Radiation Cataract: Biomicroscopic Observations in Rabbit, Monkey, and Man*

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The great variation in dose levels of ionizing radiation required to produce lens changes in various species has not been adequately explained, nor has an acceptable theory been postulated.

Single exposures of rabbit and monkey (Macaca mulatta) eyes to 1 Mev/x-irradiation and to 20 and 100 Mev/protons beam energy have required enormous dose differences to produce minimal lens changes in the two species, and the latent period after exposure and first observable lens changes was equally remarkable.

The term "cataract" has been purposely avoided in this text because of the variation in definition by various investigators and/or clinicians. It should, therefore, be understood that the most minute changes described can be regarded as a sensitive "biological dosimeter" in radiation damage to the lens, though the changes certainly would not affect vision.

The type or configuration of lens changes in these two species was quite different. This can be understood on the basis of the structural differences of their crystalline lenses based on the location of the suture lines.

On the other hand, lens changes in the monkey and those described in man are very similar. However, following irradiation, the latent period and dose requirements to produce lens changes also vary to a great extent.

* This investigation was supported by the National Aeronautics and Space Administration, (NASA), Grant NGR 47-002-005 and in part by the Old Dominion Eye Bank and Research, Inc., Richmond, Virginia, Prevention of Blindness, Inc., New York, New York, and NIH Grant No. 2B5176 and 5 T01 EY00022.

Figure 1 illustrates the *in vivo* lens changes in the rabbit after ionizing radiation, arbitrarily classified in grades of severity based on biomicroscopic findings. Such changes were similar for x-ray and proton irradiation, although dose requirements to produce such changes varied with the energy and dose level (fig. 2). A brief description of the various degrees of observed lens changes follows.

Grade 0: Double contoured white horizontal suture lines in posterior subcapsular areas, fading into a fine haze towards the center of the lens. No coarse or medium sized dots and no more than five dots present.

Grade 1: Same as 0, but moderate number of fine dust-like dots and a few larger dots, white and sharply outlined in the posterior cortex along both sides of the suture lines. The suture line shows branching mainly on the two ends but also along the entire course. Less than five coarse dots along the posterior suture lines.

Grade 2: Any features described under 0 or 1, but in addition, one or two white linear opacities near the suture lines and oriented in the direction of the individual lens fibers in that particular area. Coarse dots range up to 10.

Grade 3: Same as 2, but up to 30 linear opacities and/or increase in larger dots.

Grade 4: The suture line is branched but shows, in addition, interruptions in continuity, besides the features described in 3, and up to 50 and above coarse opacities.

Grade 5: Increasing number of hard white dots and linear opacities. Beginning of a haziness in the posterior cortex.

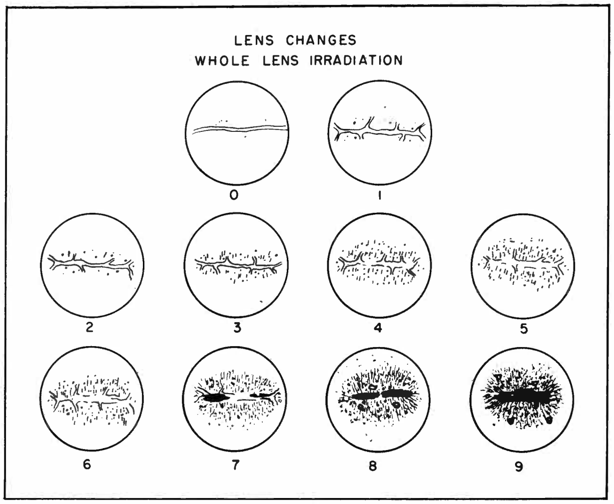

Fig. 1—Schematic drawing of observed lens changes in the Dutch rabbit eye after whole lens irradiation. The number underneath each drawing represents the grade of lens changes (see text). Zero represents the initial appearance of all lenses used in the study. One shows changes which occur with age. Two through 9 show lens changes, in order of increasing severity, which developed in irradiated lenses during the observation period.

Grade 6: Same as in 5, but more pronounced haziness. Suture line still double contoured with branching.

Grade 7: Suture lines in some areas thickened and dense white but partially still double contoured. Haziness in posterior cortex increased with radiating pattern particularly in central portion of the posterior cortex.

Grade 8: Double-contoured suture lines have disappeared leaving only dense thick white fragments in the posterior cortex within the veil-like haziness and numerous heavy dot-like opacities and occasional vacuoles. There were no changes in the lens periphery (biomicroscopically). Few dot-like opacities might be located in anterior cortex.

Grade 9: Same as in 8; however, all changes are somewhat more anterior with respect to the posterior capsule. The earlier suture lines appear to have contracted into a thick rock-like mass with a rough cratered surface. The veil-like haziness extends from this mass in a somewhat posterior direction toward the periphery.

From the *in vivo* study it was concluded that the effect of proton irradiation for the two energy levels (20 Mev, 100 Mev) in producing lens changes is significantly greater than the effect caused by 1 Mev x-radiation. Also, exposure to the higher LET 20 Mev proton beam results in more pronounced lens changes as compared with effects after a lower LET 100 Mev proton irradiation at identical dose levels and single exposure (fig. 3). The similar biomicroscopic appearance of such lens changes may indicate that the pathogenesis is the same for the two types of irradiation. Onset of first detectable lens changes after proton beam exposure was approximately the same as observed after x-ray exposure; however, the progression of lens changes to more severe degrees appeared slower for the former. No further progressions were noted after 12 months post irradiation at which time a "plateau" was reached which was not reversible over several years of follow-up examinations.

Latent periods between day of exposure and first detectable lens changes in rabbits varied slightly with beam energy and dose levels but fell in a time span of two-and-a-half to four months post irradiation in the case of single dose exposure. For fractionated doses, one exposure per month for a total

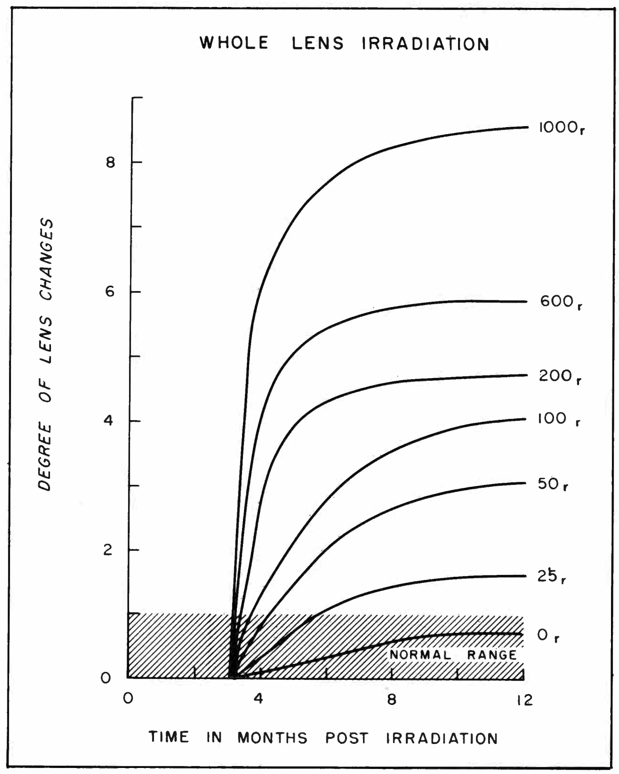

Fig. 2—Graph representing development of lens changes in Dutch rabbit eyes according to grades of severity illustrated in figure 1(1), after radiation exposure of various doses from a 1 Mev x-ray unit. Each curve represents the mean value for the individual dose groups.

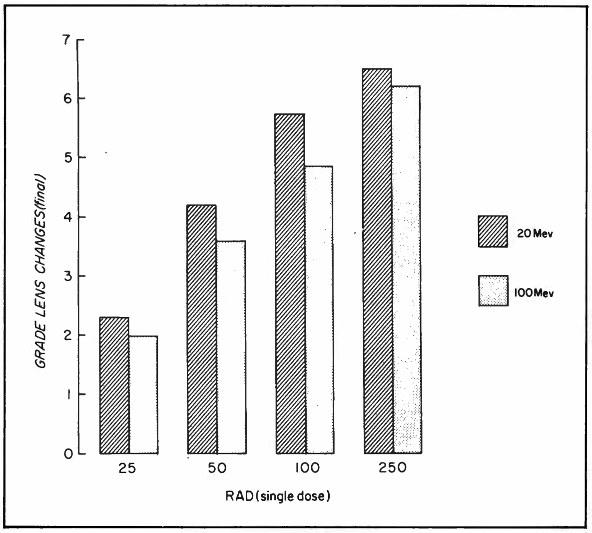

Fig. 3—Comparison of final grades of lens changes in Dutch rabbits for various dose levels and two proton beam energies.

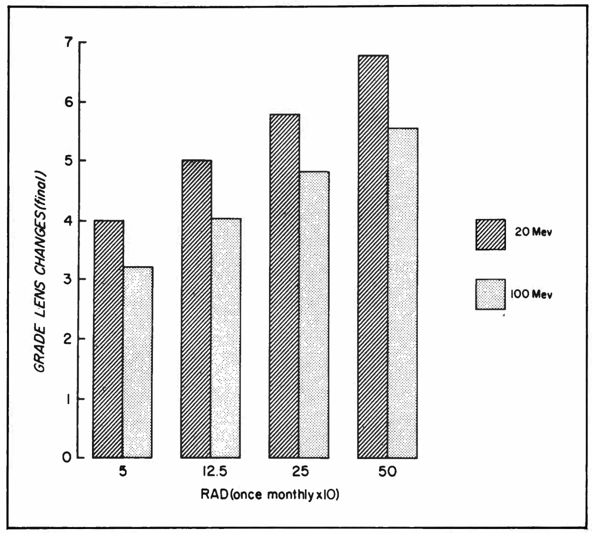

Fig. 5—Comparison of final grades of lens changes in the Dutch rabbits for various dose levels and two proton beam energies.

of 10 months, and two proton beam energies (20 and 100 Mev), the latent time is illustrated in figure 4. The final degree of lens changes for these two modes of radiation is presented in figure 5.

Comparing the grades of final lens changes after single radiation exposure with those observed after equal total doses, but administered in fractionation of 1 exposure per month over a 10-month period, it was obvious that the lens changes produced after single exposures were significantly more severe than those developed after fractionated exposures. This

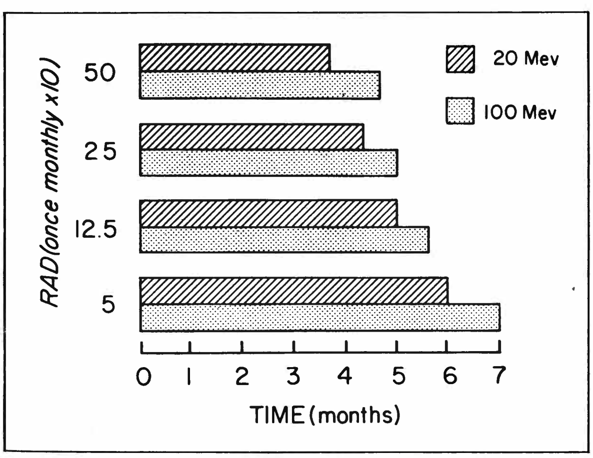

Fig. 4—Comparison of latent periods between initial irradiation and first appearance of *in vivo* observable lens changes in the Dutch rabbits for two proton beam energies (30 and 100 Mev) and four dose levels (5, 12.5, 25, 50 rad).

can be expected and has long been recognized and attributed to a biological repair mechanism in the case of protracted irradiation. It can be equally well understood that the rate of progression in lens changes is slower after fractionated exposures than after single exposures. The final degree of severity of lens changes was found to be equal if the total fractionation given was about twice that of single exposures, that is, 500 R x-ray given over 10 months caused about the same effect as 250 R x-ray given as a single dose. This observation also holds true for protracted and single proton beam irradiation within the limits of the experimental model used in this study.

From preliminary observations, these lens changes in the Rhesus monkey were arbitrarily categorized into seven severity grades and illustrated in figure 6. Grade 0 represents the normal, non-irradiated lens. Only animals with grade 0 prior to irradiation were used in this investigation.

Grade 0: Normal clear lens with occasional few fine and thin irregular lines on the posterior capsule due to vitreous adhesions. Besides some mild cortical haziness sometimes appearing with aging of the animal, no other age-related lens changes.

Grade 1: Few fine glistening dots in the posterior subcapsular region.

Grade 2: Fine crystalline appearing precipitates

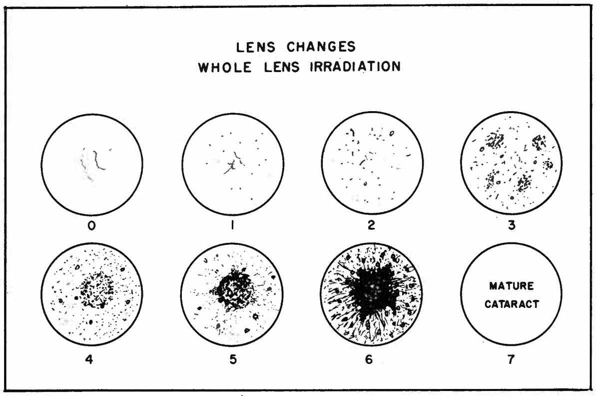

Fig. 6—Schematic drawing of observed lens changes in the Rhesus monkey eye after whole lens irradiation. Grade 0 represents the initial appearance of all lenses used in this study. Grades 1 through 7 show lens changes as they developed with time and various modes of radiation exposure.

located in the posterior subcapsular region were increased in number in the presence of a few small vacuoles. Lens otherwise clear.

Grade 3: Posterior subcapsular generalized haziness with many small, dense, dot-like opacities and a moderate number of fine vacuoles. Several areas showed more dense haziness.

Grade 4: Similar findings as in Grade 3, but the fine opacities appear in greater number and accumulate particularly in the posterior pole region.

Grade 5: Dense posterior, "typical" radiation cataract (referred to in literature as early radiation cataract). Many vacuoles primarily within posterior pole region of doughnut-shaped circular but irregular lens opacities. From this area in radiating fashion general haziness in which many fine crystalline appearing dots are interspersed. Anterior cortex still free of changes.

Grade 6: Posterior and anterior subcapsular cortical haziness and densities in radiating fashion with many whitish dot-like opacities and vacuoles of various sizes.

Grade 7: Mature cataract in which many vacuoles can still be seen in the anterior cortex. Difficult to distinguish from any other type of mature cataract if progression has not been followed, mainly through the stages of Grade 5 and 6.

Again, there were no obvious differences in the appearance of those changes after x-ray and proton irradiation though the dose requirements for the different modes of radiation, that is, beam energy and type of radiation to produce similar severity grades, varied.

From the accumulated data over a two-and-a-half-year observation period, no lens changes were detected after proton (100 Mev beam energy) exposure and 250 rads single dose. Of three animals exposed to 500 rads, only one lens showed Grade 1 changes at the two-and-a-half-year examination date. Of three animals which received 750 rads, one did not show any observable changes, while two presented Grade 1, which in one animal progressed to Grade 2 at the three-year examination follow-up. In three animals which had received 1,000 rads single exposure, only one showed Grade 1 changes two years post exposure which progressed to Grade 3 over the following six months. One animal which did not present any changes on the examination date at two and one-half years progressed rapidly to a Grade 5 at the time of three years post irradiation; one animal of this group presented Grade 1 changes at the two-and-a-half-year examination without further progression at this time. Because of the possible rapid progression after first minimal changes have become manifest, biomicroscopic examination is at present scheduled in three-month intervals.

Because of the different manifestations of lenticular changes in these two species (monkey and rabbit), comparison of energy and dose levels are made only for the first detectable minimal lens changes.

Results of protracted radiation and its effect on monkey lenses are at present under investigation and no conclusive statements can be made at this time. Based on the observations made on rabbit lenses, however, it can be assumed that a similar additive or accumulative effect will finally be noted.

A cataractogenic dose for x-ray exposure in man has been quoted in the literature with 250 to 500 rads. However, in present studies of patients receiving irradiation treatment from a Cobalt-60 source for various malignancies, where one or both eyes received considerable dose levels, no lens changes have been observed in 27 patients out of a total of 28 over a two- to four-year observation time. In all cases, dose levels to which the lenses were exposed had been carefully determined by dosimetry for each exposure area. Those dose levels to the lens ranged from 480 rads to 6,850 rads given over a six- to eight-week period in fractionated doses of 100 to 200 rads daily for five days per week. The only patient who has developed a characteristic radiation cataract to date is an 8-year-old girl. She received two series of therapeutic radiation in a four-year span (3,965 and 3,200 rads) in 1966 and 1970 respectively. Unfortunately, the parents did not bring the child for reexamination on a regular basis, so the posterior subcapsular lens changes had become quite prominent and typical for ionizing radiation exposure at the time the child was seen two months after final x-radiation in 1970. Hence, the exact latent period and the appearance of first observable minimal lens changes are not known. Certainly this observation confirms earlier statements that the age of the patient when radiation exposure took place plays an important role, that is, with younger age more severe lens changes can be expected with equal dose levels.

Because of the great variance of apparent dose requirements for production of lens changes in man, Rhesus monkeys, and Dutch rabbits, as mentioned above, it was felt that *in vitro* studies on cultured lens epithelial cells of the three species may allow greater insight on a cellular level into the mechanism involved following equal doses of x-ray exposure of the cultured cells at various times after the original explant was made.

To use such a model, it was necessary to establish that lens epithelial cultures could be maintained over long periods of time, and to study the normal, non-exposed cells of the three species, with regard to their morphological appearance and growth rate. These observations on cultures have been carried out over a four-and-a-half-year period and are described and illustrated in the following article.

Author's note: The author would like to acknowledge the extensive experimentation on the physical aspects of instrumentation design and dosimetry carried out on all animal studies by Dr. William T. Ham, Jr., Chairman, Department of Biophysics, and his staff, and to Dr. Richard King, Chairman, Division of Radiotherapy, and his staff. The author is grateful to these colleagues for making patients available who had received radiation treatment in which the lens received appreciable x-ray doses, and to Mr. Robert Howells for carrying out exact dosimetry in these patients. My thanks are also due to Dr. Thomas Nooney for his assistance in patient evaluation and clinical follow-up examinations.

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(Other pertinent literature is listed in the above mentioned papers.)