Radiation Cataract

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Opacities/Dose-response/RBE/Threshold/A-bomb Survivors

This report reviews the relationship of ionizing radiation to the occurrence of cataracts (posterior lenticular opacities) among the A-bomb survivors in Hiroshima and Nagasaki. The new DS86 doses are available for 1,983 (93.4%) of the 2,124 A-bomb survivors analyzed in 1982. The DS86 kerma neutron component for Hiroshima is much smaller than its comparable T65DR component, but still 4.2 fold higher (0.38 Gy at 6 Gy) than that in Nagasaki (0.09 Gy at 6 Gy). Thus, if the eye is especially sensitive to neutrons, there may yet be some useful information on their effects, particularly in Hiroshima. Under the best fitting dose-response model, an L(gamma)-L(neutron) with two thresholds, both the gamma and neutron regression coefficients of the occurrence of cataracts on dose are positive and highly significant for the DS86 eye organ doses. The DS86 gamma coefficient is almost the same as that associated with the T65DR gamma dose, the ratio of the two coefficients being 1.1 (95% confidence limits: 0.5–2.3) for DS86 kerma in the individual dose data, and if the risks based on the DS86 eye organ dose and DS86 kerma are compared, the ratio is 1.3 (0.6–2.8). However, the risk estimates associated with neutron exposure are 6.4 (2.2–19.2) fold higher for the DS86 kerma than the T65DR kerma and 1.6 (0.5–2.3) fold higher for the DS86 eye organ dose than for the DS86 kerma.

INTRODUCTION

Radiation cataract was the first late effect recognized unequivocally in individuals exposed to A-bomb radiation in Hiroshima and Nagasaki. Since its original description by Cogan et al. in 1949, many ophthalmologic reports of a clinical, histopathological, or statistical nature have been published. It is apparent from these studies, as well as others, that radiation-induced cataract is, in its early stages at least, a highly characteristic lesion. It is generally defined as a central, posterior subcapsular opacity, easily visible with a slit lamp biomicroscope or an ophthalmoscope. Its distinguishing feature is an initial axial opacity that ophthalmoscopically appears as a dot usually situated at the posterior pole, and as this enlarges, small granules and vacuoles appear around it. With continued enlargement, the opacity develops a relatively clear center, giving it a doughnut-shaped appearance. At this stage, it is 3 to 4 mm in diameter. Concurrently, granular opacities and vacuoles may appear in the anterior subcapsular region,
usually in the papillary area\textsuperscript{(2)}. Unfortunately, the word "cataract" connotes to many a defect that impairs vision, although it is also commonly used to describe any detectable change in translucency in the lens. Since our data are not restricted to those radiation-induced changes that impair vision measurably, to avoid confusion we have adopted the International Commission on Radiological Protection (ICRP)\textsuperscript{(3)} convention and herein used synonymously "cataracts" for the phrases "lenticular opacities," "opacity of the lens," or "lens opacification."

In March 1986, as a result of a comprehensive reevaluation of the exposures of the survivors of the A-bombing of Hiroshima and Nagasaki, a new method for the estimation of individual doses was introduced, the dosimetry system 1986 (DS86)\textsuperscript{(4)}. There are important differences between this system and its predecessor, the T65DR. The T65DR estimates of shielded kerma were estimates of free-in-air kerma multiplied by average transmission factors for structural materials, and the organ or tissue doses were based on the use of fixed coefficients to describe the transmission of radiation in tissue\textsuperscript{(5)}. The new DS86 estimates of shielded kerma are individually computed without use of explicit, average building transmission factors. Estimates of the energy deposited in the eye, based on the T65DR dosimetry, are not available, but such estimates do exist for the DS86 dosimetry. We shall hereafter refer to the latter as the DS86 eye organ dose.

The purposes of the present report are to review the relationship of radiation exposure to the occurrence of cataracts among A-bomb survivors using the newer DS86 dose estimates, and to compare these risk estimates with those derived from the earlier T65DR dosimetry.

**OPHTHALMOLOGIC STUDIES OF ATOMIC BOMB SURVIVORS**

Miller et al.\textsuperscript{(7)} reviewed the major ophthalmologic surveys conducted at ABCC in 1949–62, and undertook a large investigation in 1963–64\textsuperscript{(8)} to evaluate the effects of ionizing radiation on the lens of the eye. In 1982, Otake and Schull reviewed all of the medical records on the 84 individuals who had been diagnosed by Miller and his colleagues as having a cataract\textsuperscript{(9)}. As a result, five cases in Hiroshima and two in Nagasaki were excluded, for either there was no recorded slit lamp confirmation, or the slit lamp revealed a cortical (including anterior subcapsular) or a nuclear opacity, but no posterior subcapsular defect. Three of the five cases exhibited only nuclear opacities that were interpreted in two instances as congenital by the ophthalmologist, and one case, exhibiting only an anterior subcapsular defect, was not in the city at the time of the bombing (ATB). Finally, the children exposed in utero have also been excluded; only one of the 309 prenatally exposed survivors examined was observed to have any degree of lens opacification. Thus, our analysis rests on 76 of the 84 cases in the Adult Health Study (AHS) population\textsuperscript{(10)} reported by Miller et al.\textsuperscript{(8)}. When these earlier findings were reanalyzed\textsuperscript{(11)}, three different dosimetry systems were used, i.e., a) the tentative 1965 dose estimates revised (T65DR)\textsuperscript{(12,13)}, b) the Oak Ridge National Laboratory estimates\textsuperscript{(14)}, and c) the Lawrence Livermore National Laboratory estimates\textsuperscript{(15)}. This reassessment was tentative, for the individual doses that were available were based on the T65DR dosimetry system and the average transmission factors associated with that system. The latter were then under extensive review.
Table 1. Occurrence of cataract by city and dose based on T65DR kerma, DS86 kerma and DS86 eye organ dose*

<table>
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<tr>
<th>Dose group in gray</th>
<th>Hiroshima</th>
<th></th>
<th>Nagasaki</th>
<th></th>
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<tr>
<td></td>
<td>Total</td>
<td>Gamma</td>
<td>Neutron</td>
<td>Mean age</td>
<td>Examined</td>
<td>ATB</td>
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<td>%</td>
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**T65DR kerma**

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<th>0.00</th>
<th>0.00</th>
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<th>21.2</th>
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<td>48</td>
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<td>658</td>
<td>23.4</td>
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**DS86 eye organ dose**

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<td>658</td>
<td>23.4</td>
<td>23</td>
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* The gamma and neutron estimates for those survivors who ostensibly had a total dose of more than 5 Gy have been arbitrarily truncated to 6 Gy.
In January 1990, the same cataract data were reevaluated on the basis of the DS86 dosimetry system\textsuperscript{22}). The DS86 eye organ dose estimates in Hiroshima and Nagasaki move a large number of subjects from higher to lower dose groups in comparison with their T65DR exposures. In particular, the number of individuals exposed to 6 Gy or more decreases from 41 (T65DR kerma) to 6 (DS86 kerma) to 0 (DS86 eye organ dose) in Hiroshima and from 24 to 6 to 1 in Nagasaki. The contribution of neutrons to the total mean DS86 kerma is only 0.38 Gy (6.3%\textsuperscript{20}) at 6 Gy total kerma in Hiroshima and 0.09 Gy (1.5%) in Nagasaki as contrasted with 1.81 Gy (30.2%) in

\begin{figure}
\centering
\includegraphics[width=\textwidth]{histogram}
\caption{Occurrence of cataracts and 95\% confidence intervals by type of dosimetry and city.}
\end{figure}
Hiroshima and 0.17 Gy (2.8%) in Nagasaki for the T65DR dosimetry (Table 1). The observed risk rates based on the DS86 dose estimates are higher than those seen with the T65DR doses. This trend is stronger in Hiroshima than in Nagasaki (Figure 1).

Since age at exposure could be a determinant in the occurrence of a cataract and ages ATB may be unequally distributed among the exposed and the nonexposed, age ATB was a potential source of obfuscation in the determination of the appropriate dose-response relationship. The mean age of individuals in the city-specific data is 29.3 years ATB in Hiroshima and 23.4 years ATB in Nagasaki for the DS86 subsample. This difference in mean age at exposure is highly significant, but in neither city does age change systematically with dose. A test of the homogeneity of the mean ages within the five dose categories by city reveals significant heterogeneity for the DS86 dosimetry. Significance appears to be ascribable largely to a difference in mean ages between the lower and higher dose groups. The mean age in the higher dose group is significantly smaller than that in the lower dose group in both cities.

A better analytic approach than the analysis of variance, one that provides explicit estimates of risk, is to fit a regression of individual binary response (1 or 0) on age ATB, DS86 gamma dose and DS86 neutron dose. When a linear regression was fitted to the city data, no significant effect of age ATB was observed in either Hiroshima or Nagasaki, or in the cities combined. This suggests that age ATB is not likely to contribute importantly to the effect of radiation. In the clinical study in 198323), however, cataracts, other lens changes, and loss of visual acuity and accommodation did increase with increasing age in both exposed and control subjects as manifestations of the normal aging process.

In 1975, Merriam and Szechter24) investigated the effect of age on the development of radiation cataracts in the lenses of rats. They made three interesting observations: 1) with doses of about 2–3 Gy, the early lens changes occurred sooner and progressed faster in the adult lenses than in the lenses of the young; 2) at doses of about 3–9 Gy, opacities developed sooner in young lenses, but progression was faster and severe opacities developed sooner in adult lenses; and 3) at about 9 Gy cataracts appeared sooner in young lenses and progressed faster to severe opacification. Their data, however, did not support statistically the hypothesis that the lenses of young persons are more sensitive to radiation than are those of older persons.

STATISTICAL REVIEW

The extent of the biological effects on the eye resulting from exposure to ionizing radiation is determined primarily by the quantitative and qualitative relationship of dose to its effect. However, given that the cellular events involved in radiation-related cataractogenesis in man are imperfectly known, all dose-response models are conjectural to some extent. It is commonly assumed, nonetheless, that the production of cataracts is a nonstochastic phenomenon, one that can be totally avoided with appropriate dose limits; that is to say, there exists a threshold below which radiation cataracts do not occur13). The low LET threshold dose, for a single acute exposure to x-rays, has been commonly taken to be around 2 Gy.

Insofar as the shape of the dose-response curve is concerned, two Task Groups of the
International Commission on Radiological Protection have maintained that "the dose response for cataract induction by ionizing radiation, whether of high or low LET, seems to be highly sigmoid\textsuperscript{13}." The analysis of Otake and Schull\textsuperscript{22} supports a sigmoid dose-response relationship with a threshold (or thresholds) for lens opacification. In their study, however, the extent of the opacification of the lens in either or both eyes was classified biomicroscopically as equivocal, minimal, small, moderate, or large. In most instances, the degree of opacification was small or less (about 70%), and only five opacities were considered large. It should also be noted, indeed emphasized, that bilateral involvement (67 cases out of 76) is much more common than unilateral, and the correlation between the degree of opacification in the left and right eyes is high (0.81, based upon the assignment of the numeric values 1, 2, ..., 5 to the successive degrees of opacification). This suggests, in turn, a high correlation in the exposure received by the left and right eyes of a given individual, and militates against an analysis that treats the two eyes of an individual independently.

Otake and Schull\textsuperscript{16,22} fitted a variety of models with and without gamma and neutron thresholds to the grouped or individual data from Hiroshima and Nagasaki. The parameters of their models were estimated by the method of maximum likelihood, assuming the observed number in each cell or binary array (1 for an individual with cataracts and 0 for others) to be a binomial variate having an expected value based on the model equation\textsuperscript{25,26}.

**GENERAL CONSIDERATIONS**

The eye is generally presumed to be sensitive to radiation. Damage to any part of it may occur, but for the long-term effects the most sensitive structure is thought to be the lens. As previously stated, the first late radiation effect observed among A-bomb survivors at ABCC was the occurrence of lenticular changes\textsuperscript{1,2,7}. The most frequently described lesion was a posterior lenticular plaque of polychromatic sheen in heavily irradiated individuals. In 1963–64, in a comprehensive ophthalmologic study, Miller et al.\textsuperscript{8} corroborated the occurrence of posterior lenticular lesions seen earlier in Hiroshima and Nagasaki in the more heavily irradiated individuals, and noted that there had been very little progression in these radiation-related lesions in comparison to the observations made 10 years previously. Dodo\textsuperscript{11} has also observed that in the majority of affected survivors the degree of opacification is minimal to moderate, and unchanging.

The exact nature of the involvement of the germinative epithelium in the occurrence of radiation-related cataracts is not clear, but the BEIR report\textsuperscript{27} notes that evidence from animal studies strongly suggests these epithelial cells are involved. Their argument rests on the basis of the differentiation of the affected cells into abnormal lens fibers, and the time coincidence between the appearance of cataract and the rate of migration of lens epithelial cells into the posterior lens cortex. It is not so much the rate of migration but the rate of differentiation and displacement into the posterior cortex that is the basis of the suggested mechanism. The report points out furthermore that there is no direct evidence that cataract depends on the killing of epithelial cells in the germinative zone. The sigmoidal nature of the cataract dose-response curve and the protective effect of partial lens shielding provide evidence that other factors are involved in radiation
CATARACTOGENESIS IN ADDITION TO, OR INSTEAD OF, CELL-KILLING.

Merriam and Focht (1976), based on the examination of 173 individuals (100 with and 73 without lens opacities), note that the interval from the time of treatment with x-ray or gamma radiation to the appearance of lens opacities in humans varies from six months to 35 years, with an approximate average of 2–3 years. In a group exposed to doses from 2.00–6.50 Gy, the average time at which cataracts were first discovered was eight years and seven months following treatment; whereas with doses of 6.51–11.50 Gy, this time was four years and four months. Thus, the period between exposure to radiation and the appearance of cataracts is inversely related to dose. They also found that 5.50 Gy was the minimum dose for producing detectable lens opacities when the exposure was protracted over periods varying from three months to eight years. The experiences of patients who received x-ray or gamma radiation fractionated over three weeks to three months indicate that doses between 5.50 Gy and 9.50 Gy produce an opacity in about 70% of cases. Some 30% will be progressive with eventual impairment of vision. Unfortunately, the time of onset of the cataracts seen in Hiroshima and Nagasaki is unknown in most instances because the data are cross-sectional observations; however, insofar as is known, the first cataracts were seen about three years after the bombing in 1948 by Ikui, Hirose and Fujino.

DOSE-RESPONSE RELATIONSHIP AND RBE

Characterization of the shape of the dose-response relationship for radiation-induced cataracts among atomic bomb survivors is an essential prerequisite in predicting and quantifying the effect of radiation exposure. And the apparent difference seen in Figure 1 in the dose-response between the two cities, based on the DS86 dosimetry system, is important from the radiobiological standpoint, specifically with regard to the RBE. Although the neutron component of the radiation emitted by the Hiroshima bomb, based on the new doses, is much smaller than that computed with the T65DR dosimetry, it is still 4.2 fold higher than in Nagasaki (0.38 Gy at 6 Gy versus 0.09 Gy in Nagasaki). If the eye is especially sensitive to neutrons, this difference could still produce a difference in risk between the cities, and the observed frequencies of lenticular opacities as seen in Figure 1 are strikingly different, higher in Hiroshima than in Nagasaki. Couched in terms of dose equivalent, in Hiroshima, a neutron eye organ dose of roughly 0.28 Gy (at a total eye organ dose of 6 Gy), given an RBE of 36 (95% CI: 12 to 95), would be the equivalent of 10.1 Sv ( = 36 x 0.28) with a range from 3.4 to 26.6 Sv; whereas 0.08 Gy of neutrons in Nagasaki with an RBE of 69 (95% CI: 12 to 158) is 5.5 Sv ( = 69 x 0.08) with a range from 1.0 to 12.6 Sv. This fact suggests that the neutron component could be important for the eyes, reflecting either the relatively greater contribution of neutrons to the total absorbed dose to the eye than to the total absorbed dose for deep organs, or an inherently higher RBE for cataracts than other endpoints, or both.

Since the A-bomb survivors were simultaneously exposed to gamma and neutron doses, the question naturally arises as to whether or not an interaction exists in their radiobiological effects when simultaneous exposure occurs. It is difficult, however, given the limited data available on the survivors, to determine whether an interaction exists and to estimate its effect. When we
evaluated the interaction between the gamma and neutron components in the L-L model with two thresholds, neither the neutron nor the interaction effect, which was negative, was statistically significant; the only significant effect involved an elevation in the frequency of cataracts with increasing gamma dose. Nevertheless, the individual thresholds for gamma and neutron doses may not be comparable with the results from a single x-ray exposure, and it seems prudent to consider both thresholds in defining a "safety" zone. If we assume no interaction, and an RBE for neutrons of 12.2, the 0.73 Gy threshold for gamma rays gives the same "safety" zone as the 0.06 Gy threshold for neutrons, and their joint effect leads to an estimated minimal dose of 1.46 Sv (146 rem). If these two threshold estimates are assumed to be 5%-15% lower than the unbiased ones derived from the DS86 dosimetry system, as pointed out by Pierce et al.31', the threshold is in the range from 1.54 Sv to 1.68 Sv.

Shimizu et al.32) argue that a meaningful estimation of the neutron RBE with regard to cancer mortality data is difficult, but that neutrons cannot be totally neglected in Hiroshima, even though the neutron dose is substantially smaller under the DS86 dosimetry system than the T65DR. They augmented the models they fitted to the cancer mortality data to include the individual contributions of gamma rays and neutrons, but it was impossible to assert that one of the models was significantly better than any other. Consequently, they estimated the risk coefficients per sievert (Sv) assuming an arbitrary but constant RBE of 1, 10 and 20. Using the cancer mortality data for leukemia and cancers other than leukemia, Preston and Pierce33) also determined a dose-response relationship assuming a constant RBE, and showed that the goodness of fit varies almost negligibly with RBE values in the range of 1 to 50 for the DS86 dosimetry system. They concluded that the city difference in the excess risk of cancer is not statistically significant even at an RBE of one, and does not diminish rapidly as the RBE is increased.

It is well known that the RBE generally increases with decreasing dose34,35). The difference observed in the dose-response for cataracts between the two cities strongly suggests not only the possibility of estimating a RBE, but also seems to provide information that the RBE is higher for survivors who were exposed at low dose. The estimated parameters are significantly positive for gamma and neutron doses under the most suitable L-L model with two thresholds. The T65DR, DS86 kerma and eye organ dose all suggest the existence of two thresholds, probably in the range from 0.70 to 1.40 Gy for gamma rays and from 0.06 to about 0.60 Gy for neutrons. It should be noted that the LQ-L model with two thresholds, which fits the A-bomb survivor data less well, but not significantly so, yields very similar estimates of the two thresholds as the L-L model. Finally, we have also fitted a Q-L model with two thresholds. This model fits the survivor data more poorly than the LQ-L model with two thresholds, both with respect to the dose grouped data and the individual dose data. The best fit in the Q-L model with two thresholds gives 0 Gy for the gamma threshold, which seems implausible on the basis of the clinical studies, and 0.04 or 0.05 Gy for the neutron threshold, and suggests a highly significant effect of gamma rays but not of neutrons.

Only the T65 dosimetry gives an appreciably different estimate of the neutron threshold for the individual binary data. If we use a threshold for neutrons and calculate the RBE corresponding to neutron doses of 0.07, 0.08, 0.25, 0.50 and 1.00 Gy, the values are 105, 69, 36, 34 and 33 for the DS86 eye organ dose. However, the RBE value based on the 95% lower bound suggests
a constant 11.8. If this constant is valid, neutron doses ranging from 0.07 Gy to 1.0 Gy correspond to 0.83 to 11.8 Sv. If we take into account the 95% lower bound of the neutron threshold including zero for the DS86 eye organ dose, the RBE values are estimated to be 32.4 + 0.73/Dn with the 95% confidence limits ranging from 11.8 to 88.3 + 1.39/Dn, where Dn is the neutron dose in gray. Rossi\textsuperscript{36} and Bateman et al.\textsuperscript{37}, comparing a number of neutron energies against x-rays, reported that the RBE for opacification of the murine lens was 0.44/√Dn. The ICRP\textsuperscript{13} gives a table of RBE values for production of opacities of the lens with single exposures to x-rays, gamma rays, or to fission neutrons. These values range from 2 to 20. The BEIR report\textsuperscript{27} suggests that the RBE for high LET radiation for a single cataractogenic exposure is in the range of 2–9.

A recent NCRP report\textsuperscript{38} summarizes the general findings on cataractogenesis in many experimental animals and human beings, and on the existence of time thresholds for lens-opacity in rabbits from acute exposure, but does not review the RBE of neutrons.

UNCERTAINTIES

The estimates of risk just cited are substantially higher than those based on the DS86 eye organ dose. However, there are a number of uncertainties associated with the estimates of risk. These include errors resulting largely from inadequate information on the location, posture, orientation and shielding of individual survivors, and the limited number of “heavily” exposed individuals with cataracts observed in 1963–64. The presence of nonsystematic errors in the individual radiation dose estimates for the A-bomb survivors results in underestimation of radiation effects in dose-response analyses, and the unbiased estimates of linear excess risk for cancer mortality are about 5%–15% greater than the estimates making no allowance for such errors\textsuperscript{31}.

The degree of cataract does not always appear consistent with estimated dose (see Appendix 1 (13)). However, the occurrence of a cataract may depend on individual sensitivity and the angular distribution of the flash radiation upon the lens. The DS86 eye organ dose estimates are based on 12 mean angles to the burst point, but the occurrence of cataract in the atomic bomb survivors is not entirely consistent with the angular distribution of the flash. The 68 individuals with cataracts on whom the angles are known (after the exclusion of 8 cases who belong to the “not-in city” or “distal group” on whom no information exists on angular distribution) are randomly distributed with respect to the 12 directions from the burst point. This seems counter intuitive, and could be interpreted as suggesting that orientation is poorly ascertained (the head is certainly more mobile than the remainder of the body, and a brief rotation may not have been recalled), that the scatter of radiant energy within a home was more uniform than supposed (most survivors were exposed in wooden structures), that the eye doses which are actually kerma in the lens rather than absorbed energy are inexact (the shallow depth of the lens and its small size could militate against an equilibrium between the released and absorbed energy), or some combination of these factors.

REFERENCES


