BIR Report 21

Risks from Radium and Thorotrast

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The cataract response in radium 224 patients

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Abstract. Among a group of 831 patients who were injected with known dosages of radium 224 in Germany shortly after the Second World War there has been a greatly enhanced incidence of severe cataracts. From a total of 58 diagnoses, 25 occurred before the age of 54. The epidemiological data consist of the ophthalmological reports from examinations after vision impairment had become sufficiently serious. At this stage the aetiology of cataracts could not be established. But the mathematical analysis can use the strong correlation between the observed incidence and the injected activity. The form of this correlation suggests that almost all of the 25 early cataracts and a substantial part of the later cataracts are treatment-related. The probability of induction of severe cataracts is roughly proportional to the square of the dosage, that is, the radium 224 activity per unit body weight, and also to the square of the time after treatment. An extended analysis also accounts for spontaneous cataracts; this shows for the spontaneous cataracts a probability that increases with roughly the eighth power of the age. The results of the present analysis have motivated a programme of systematic cataract examinations among the remaining patients.

Shortly after the Second World War, from 1945 to about 1952, numerous adults and children were given repeated injections of radium 224 in a German clinic for the intended treatment of ankylosing spondylitis or bone tuberculosis. Several contributions in this volume deal with this cohort. In brief, radium 224 activities were administered intraveneously which were far higher than those presently utilized in the continued treatment of ankylosing spondylitis with radium 224. Furthermore, the treatment was entirely ineffective against bone tuberculosis. Spiess, and subsequently Spiess and Mays, performed the follow-up of the about 850 patients and found a great variety of stochastic and non-stochastic radiation effects, particularly in the juveniles who had received the highest dosages, that is, activities per unit body weight.

Earlier in the study, Spiess (1969) noted the occurrence of a few cataracts at an early age among the radium 224 patients. The evidence was substantiated in subsequent years, and a statistical analysis was, therefore, performed to seek a possible correlation between the frequency of cataracts and the dosage of radium 224.

Cataract data

In the initial phases of the follow-up there had been no expectation of lenticular damage due to the radium 224 treatment and, accordingly, no systematic investigations were performed. Most of the cataracts among the radium 224 patients became known when the patients suffered from impaired vision and consulted an ophthalmologist. The present analysis could, therefore, not be based on data from repeated examinations. Instead, it had to use the information from individual examinations. However, in almost all cases the diagnoses of cataract with ophthalmological reports are available. In a few cases the data consist only of information that a cataract extraction was performed; in this regard, it should be noted that in the Federal Republic of Germany extractions were never performed without a proper slitlamp diagnosis. A recent report by Stefani,

Spiess & May (1986) deals in detail with the ophthalmological findings. A list of all cataract cases seen up to 1987 is appended to the article by Chmelevsky et al (1988).

The availability of serial examinations and the possibility of recognizing the aetiology of incipient cataracts would have made the quantitative analysis far simpler and the results more reliable. Nevertheless, it was felt that the finding of an increased incidence of cataracts and a possible correlation to the radium 224 treatment was sufficiently important that use had to be made even of the incomplete information. The statistical analysis and the results are outlined below.

Meanwhile a programme of systematic examination of the eyes of the younger patients has been initiated with the aim of observing incipient cataracts, recognizing their aetiology, and following their evolution. This is presented by Stefani, Spiess & Mays (this volume, pp. 12–21). It is hoped that a closer connection can ultimately be established in this way between observations in the radium 224 patients and the earlier detailed findings from therapy patients (Merriam & Focht, 1957), and the A-bomb survivors (Otake & Schull, 1982).

Summary of methods and results

As stated, the analysis had to be based on fragmentary information, namely the data of all radium 224-patients and the dates of diagnosis for those patients who eventually developed a severe lens opacification. Table I summarizes the data which were employed for an actuarial analysis of the dosage and age dependence of the incidence of several cataracts.

The analysis could be affected by a number of confounding factors which are partly correlated with dosage. Sex, type of original disease and varying length of the injection period were disregarded after exploratory analyses provided no indication of their correlation with the cataract incidence. The age of the patients is obviously important, at least for the severe cataracts diagnosed in older patients.

Figure 1 gives, in the form of a scatter diagram, the dosage and age at treatment for each patient. Patients who later developed a cataract are represented by heavier symbols. Dots show cataracts diagnosed before the age of 54, triangles cataracts that were diagnosed later.

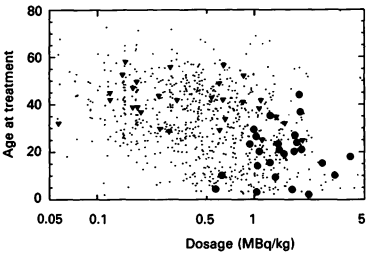

Figure 1. Ages at treatment and the injected radium 224 activities per unit body weight. Each patient is represented by a point; those who subsequently developed a severe cataract are represented by a solid dot (diagnosis before the age of 54) or by a triangle (diagnosis at a greater age).

Table I. Synopsis of input data[a]

	Number of		Mean age[b]			
	Patients[a]	Cataracts	At first injection	At last follow-up	At cataract	Mean dosage[b] (MBq/kg)
All adults	627	44	38.7(10.8)	63.1(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	35.5(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)

[a] Number of patients included in analysis = 831. Number of patients with cataract = 58 (two before treatment: one within 1 year after treatment); 38 patients were excluded from analysis because of missing dose information; 30 were without follow-up.
[b] Mean and standard deviation.

Further diagrams in the report of Chmelevsky et al (1988) provide a wider synopsis of the data.

It is strikingly evident, even from Fig. 1, that the early cataracts occur predominantly at the larger dosages. One hardly needs the statistical analysis to recognize the correlation of the incidence of early cataracts with dosage and to conclude that the increased cataract rate is not merely an association with the original diseases but that it is related to the dosage which varied greatly in subsequent calendar years when one became – much too slowly – aware of the dangers of the high dose treatment. It is also apparent that the cataracts in older patients are much less, if at all, correlated with dosage. To quantify the dosage dependence for treatment-related cataracts, the mathematical analysis was initially based solely on cataracts diagnosed before the age of 54.

The aim of the analysis is the quantification of the underlying dose and time dependence for reaching mature cataracts that impair vision. A preliminary stage of the investigation, based on dose groups, showed substantially enhanced rates in the groups with higher doses. It showed also that all dependences were equally consistent with cumulative rates proportional to the square of the time after treatment. Separate analyses for different age groups gave no indication of differing sensitivity of younger and older patients at equal dosage, that is, injected activity per unit body weight. Age at treatment was, therefore, disregarded in this initial step of the analysis.

A maximum likelihood computation in terms of a proportional hazards model led to the notable finding that the dependences of the cumulative rate on time, t, after treatment and on dosage, A, are both quadratic. Details of the numerical procedures have been given by Chmelevsky et al (1988). The overall relation can be expressed as:

$$R(t,A) = ct^2A^2 \qquad (1)$$
with: $c = 9 \times 10^{-5}$ (year)$^{-2}$ (MBq/kg)$^{-2}$

where R is the cumulative rate and, accordingly, $P = 1 - \exp(-R)$ is the probability of incurring a severe cataract up to time t after radium 224 injection. At small values P equals R, and the cumulative rate can roughly be understood as the probability of incurring a cataract up to the specified time after the exposure.

Non-parametric dependences and minor deviations of the maximum likelihood exponents from the above relations have been considered by Chmelevsky et al (1988). In the present context it is of most interest to note that equation (1) yields a dose dependence for the probability of incurring a severe cataract which is proportional to the square of the dose. A similar relation was found earlier for therapeutic X-rays by Merriam & Focht (1957), and for atomic bomb γ-rays by Otake and Schull (1982), but it was uncertain whether it would also apply to densely ionizing α-particles. Cataracts in cyclotron workers who had disregarded radiation-protection procedures have demonstrated that fission neutrons induce cataracts (Wood, 1959), but the uncertainty about doses made statements on the shape of the dose–effect relation impossible.

In the above formulation equation (1) may suggest that the induced cataracts develop at a dosage independent rate, and this would be at variance with a number of studies which were based on more complete experimental or clinical evidence from serial examinations and which showed generally faster development of the lenticular lesions at higher doses (see, for example, Merriam and Focht, 1957; Merriam et al, 1986). However, there is no actual contradiction with these results; one can write equation (1) in the modified form:

$$R(t,A) = (\alpha t)^2 \qquad (2)$$
with: $\alpha = kA$ and $k = 9.5 \times 10^{-3}$/(year MBq/kg)

which shows that the process can be seen equally as an accelerated progression of cataracts, with an acceleration factor, α, that is proportional to dosage. In fact, one must assume an intermediate situation of increased probability of the occurrence of cataracts but also of faster progression at higher dosages. The remaining uncertainty indicates the limitation of the present analysis and shows the need for the serial studies which have now been initiated.

Additional computations have shown that a similarly good fit in terms of maximum likelihood is achieved by a linear dependence beyond a threshold at a dosage of 0.5 MBq/kg (Chmelevsky et al, 1988). The pragmatic conclusion is that there is a "practical threshold"; the statistical uncertainty permits no more precise statements on the response at small doses.

Analysis to include all diagnosed cataracts

The separate analysis of early cataracts has the advantage of simplicity, but it suffers from the arbitrary choice of a cut-off age. So we have also performed a maximum likelihood analysis to determine the fit to a compound relation that includes, in addition to the term in equations (1) or (2), a term for the probability of incurring a "spontaneous" age-related cataract. A power function for the dependence on age, τ, was suggested by epidemiological studies of the frequency of severe spontaneous cataracts in various populations (Caird, Hutchinson & Pirie, 1965; Mauder et al, 1980).

The computations confirmed the results of the previous analysis which had been based merely on the early cataracts. The result is:

$$R(t,A) = (0.009t)^2A^2 + (0.01\tau)^8 \qquad (3)$$

with the units (year) for time t after treatment and age τ and (MBq/kg) for the dosage A.

More detailed considerations were presented by Chmelevsky et al (1988). In the present summary it suffices to quote the parameters with their standard errors, 0.009 ± 0.003 and 0.01 ± 0.001. The standard error of the exponent for t is about ± 0.4 and for τ it is ± 1.3. There is no indication of a linear component in A, and this agrees with the fact that no early cataract has been diagnosed below a dosage 0.5 MBq/kg. As in the analysis of early cataracts only, it was concluded that a

linear dependence beyond a threshold of 0.5 MBq/kg fits the data equally well.

Figure 2 represents the estimated partition of the total incidence of severe cataracts (up to the specified age) into a spontaneous and a treatment-related contribution. As stated, the lack of serial examinations has precluded a determination of the aetiology in the individual cases. The partition is, therefore, entirely based on the analysis of the correlation with dosage, and a comparison of the theoretical relations can be made merely with the total cumulative incidence which has been observed. Figure 2 justifies *a posteriori* the choice of a cut-off age of 54 years in the first part of the analysis; all or nearly all of the 25 cataracts diagnosed before the age of 54 are assigned to the treatment-related contribution. Of the remaining 33 cataracts about a third may be treatment-related, but this latter estimate is less certain.

Figure 3 facilitates a general judgement of the magnitude of the risk of severe visual impairment due to radium 224 injection. A probability of 20% for induction of a severe cataract up to the specified age is taken as the reference values and is plotted versus dosage. It is evident that the risk is most apparent for injections at a young age (solid line); if the injections occur later in life (broken curves), their effects will be largely masked by the frequency of spontaneous cataracts.

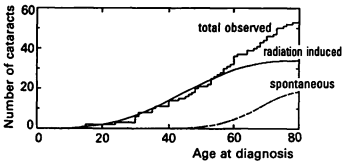

Figure 2. The cumulative number of severe cataracts in 831 radium 224 patients versus age at diagnosis. The total observed number is compared to the number of severe radiation-induced and spontaneous cataracts which are expected according to equation (3) (see text), with the dosages, age distribution and times in the follow-up of the patients.

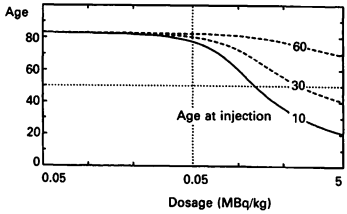

Figure 3. The age at which a 20% probability of severe cataract is reached versus injected radium 224 dosage according to equation (3). The solid line corresponds to injection at the age of 10, the broken lines to injection at the ages of 30 and 60.

Conclusions

One essential conclusion from this study is the highly significant correlation of the incidence of early cataracts with the radium 224 dosage. This removes the possibility that the high incidence of cataracts is merely an association with the original diseases, bone tuberculosis or ankylosing spondylitis. A second important finding is the non-linearity of the correlation, that is the virtual absence of any enhancement at small doses. Proportionality to the square of the dosage, measured in activity per unit body weight, is consistent with the data. But, as explained in the earlier report, there could also be an actual threshold, at about 0.5 MBq/kg. The statistical uncertainty precludes precise statements on the shape of the response curve at small doses; this does not lessen the pragmatic importance of the finding of reduced efficiency at small doses for a densely ionizing radiation.

There are, up to now, only uncertain data on the absorbed doses which can be produced by radium 224 and its daughter products in the lens epithelium of the eye. In a recent study Taylor & Thorne (1988) have provided rough theoretical estimates of the absorbed dose to the lens epithelium after radium 224 injection. The estimated values were between 0.05 and 0.32 Gy/MBq/kg. This would mean that a possible threshold lies between 0.025 and 0.16 Gy, which is substantially lower than the values of about 8 Gy for severe cataracts which have been deduced from observations on patients treated with X-rays. The absorbed dose per MBq/kg may, of course, depend on age, and our finding of apparently equal sensitivity for cataract induction in juveniles and adults would then merely refer to the injected activity per unit body weight.

The analysis had to utilize incomplete data and refers only to the probability of causing severe cataracts. This is the relevant end point for the quantification of the cataract risk. For mechanistic explanations the conclusions remain insufficient. The dependence of the cumulative incidence on the square of the dosage and on the square of the time after treatment are a special case of the Weibull model which postulates effect rates proportional to a power of time. Such dependences could be due to increases of the frequency of the damage (see equation (1)); they can also reflect an acceleration of the development of lenticular lesions (see the equivalent equation (2)); and such an acceleration has been inferred from a number of earlier studies with systematic examinations (Merriam & Focht, 1957; Merriam et al, 1984). Distinguishing the two possibilities requires systematic examinations of the prevalence and the temporal development of incipient cataracts, as they have now been initiated for the patients who are still alive. Even without the missing information one notes a high correlation of cataracts in both eyes of the affected patients (see also Stefani, Speiss & Mays, this volume, pp.

12–21). This indicates that the lenticular damage is not primarily provoked by initial random lesions in individual cells, but that it is a largely deterministic or – in a terminology proposed by Mole – polycytic process.

Acknowledgements

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