)]^{p_2}, \tag{6}$$

where $R(t, A)$ is, in this model, the cumulative rate including both spontaneous and treatment-related cataracts. The time after treatment is t, and τ is the age at injection, so that $(t + \tau)$ is the age of a patient at follow-up time t. The first component represents the ^{224}Ra treatment-related cataracts. Their cumulative rate is set proportional to the square of the dosage and to a power of time after injection. One speaks of Weibull models (*37*) when event rates are assumed to be proportional to a power of time (or of some other reference variable). The first term of Eq. (6) is a Weibull model with reference to both time after injection and dosage. The second component represents the spontaneous cataracts, as a power of age, with a different and, as one infers, substantially larger exponent.

For the numerical solution of a Weibull model standard optimization routines are sufficient. Equation (6), as a sum of two terms, necessitates somewhat more complex procedures. In the present context it is not necessary to deal with details of the algorithm to determine the maximum likelihood values of the four parameters c_1, c_2, p_1, and p_2.

In Table III results are given for the collective of 831 patients who were followed for more than 1 year after injection. The dashed lines in Fig. 9, which represent the dose-dependent term in Eq. (6), show that the inferred dosage and time dependence agrees well with the results of the previous analysis which has been restricted to ages below 54. Figure 10 depicts, for different age cohorts, the total prevalences, including the cataracts which are unrelated to treatment (broken curve).

As a final step the threshold model is considered with inclusion of the age- or disease-related cataracts

$$R(t, A) = \begin{cases} [c_1 t]^{p_1}(A - A_T) + [c_2(t + \tau)]^{p_2} & \text{for} \quad A > A_T \\ [c_2(t + \tau)]^{p_2} & \text{for} \quad A \leqslant A_T. \end{cases} \tag{7}$$

The numerical solution is obtained in analogy to the computations described in the preceding sections. Again it is seen that the threshold dependence fits equally well as the quadratic dependence.

Table III also summarizes additional computations which show that the results remain largely unchanged when somewhat different subgroups of patients are considered. The lines labeled "no exclusions" refer to all 861 patients of known dosage,

TABLE III

Analysis in Terms of Weibull Models

Age at injection (years)	*Number of patients (patients with cataracts)*	c_1	p_1	c_2	p_2	*Log-likelihood*
		Dose-squared model (Eq. (6))				
All ages	831 (55)	0.0108 (±0.003)	2.25[a] (±0.36)	0.0104 (±0.0005)	9.7 (±1.6)	−334.5
No exclusions	861 (58)	0.0099 (±0.003)	2.12 (±0.5)	0.010 (±0.001)	7.7 (±1.5)	−359.4
Spondylitis excluded	487 (34)	0.0105 (±0.002)	2.2 (±0.34)	0.0096 (±0.002)	9.9 (±1.5)	−204.2
Age <21	204 (14)	0.0092	2.04	—	—	−84.3
		Linear model with threshold (Eq. (7)) (A_T = 0.48 MBq/kg)				
All ages	831 (55)	0.0151 (±0.0024)	2.22 (±0.4)	0.0104 (±0.0005)	9.6 (±1.5)	−332.4
No exclusions	861 (58)	0.0146 (±0.003)	2.02 (±0.6)	−0.01 (±0.001)	7.9 (±1.5)	−358.3
Age <21	204 (14)	0.0145	2.1	—	—	−84.3

Note. Units: time and age in years, dosage in MBq/kg. Asymptotic standard errors (see (*36*)) are in parentheses.

[a] Excludes proportionality ($p_1 = 1$) with $P < 0.001$.

including those who were followed only briefly after treatment, or who had a cataract diagnosed prior to or within 1 year after treatment. Further lines refer to the Weibull analysis restricted to those of age below 21 at treatment. Finally, results are given for computations excluding all ankylosing spondylitis patients. The results are close to those for all patients, and this suggests no substantially higher association of cataracts with the original disease in the spondylitis patients.

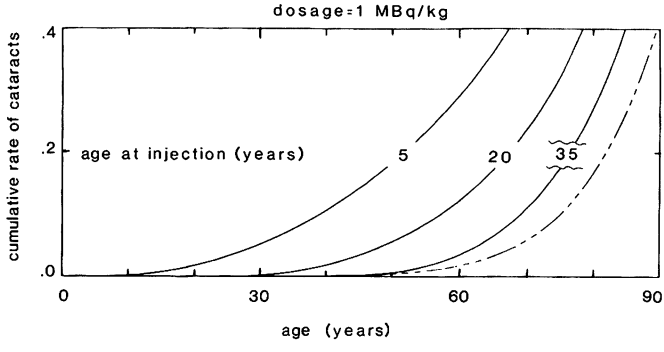

FIG. 10. Cumulative rates of cataracts according to the Weibull model in Eq. (6) versus age for patients with an assumed dosage of 1 MBq/kg at the ages specified on the graph. The broken curve represents the contribution of spontaneous cataracts.

VII. DISCUSSION

The present study is concerned with lens opacifications with impaired vision among the ^{224}Ra patients who have been followed by Spiess since their treatment several decades ago. The earlier finding (*26*) of a strong correlation with ^{224}Ra dosage has been extended to an analysis of functional dependences on dosage and time after treatment. Dosage is expressed as injected activity per body weight. The inferred dosage dependence did not appear to depend on age at treatment; the distribution of times from ^{224}Ra injections to diagnosis did not recognizably change with dosage or age at treatment. This may seem to be in conflict with earlier observations (*12, 42, 43*); but the failure to see a correlation between dosage and time to diagnosis may be due to the limited number of cases and to the uncertainty on how long vision had been impaired before some cataracts were reported.

To make the analysis more transparent, it has been performed in a stepwise fashion. A series of diagrams has first been utilized to relate the diagnoses of severe lens opacifications to the number of patients at risk, to the dosage of ^{224}Ra, to the age at treatment, and to the age at diagnosis. These diagrams show the strong correlation of the incidence of cataracts with dosage. This correlation applies to all ages at treatment and equally to the patients whose intended treatment was for tuberculosis and for ankylosing spondylitis. It is also seen that the correlation to the injected activity relates predominantly to the cataracts diagnosed at relatively early ages. Diagnoses between ages 50 to 60 show less correlation with dosage, and diagnoses beyond age 60 exhibit a correlation predominantly with age.

On a first, exploratory level of the analysis the patients were considered only up to age 54. A linear nonthreshold relationship was strongly rejected ($P < 0.001$). However, the data are consistent with either a dependence on the square of the dosage or a similar dependence with threshold at 0.5 MBq/kg and a linear dependence beyond this threshold. The cumulative incidence of the treatment-related cataracts increases approximately as the square of the time after treatment. This type of dependence appears to apply regardless of age at injection and regardless of dosage.

A more general analysis utilizes a maximum likelihood fit of the data for all ages. It takes account of a component that is dosage correlated and a component that is independent of dosage but is correlated with age. This analysis which relates to all 58 diagnoses of cataracts yields substantially the same results for the dose-related component as was obtained when patients were followed only up to age 54. As shown in Table III, the dosage exponent is substantially larger than unity, i.e., simple linear proportionality is rejected on a high level of significance. Again one concludes that the cumulative rate is equally consistent with a dependence on the square of dosage or with a linear dependence on dosage beyond a threshold of 0.5 MBq/kg.

The same computations, based on the Weibull model, are also applied to subgroups of the patients, such as those treated before age 21, or those who did not suffer from ankylosing spondylitis. In all of these computations one obtains essentially the same result; i.e., the dependence on dosage of injected ^{224}Ra appears to mask whatever differences there may be between individual groups of patients. Specifically one cannot recognize an increased association of lens opacifications with the original disease for any of the groups of patients. In view of the overriding correlation with dosage this is not surprising, and it does not exclude some degree of such associations.

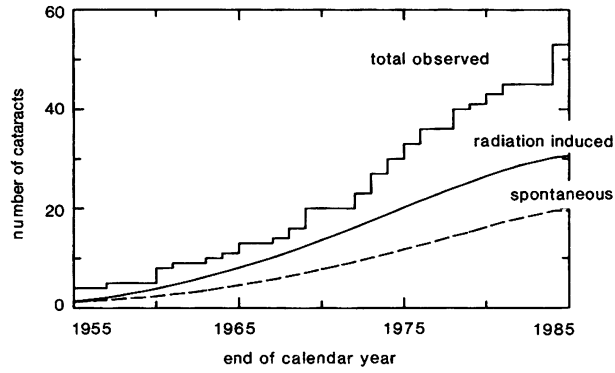

FIG. 11. The cumulative number of cataracts up to the specified calendar year. Step function, observed number of cataracts; continuous curves, the expected number of radiation-induced and spontaneous cataracts according to the Weibull model (Eq. (6)).

Figure 11 gives the observed cumulative frequency of cataracts vs calendar year. It also gives the partition, according to the maximum likelihood fit, into the dosage correlated and the spontaneous cases. Figure 12 gives the analogous information vs age. Nearly 400 surviving patients are still in the follow-up, and in view of the present results the decision has been made to conduct—during the forthcoming years—a systematic examination of those who were treated at younger ages.

Since there is too little knowledge about the metabolism of ^{224}Ra and the absorbed doses to the lens and its surrounding structures, it would be desirable to examine the question in animal experiments. In such studies attention would also have to be given to a possible influence of the colloidal platinum and eosin which were present in trace amounts in most of the ^{224}Ra injections (*44*).

The induction of cataracts is conventionally treated as a nonstochastic effect of ionizing radiations (*45*). The results of the present investigation agree with such a classification, as far as the threshold-like response is concerned. The inferred threshold of 0.5 MBq/kg lies above the dosage of about 0.15 MBq/kg which is applied

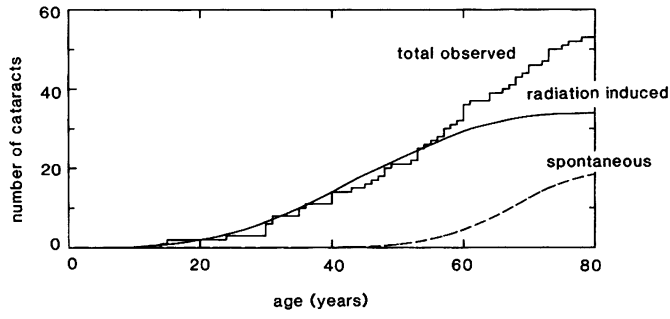

FIG. 12. The cumulative number of cataracts up to the specified age of the ^{224}Ra patients. Step function, observed number of cataracts; continuous curves, the expected number of radiation-induced and spontaneous opacifications according to the Weibull model (Eq. (6)).

in present-day ^{224}Ra treatment of ankylosing spondilitis (*46*); the follow-up of 1600 patients subjected to this treatment has not, up to now, provided evidence of increased frequencies of cataracts (*47*).

APPENDIX: CATARACTS IN ^{224}Ra PATIENTS (AUGUST 1986)

Patient No.		*Age at 1st injection (years)*	*Time to diagnosis (years)*	*Age at diagnosis (years)*	*Injection span (months)*	*Radium-224 dosage (μCi/kg)*	*Skeletal dose (Gy)*	*Original disease*
			Age* 1–10 (94 patients, $\bar{D}$ = 31.5 μCi/kg)					
+1114	m	2 2/12	28	30	27	59.0	24.8	TB
1507	f	3 6/12	37	40	3	28.8	12.1	TB
1113	m	4	27	31	32	45.9	19.3	TB
1503	f	4 5/12	10	14	6	15.6	6.6	TB
1626	f	8 8/12	27	36	19	36.4	15.3	TB
1619	f	10 5/12	35	45	11	16.7	7.0	TB
+1632	f	10 7/12	5	15	39	85.7	36.0	TB
			Age 11–20 (110 patients, $\bar{D}$ = 25.0 μCi/kg)					
1720	f	14 7/12	29	43	7	28.3	11.9	TB
+1724	f	15 6/12	14	30	21	71.9	30.2	TB
+1320	m	15 8/12	15	31	23	35.0	14.7	TB
1431	m	18 2/12	6	24	20	110.7	31.0	TB
+1819	f	19 5/12	20	40	11	29.0	8.1	TB
1825	f	20 4/12	26	46	5	40.3	11.3	TB
1428	m	20 7/12	20	41	15	48.1	13.5	TB
			Age 21–29 (157 patients, $\bar{D}$ = 20.2 μCi/kg)					
494	m	21	32	53	27	38.6	5.4	TB
912	f	21	10	31	8	55.0	7.7	TB
+895	f	23	30	53	23	38.2	5.4	TB
469	m	23	25	48	12	24.8	3.5	TB
505	m	24	11	35	14	50.8	7.1	TB
880	f	25	32	57	14	30.3	4.2	TB
913	f	25	36	61	37	55.7	7.8	TB
974	f	27	21	48	3	28.0	3.9	Arthritis
344	m	27	28	55	15	27.0	3.8	ANK
+502	m	27	26	53	25	48.3	6.8	TB
+475	m	29	6	35	11	27.6	3.9	TB
294	m	29	28	57	3	16.2	2.3	ANK
157	m	29	37	66	2	7.6	1.1	ANK
			Age 30–39 (178 patients, $\bar{D}$ = 12.2 μCi/kg)					
+416	m	30	24	54	?	6.8	1.0	TB
499	m	32	37	69	20	42.8	6.0	TB
7	m	32	24	56	1	1.6	0.2	ANK
(315)	m	32	0	32	5	19.8	2.8	ANK
449	m	34	26	60	8	17.6	2.5	TB
+486	m	35	17	52	19	34.3	4.8	TB
889	f	35	33	68	16	36.0	5.0	TB

APPENDIX—*Continued*

Patient No.		Age at 1st injection (years)	Time to diagnosis (years)	Age at diagnosis (years)	Injection span (months)	Radium-224 dosage (μCi/kg)	Skeletal dose (Gy)	Original disease
				Age 30–39 (178 patients, $\bar{D}$ = 12.2 μCi/kg)				
704	f	37	23	60	1	5.0	0.7	ANK
+353	m	37	10	47	11	52.0	7.3	ANK
879	f	38	37	75	7	28.8	4.0	TB
77	m	39	25	64	?	4.4	0.6	ANK
102	m	39	33	72	1	4.8	0.7	ANK
				Age 40–49 (185 patients, $\bar{D}$ = 12.2 μCi/kg)				
+50	m	41	0	41	4	4.0	0.6	ANK
+329	m	41	26	67	10	22.8	3.2	ANK
189	m	42	28	70	2	8.8	1.2	ANK
297	m	42	22	64	5	17.5	2.5	ANK
+28	m	42	16	58	1	3.2	0.5	ANK
721	f	42	31	73	3	30.0	4.2	ANK
848	f	43	30	73	?	14.5	2.0	TB
+506	m	44	5	49	22	53.8	7.5	TB
149	m	44	16	60	1	6.8	1.0	ANK
32	m	45	31	76	2	3.2	0.5	ANK
78	m	47	23	70	5	4.4	0.6	ANK
+442	m	49	19	68	7	16.0	2.2	TB
				Age 50+ over (107 patients, $\bar{D}$ = 12.3 μCi/kg)				
111	m	50	11	61	3	4.8	0.7	ANK
+868	f	52	26	≈78	6	23.0	3.2	TB
73	m	53	29	82	2	4.0	0.6	ANK
+162	m	56	17	73	1	8.0	1.1	ANK
+299	m	57	24	81	5	17.6	2.5	ANK
+52	m	58	2	60	1	4.0	0.6	ANK
(12)	m	59	0	59	?	2.0	0.3	ANK

Note. +, Deceased; TB, tuberculosis; ANK, ankylosing spondylitis; m, male; f, female. Patient records are in traditional units of activity. To convert to SI units, 1 μCi/kg = 37 mBq/kg.

* Age at first injection.

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REFERENCES

1. H. CHALUPECKY, Über die Wirkung der Röntgenstrahlen. In *Centralblatt für praktische Augenheilkunde* (J. Hirschberg, Ed.), pp. 386–401, Veit, Leipzig, 1897.

2. TREUTLER, Discussion to E. v. Hippel jun. (Über angeborenen Zentral- und Schichtstar - experimentelle Untersuchungen). *Ber. Dtsch. Ophtalmol. Ges., Heidelberg,* 1905; J. F. Bergmann, Wiesbaden, p. 338, 1906.
3. E. KROKOWSKI and U. EHLING, Die Entwicklung der Radiokatarakte in Abhängigkeit vom Alter. *Fortschr. Röntgenstr.* **88,** 591–595 (1958).
4. U. EHLING and E. KROKOWSKI, Der Einfluss von Kataraktgenen auf die Strahlenempfindlichkeit der Linse. *Z. Naturforsch. B* **15,** 110–115 (1960).
5. G. R. MERRIAM, B. J. BIAVATI, J. L. BATEMAN, H. H. ROSSI, V. P. BOND, L. GOODMAN, and E. F. FOCHT, The dependence of RBE on the energy of fast neutrons. IV. Induction of lens opacities in mice. *Radiat. Res.* **25,** 123–138 (1965).
6. G. R. MERRIAM and B. V. WORGUL, Experimental radiation cataract—Its clinical relevance. *Bull. N.Y. Acad. Med.* **59,** 372–392 (1983).
7. B. V. WORGUL, G. R. MERRIAM, and C. MEDVEDOVSKY, Accelerated heavy particles and the lens II. Cytopathological changes. *Invest. Opthalmol. Visual Sci.* **27,** 108–114 (1986).
8. D. G. COGAN, S. F. MARTIN, and S. J. KIMURA, Atomic bomb cataracts. *Science* **110,** 654–655 (1949).
9. R. J. MILLER, T. FUJINO, and M. D. NEFZGER, *Ophthalmology Research Protocol, Hiroshima–Nagasaki,* ABCC TR, pp. 13–64, 1964.
10. K. CHOSHI, I. TAKAKU, H. MISHIMA, T. TAKASE, S. NERIISHI, S. C. FINCH, and M. OTAKE, Ophthalmologic changes related to radiation exposure and age in adult health study sample, Hiroshima and Nagasaki. *Radiat. Res.* **96,** 560–579 (1983).
11. A. C. WOOD, Cyclotron cataracts. *Am. J. Ophthalmol.* **47,** 20–28 (1959).
12. G. R. MERRIAM and E. F. FOCHT, A clinical study of radiation cataracts and the relation to dose. *Am. J. Roentgenol. Radium Ther. Nucl. Med.* **77,** 759–785 (1957).
13. G. R. MERRIAM and E. F. FOCHT, A clinical and experimental study of the effect of single and divided doses of radiation on cataract productions. *Trans. Am. Ophthalmol. Soc.* **60,** 35–62.
14. H. SPIESS, ^{224}Ra-Induced tumors in children and adults. In *Delayed Effects of Bone-Seeking Radionuclides* (C. W. Mays *et al.*, Eds.), pp. 227–247. Univ. of Utah Press, Salt Lake City, 1969.
15. E. E. ADAMS, A. M. BRUES, and G. A. ANAST, Survey of ocular cataracts in radium dial workers. *Health Phys.* **44,** 73–79 (1983).
16. T. P. GRIFFITH, A. PIRIE, and J. VAUGHAN, Possible cataractogenic effect of radionuclides deposited within the eye from the bloodstream. *Br. J. Ophthalmol.* **69,** 219–227 (1985).
17. H. J. DEEG, N. FLOURNOY, K. M. SULLIVAN, K. SHEEHAN, C. D. BUCKNER, J. E. SANDERS, R. STORB, R. P. WITHERSPOON, and E. D. THOMAS, Cataracts after total body irradiation and marrow transplantation: A sparing effect of dose fractionation. *Int. J. Radiat. Oncol. Biol. Phys.* **10,** 957–964 (1984).
18. I. BENDEL, W. SCHÜTTMANN, and O. ARNDT, Cataract of lens as late effect of ionizing radiation in occupationally exposed persons. In *Late Biological Effects of Ionizing Radiation,* pp. 309–319. International Atomic Energy Agency, Vienna, 1978.
19. K. MARTIGNONI, *Spontane und strahleninduzierte Trübungen der menschlichen Linse.* Institut für Strahlenhygiene des Bundesgesundheitsamtes, Neuherberg/München, ZSH-Heft 62, April 1985.
20. C. W. MAYS and H. SPIESS, Bone sarcomas in patients given radium-224. In *Radiation Carcinogenesis: Epidemiology and Biological Significance* (J. D. Boice and J. F. Fraumeni, Eds.), pp. 241–252. Raven Press, New York, 1984.
21. C. W. MAYS, H. SPIESS, D. CHMELEVSKY, and A. M. KELLERER, Bone sarcoma cumulative tumor rates in patients injected with Ra-224. In *Radiobiology of Radium and Thorotrast* (W. Gössner *et al.*, Eds.), pp. 27–31. Urban & Schwarzenberg, Munich, 1986.
22. D. CHMELEVSKY, A. M. KELLERER, H. SPIESS, and C. W. MAYS, A proportional hazards analysis of bone sarcoma rates in German radium-224 patients. In *The Radiobiology of Radium and Thorotrast* (W. Gössner *et al.*, Eds.), pp. 32–37. Urban & Schwarzenberg, Munich, 1986.
23. H. SPIESS, C. W. MAYS, and E. SPIESS-PAULUS, Growth retardation in children injected with Ra-224. In *Radiobiology of Radium and Thorotrast* (W. Gössner *et al.*, Eds.), pp. 45–50. Urban & Schwarzenberg, Munich, 1986.
24. E. SONNABEND, H. SPIESS, and C. W. MAYS, Tooth breakage in patients injected with Ra-224. In *Radiobiology of Radium and Thorotrast* (W. Gössner *et al.*, Eds.), pp. 60–64. Urban & Schwarzenberg, Munich, 1986.

25. H. SPIESS, A. GERSPACH, and C. W. MAYS, Soft-tissue effects following Ra-224 injections into humans. *Health Phys.* **35,** 61–81 (1978).
26. F. STEFANI, H. SPIESS, and C. W. MAYS, Cataracts in patients injected with radium-224. In *The Radiobiology of Radium and Thorotrast* (W. Gössner *et al.*, Eds.), pp. 51–59. Urban & Schwarzenberg, Munich, 1986.
27. G. N. TAYLOR, T. F. DOUGHERTY, C. W. MAYS, R. D. LLOYD, D. R. ATHERTON, and W. S. S. JEE, Radium-induced eye melanomas in dogs. *Radiat. Res.* **51,** 361–373 (1972).
28. D. E. HENDERLY, A. J. GENSTLER, R. E. SMITH, and N. A. RAO, Changing patterns of uveitis. *Am. J. Ophthamol.* **103,** 131–136 (1987).
29. P. BERNTH-PETERSEN and E. BACH, Epidemiologic aspects cataract surgery. II. Regional variation in frequencies. *Acta Ophthalmol.* **61,** 397–405 (1983).
30. P. BRAENDSTRUP, Senile cataract. *Acta Ophthalmol.* **55,** 337–346 (1977).
31. M. E. BRENNAN and E. G. KNOX, The incidence of cataract and its clinical presentation. *Community Health* **7,** 13–20 (1975).
32. F. I. CAIRD, M. HUTCHINSON, and A. PIRIE, Cataract extraction in an English population. *Br. J. Prev. Soc. Med.* **19,** 80–84 (1965).
33. M. M. KINI, H. M. LEIBOWITZ, T. COLTON, R. J. NICKERSON, J. GANLEY, and T. R. DAWBER, Prevalence of senile cataract, diabetic retinopathy, senile macular degeneration, and open-angle glaucoma in the Framingham eye study. *Am. J. Opthalmol.* **85,** 28–34 (1978).
34. D. J. NADLER and B. SCHWARTZ, Cataract surgery in the United States 1968–1976, descriptive epidemiologic study. *Am. Acad. Ophthalmol.* **87,** 10–18 (1980).
35. L. R. MAUNDER, R. C. MILTON, M. M. KINI, H. A. KAHN, R. J. NICKERSON, J. POOL, T. COLTON, J. P. GANLEY, J. I. LOEWENSTEIN, and T. R. DAMLER, The Framingham Eye Study, Monograph. *Surv. Ophthalmol.* **24,** 335 (1980).
36. J. D. KALBFLEISCH and R. L. PRENTICE, *The Statistical Analysis of Failure Time Data.* Wiley, New York, 1980.
37. J. F. LAWLESS, *Statistical Models & Methods for Life Time Data.* Wiley, New York, 1982.
38. A. M. KELLERER and D. CHMELEVSKY, Analysis of tumor rates and incidences. A survey of concepts and methods. In *Proceedings, European Seminar on Neutron Carcinogenesis* (J. J. Broerse and G. B. Gerber, Eds.), pp. 209–231. Commission of the European Communities, Luxembourg, 1982.
39. A. M. KELLERER, Mathematical methods and models for radiation carcinogenesis studies. *Leukemia Res.* **10,** 711–717 (1986).
40. M. OTAKE and W. J. SCHULL, *Relationship of Gamma and Neutron Radiation to Posterior Lenticular Opacities among Atomic Bomb Survivors in Hiroshima and Nagasaki,* RERF Technical Report Series, RERF TR, pp. 17–81, 1982.
41. M. OTAKE and W. J. SCHULL, The relationship of gamma and neutron radiation to posterior lenticular opacities among atomic survivors in Hiroshima and Nagasaki. *Radiat. Res.* **92,** 574–595 (1982).
42. G. R. MERRIAM, A. SZECHTER, and E. F. FOCHT, The effects of ionizing radiations on the eye. *Front. Radiat. Ther. Oncol.* **6,** 346–385 (1972).
43. G. R. MERRIAM, B. V. WORGUL, C. MEDVEDOVSKY, M. ZAIDER, H. H. ROSSI, Accelerated heavy particles and the lens. I. Cataractogenic potential. *Radiat. Res.* **98,** 129–140 (1984).
44. A. H. W. NIAS, Radiation and platinum drug interaction. *Int. J. Radiat. Biol.* **48,** 297–314 (1985).
45. ICRP, *Nonstochastic Effects of Ionizing Radiation.* Publication 41, International Commission on Radiological Protection, Pergamon, Oxford/New York/Frankfort, 1984.
46. R. R. WICK, D. CHMELEVSKY, and W. GÖSSNER, Radium-224 risk to bone and haematopoietic tissue in ankylosing spondylitis patients. In *The Radiobiology of Radium and Thorotrast* (W. Gössner *et al.*, Eds.), pp. 38–44. Urban & Schwarzenberg, Munich, 1986.
47. R. R. WICK and W. GÖSSNER, Follow-up study of late effects in 224-Ra treated ankylosing spondylitis patients. *Health Phys.* **44,** Suppl. 1, 187–195 (1983).

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NOTICE

The Subject Index for Volume 115 will appear in the December 1988 issue as part of a cumulative index for the year 1988.