The Effect of Continuous Low Doses of X-ray Irradiation on the Rat Lens

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Purpose: To clarify the morphological changes in the rat lens after irradiation with continuous low doses of x-ray at different intervals.

Methods: Male Wistar rats at the age of 8 weeks were irradiated with three doses of 2 Gy at intervals of either 1 week or 1 day. Over the period from the first week to the eighth week after irradiation, the eyeballs of the rats were enucleated progressively and changes in the lenses were examined morphologically. A comparison was made with specimens from control rats at each time of enucleation.

Results: (1) Three doses of weekly irradiation: 1 week later, the lens epithelium and fibers at the equator showed mild swelling. Bow configuration was slightly disturbed. Eight weeks later, swelling and uneven height of epithelial cells in the equatorial area, irregular bow configuration, swelling of cortical fibers and epithelial loss and deformed nuclei at the central epithelium were observed. (2) Three doses of daily irradiation: 1 week later, mild changes in the lens such as uneven height of epithelial cells, irregular bow structures, and swelling of cortical fibers were observed. Eight weeks later, irregular bow configuration, posterior dislocation of nuclei, severe epithelial loss and marked swelling of cortical fibers were observed at the equatorial area. Epithelial loss and deformed nuclei of the epithelium were observed in the central area.

Conclusion: The lens was damaged by continuous irradiation even though the dose was low. The damage to the lens caused by daily irradiation was more severe than that by weekly irradiation. The main symptoms were degeneration and loss of epithelial cells and swelling of cortical fibers. **Jpn J Ophthalmol 2003;47:427–436** © 2003 Japanese Ophthalmological Society

Key Words: Continuous low x-ray doses, cortical fiber swelling, deformed nuclei, rat lens, x-ray irradiation.

Introduction

Radiotherapy has been widely used for the treatment of tumor and thyroid oculopathy. X-ray is often used for radiotherapy, and repeated irradiation at a low dose of 2 Gy is commonly conducted. However, it is well known that tissues are damaged by increases in the total dose of multiple irradiation. Among the eye tissues, the sensitivity of the lens to irradiation is high,[1] and irradiation can cause cataract, which is called radiation cataract. It is known that the occurrence pattern and level of radiation cataract vary with the irradiation dose, age, interval of irradiation and animal species. As biochemical causes of radiation cataract, reduction of reductases such as glutathione peroxidase, reduced form nicotinamide adenine dinucleotide phosphate and glucose-6-phosphate dehydrogenase,[2,3] reduction of Na-K-ATPase activity,[4] and reduction of the concentration of ascorbic acid[5] have been reported. Morphologically, collapse of bow configuration, nuclear deformation and abnormal mitosis of

epithelial cells in the lens,[6–8] vacuolation of epithelial cytoplasm, and cyst formation in the posterior cortex[9] have been reported. These findings were obtained by a single high dose of irradiation,[10,11] but the effects on the lens of the repeated low doses of x-ray irradiation used for radiotherapy have not been sufficiently examined. In this study, we morphologically examined the effects on the lens of multiple x-ray irradiation at a low level at different intervals, and evaluated the probability of damage to the lens from x-ray irradiation.

Materials and Methods

Seventy-two eyes from 36 male 8-week-old Wistar rats were used in this study. These rats were divided into three groups; three doses of weekly irradiation group, three doses of daily irradiation group, and control group. The rats were raised in an animal room maintained on a light–dark cycle of 12 hours. Food and water were available ad libitum. Intraperitoneal injection of a mixture of sodium pentobarbital and ketamine chloride at the dose of 30 mg/kg was given before irradiation and enucleation.

The x-irradiation device used in this study was an MBR-1505 (Hitachi Medical, Tokyo) and the radiation dose was 2 Gy (FDD 300 mm, 150 kV, 5 mA, 167 s). The irradiation site was limited to the head, and the body below the head was shielded by a lead plate. At 1, 4, and 8 weeks after irradiation, eyeballs were enucleated from the animals under general anesthesia. Time schedules of x-ray irradiation and of enucleation after irradiation are indicated in Scheme 1. All the animals were treated in accordance with the ARVO resolution regarding animals used in research.
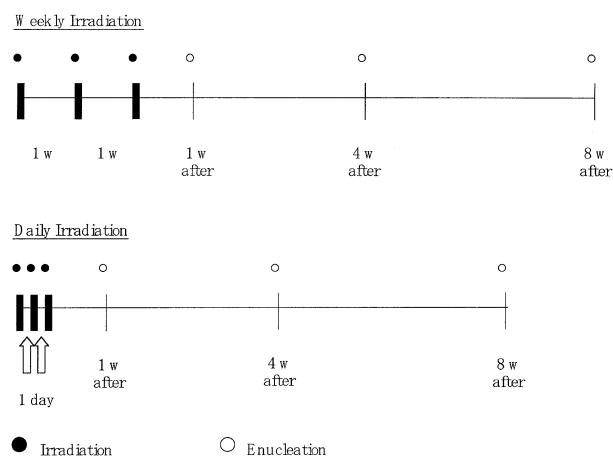
Irradiated animals were divided into two groups. One group was irradiated with three doses at weekly intervals. The other was irradiated with three doses at daily intervals. After irradiation, the enucleation in both groups, and controls, was made at 1, 4, and 8 weeks.

For transmission electron microscopy, some lenses were fixed with 4% glutaraldehyde in 0.075 M phosphate buffer (pH 7.5) for 3 days and cut into halves at the end of this period. After a washing in buffer, the specimens were postfixed with 1% OsO_4 in the same buffer solution overnight, and embedded in Quetol 812. Semi-thin sections were prepared for light microscopy and stained with toluidine blue. Thin sections were stained with uranyl acetate and lead citrate and examined by electron microscopy.

For whole-mount flat preparations of the lens epithelium, other specimens were fixed overnight in a 3:1 solution of ethanol and acetic acid. After rinsing in 70% alcohol, the specimens were stained lightly with hematoxylin and transferred to water. The epithelium was peeled off under the dissecting microscope, restained in hematoxylin, and mounted with resin.

Results

Unirradiated Controls

In control lenses observed under the dissecting microscope there was no unusual reflection or opacity (Figure 1a). In the flat preparation of the equatorial epithelium the meridional array showed a regular arrangement (Figure 1b). Histologically, the typical lens bow was observed at the equatorial region of the lens (Figure 1c). By electron microscope, the equatorial epithelial cells showed almost constant density of the cytoplasm (Figure 1d).

Rats given three doses of weekly irradiation. In flat preparations of the equatorial epithelium at 1 week after 3 weeks of weekly irradiation, the alignment of the end of the epithelium was slightly irregular in the meridional direction, but the height was almost the same (Figure 1e). Histologically, a small number of dark cells alternated with epithelial cells in the equatorial area, and the bow configuration was slightly disturbed (Figure 1f).

In flat preparations of the equatorial epithelium at 4 weeks after 3 weeks of weekly irradiation, a small number of deformed nuclei were observed in the epithelial cells in the equatorial area (Figure 1g). Histologically, slightly disturbed bow configuration and mild swelling of cortical fibers were observed (Figure 1h).

There was no difference in the whole lens between the unirradiated controls and the weekly irradiation group at

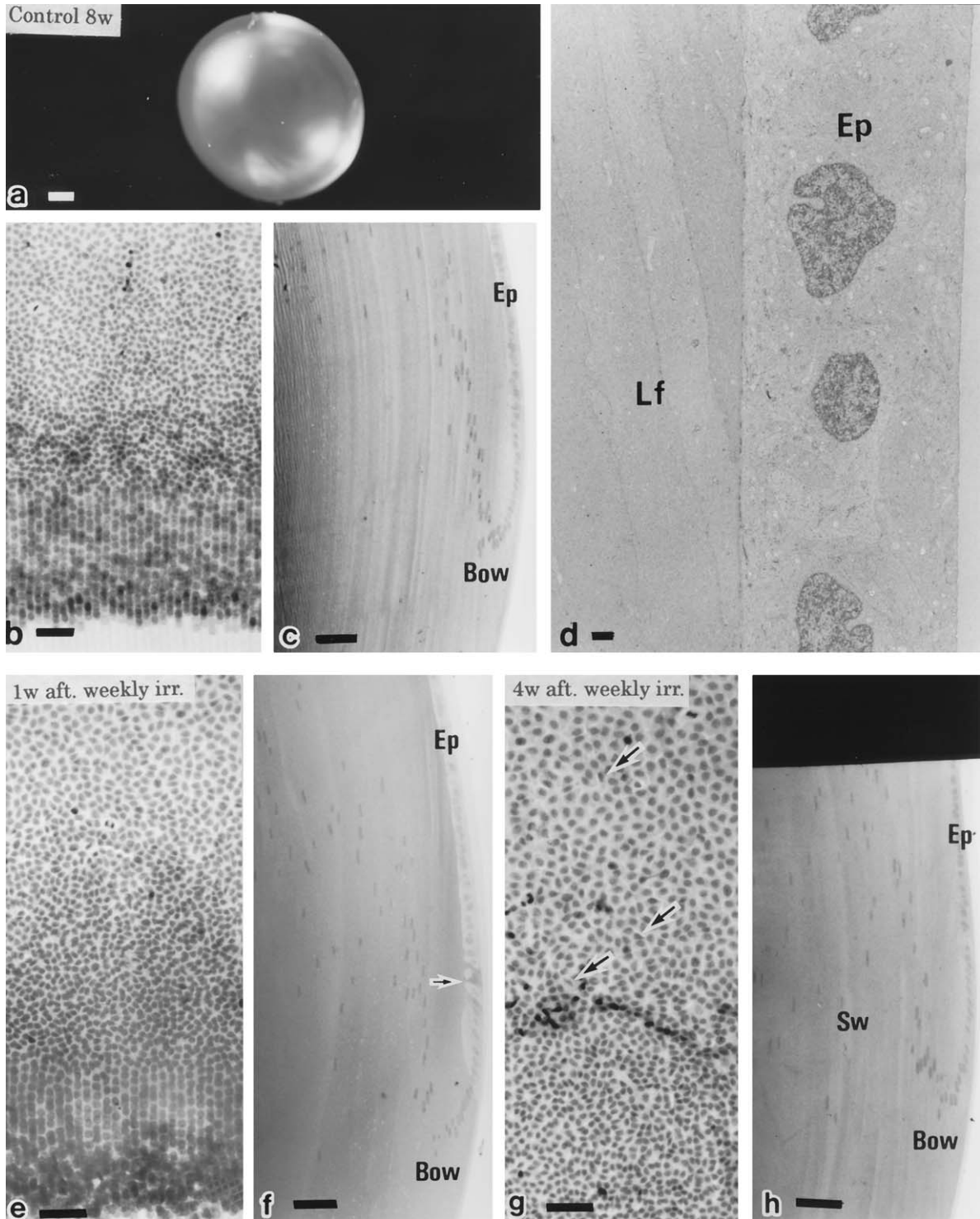Weekly Irradiation

1 w　1 w　1 w
after

4 w
after

8 w
after

Daily Irradiation

1 w
after

4 w
after

8 w
after

1 day

● Irradiation　○ Enucleation

Scheme 1

Figure 1. (**a**) Anterior view of the unirradiated control rat lens at 11 weeks of age. Bar = 100 μm. (**b**) Flat preparations of the equatorial region in a control lens at 11 weeks. Meridional array is distributed regularly. Bar = 50 μm. (**c**) Photomicrograph of the equatorial region in a control lens at 11 weeks. Bow configuration is clearly formed. Ep: epithelium. Bar = 50 μm. (**d**) Electron micrograph of the equatorial epithelium (Ep) in a control lens at 11 weeks. Lf: lens fiber. Bar = 1 μm. (**e**) Flat preparations of the equatorial region at 1 week after weekly irradiation for 3 weeks. Meridional arrays at the epithelial ends appear nearly normal. Bar = 50 μm. (**f**) Photomicrograph of the equatorial region at 1 week after weekly irradiation for 3 weeks. A small number of dark cells (arrow) are seen in the epithelium (Ep). Bar = 50 μm. (**g**) Flat preparations of the equatorial region at 4 weeks after weekly irradiation. Nuclear distribution of the equatorial region is mildly irregular. A small number of deformed nuclei (arrows) can be seen. Bar = 50 μm. (**h**) Photomicrograph of the equatorial region at 4 weeks after weekly irradiation for 3 weeks. Bow configuration at the equator is slightly disturbed. Some cortical fibers are swollen (Sw). Bar = 50 μm.
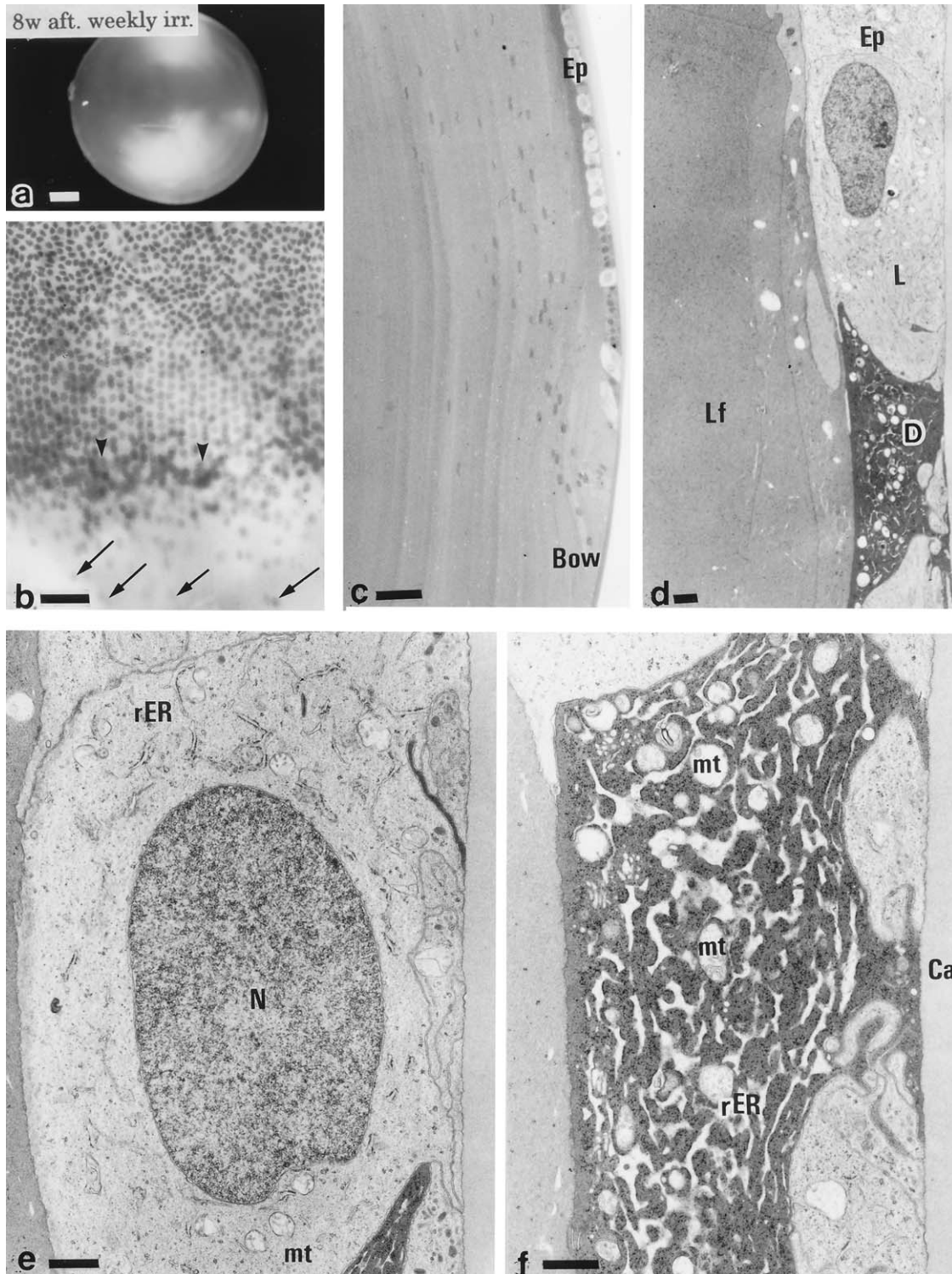
Figure 2. (**a**) Anterior view of the rat lens at 8 weeks after weekly irradiation for 3 weeks. The lens appears almost normal. Bar = 100 μm. (**b**) Flat preparations of the equatorial region at 8 weeks after weekly irradiation for 3 weeks. Meridional arrays at the epithelial ends are markedly disturbed (arrowheads). Numerous nuclei are displaced posteriorly (arrows). Bar = 50 μm. (**c**) Photomicrograph of the equatorial region at 8 weeks after weekly irradiation for 3 weeks. Light and dark cells are intermingled in the equatorial epithelium (Ep). Bow configuration at the equator is markedly disturbed. Cortical fibers are frequently swollen. Bar = 50 μμm. (**d**) Electron micrograph of the equatorial epithelium (Ep) consisting of light (L) and dark cells (D). Cortical fibers (Lf) are swollen. Bar = 1 μm. (**e**) Electron micrograph showing the light cell in the equatorial epithelium. Cell organelles such as mitochondria (mt) and rough endoplasmic reticulum (rER) are sparsely distributed. N: nucleus. Bar = 1 μm. (**f**) Electron micrograph showing the dark cell in the equatorial epithelium. Mitochondria (mt), rough endoplasmic reticulum (rER), and free ribosomes are abundantly present. Ca: capsule. Bar = 1 μm.
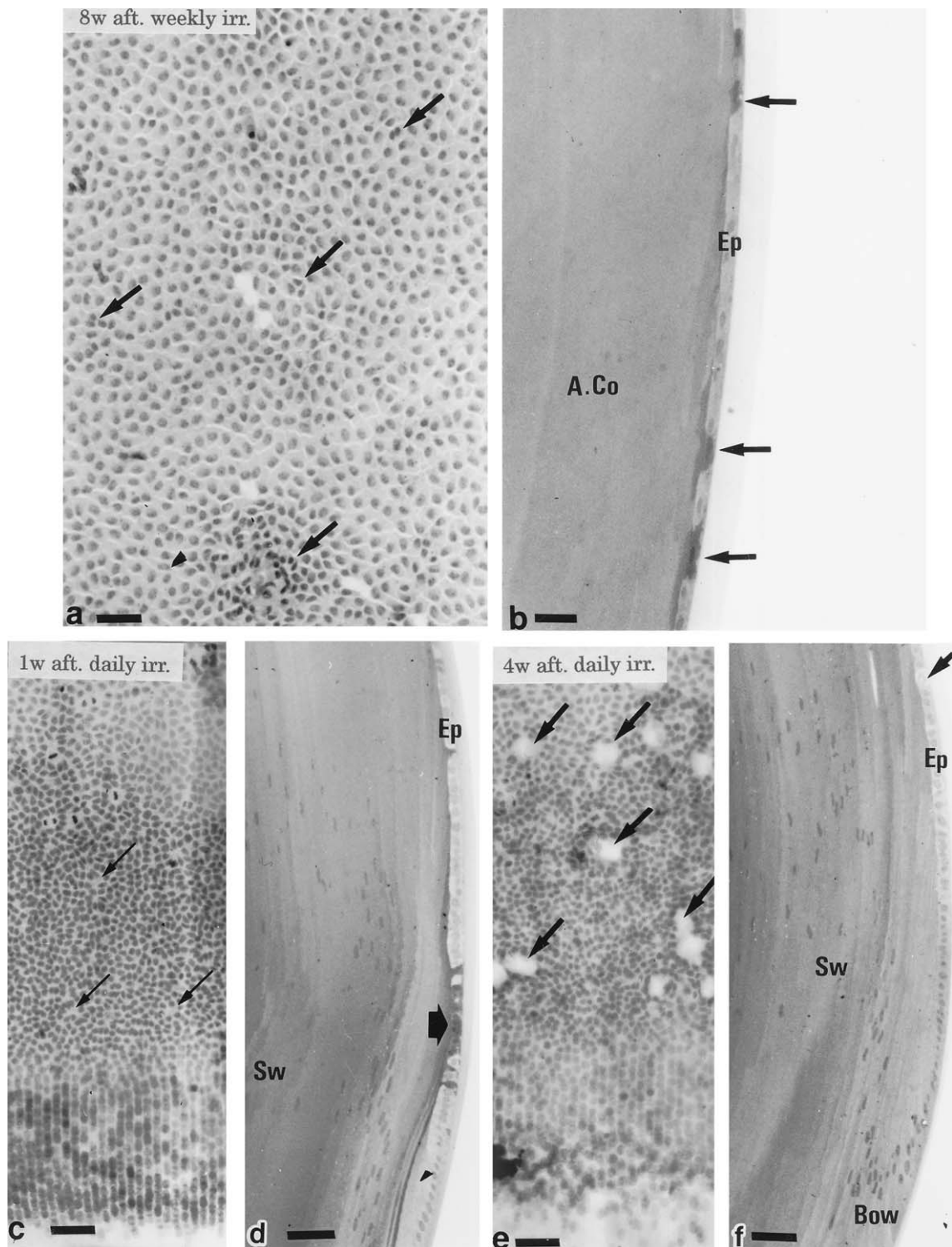
Figure 3. (**a**) Flat preparations of the central epithelium at 8 weeks after weekly irradiation for 3 weeks. A small number of deformed nuclei are distributed (arrows). Some acellular areas are seen. Bar = 50 μm. (**b**) Photomicrograph of the central epithelium (Ep) containing dark cells (arrows), suggesting cellular degeneration. A.Co: anterior cortex. Bar = 50 μm. (**c**) Flat preparations of the equatorial epithelium at 1 week after daily irradiation for 3 days. Meridional arrays at the epithelial ends appear nearly normal. Nuclear distribution at the germinative zone is slightly irregular (arrows). Bar = 50 μm. (**d**) Photomicrograph of the equatorial region at 1 week after daily irradiation for 3 days. Equatorial epithelium (Ep) often contains dark cells (arrow). Cortical fibers are swollen (Sw). Bar = 50 μm. (**e**) Flat preparations of the equatorial epithelium at 4 weeks after daily irradiation for 3 days. Many acellular areas are seen (arrows). Meridional arrays at the epithelial ends are fairly disturbed. Bar = 50 μm. (**f**) Photomicrograph of the equatorial region at 4 weeks after daily irradiation for 3 days. Acellular area (arrow) is seen in the epithelium (Ep). Bow configuration is mildly disturbed. Cortical fibers are often swollen (Sw). Bar = 50 μm.
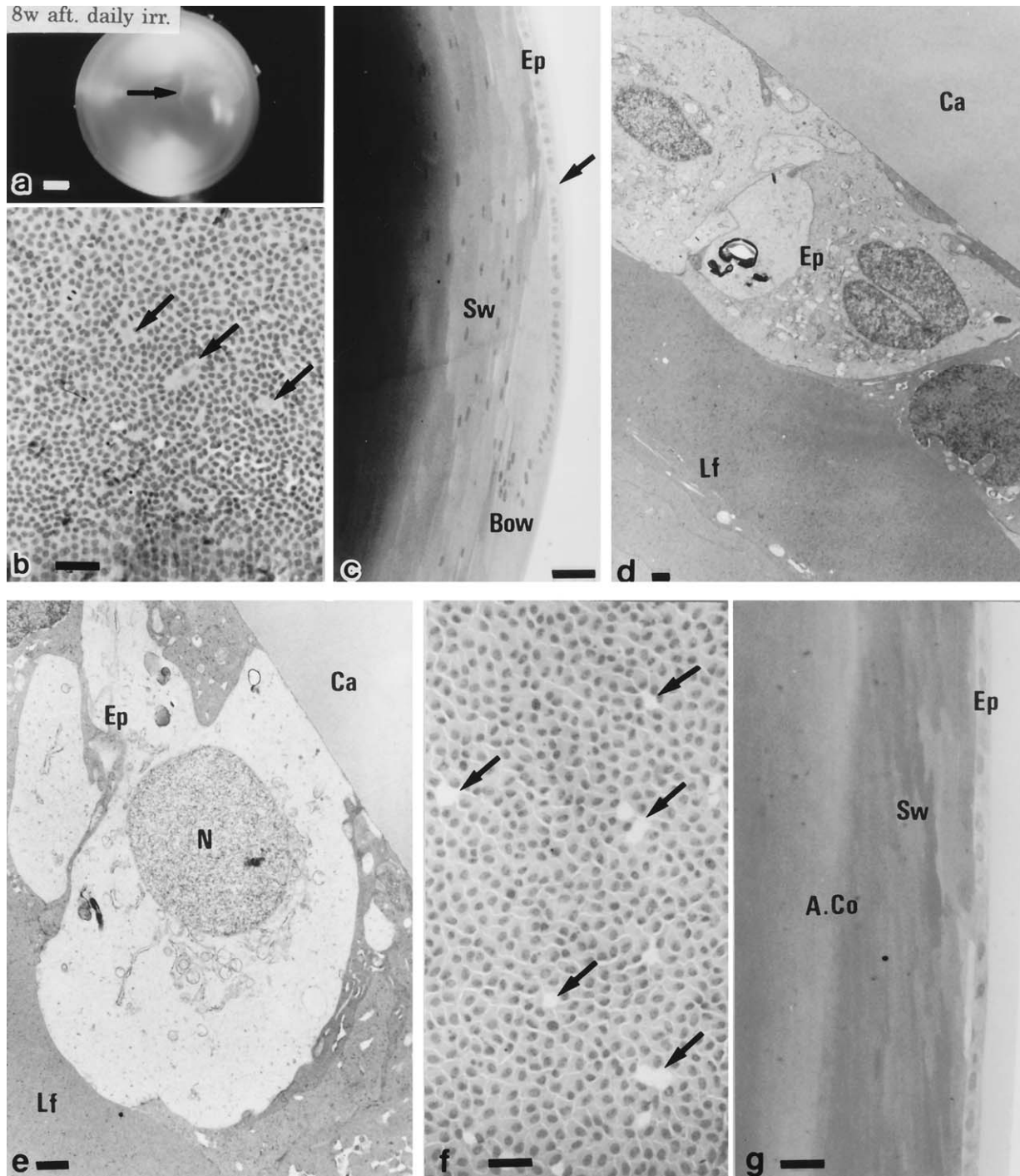
Figure 4. (**a**) Anterior view of the rat lens at 8 weeks after daily irradiation for 3 days. Opaque area is seen at the surface of the lens (arrow). Bar = 50 μm. (**b**) Flat preparations of the equatorial epithelium at 8 weeks after daily irradiation for 3 days. Many acellular areas are still present at this stage (arrows). Numerous deformed nuclei are also seen. Bar = 50 μm. (**c**) Photomicrograph of the equatorial region at 8 weeks after daily irradiation for 3 days. The acellular area (arrow) is seen in the epithelium (Ep). Bow configuration is fairly disturbed. The cortical fibers are often swollen (Sw). Bar = 50 μm. (**d**) Electron micrograph of the equatorial region at 8 weeks after daily irradiation for 3 days. The height of epithelial cells (Ep) is irregular. The cells contain dense granular substances, suggesting degeneration of cell organelles. Lens fibers (Lf) are swollen. Ca: capsule. Bar = 1 μm. (**e**) Electron micrograph showing the light cell in the equatorial epithelium (Ep). The cytoplasm appears swollen, together with a few cell organelles. Ca: capsule, Lf: lens fiber, N: nucleus. Bar = 1 μm. (**f**) Flat preparations of the central epithelium at 8 weeks after daily irradiation for 3 days. Many acellular areas are seen (arrows). Deformed nuclei are present. Bar = 50 μm. (**g**) Photomicrograph of the central region of the lens at 8 weeks after daily irradiation for 3 days. The size and density of the epithelial nuclei (Ep) is irregular. Cortical fibers (A.Co) are often swollen (Sw). Bar = 50 μm.
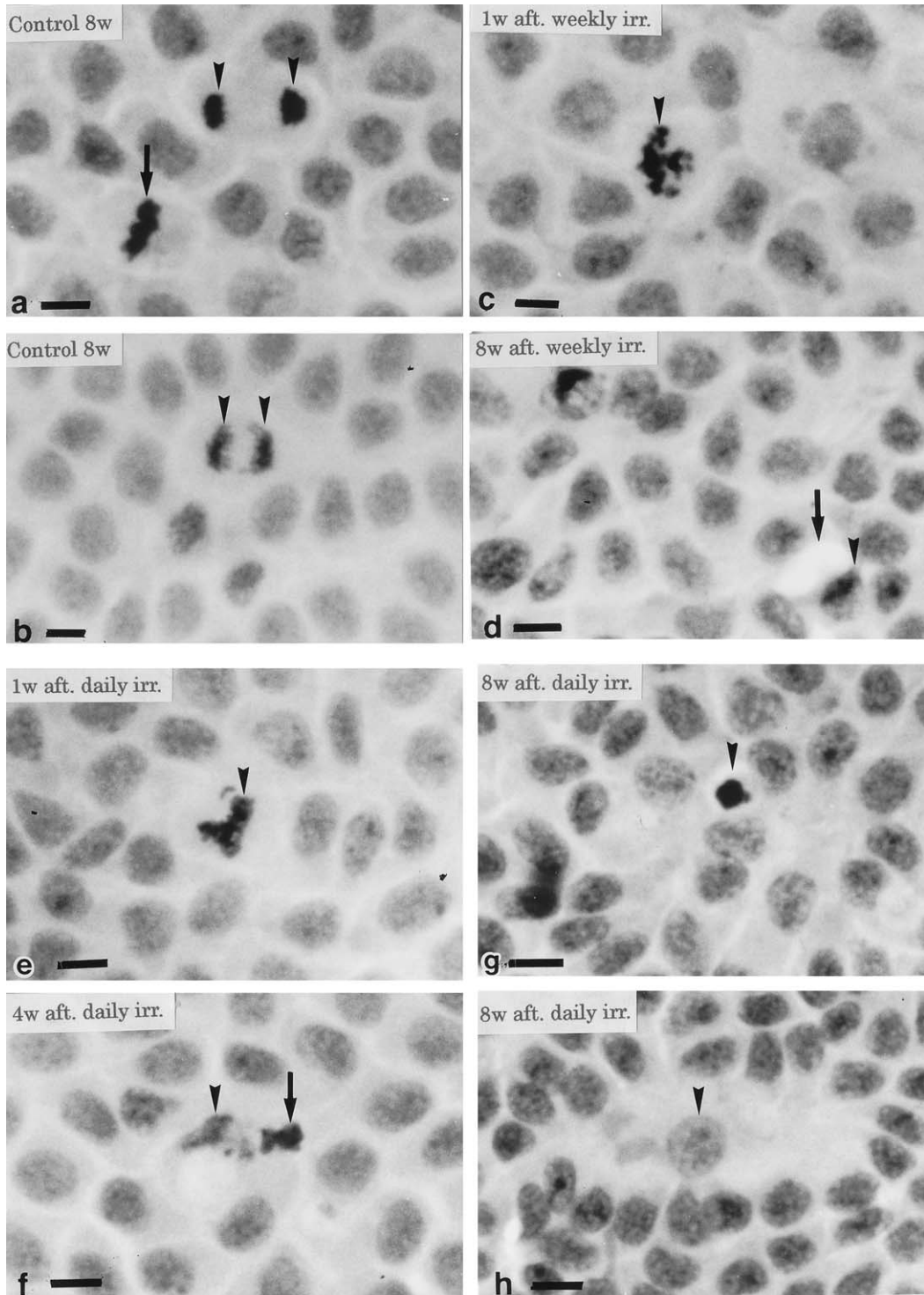
Figure 5. (**a**) Metaphase (arrow) and telophase (arrowheads) in the dividing cell of the controls are shown. Bar = 100 μm. (**b**) Anaphase in the dividing cell of the controls is shown (arrowheads). Bar = 100 μm. (**c**) Metaphase in a dividing cell at 1 week after weekly irradiation for 3 weeks. Unusual chromosomal arrangement is seen (arrowhead). Bar = 100 μm. (**d**) Telophase in a dividing cell at 8 weeks after weekly irradiation for 3 weeks (arrowhead). Acellular space is formed (arrow). Bar = 100 μm. (**e**) Metaphase in the dividing cell at 1 week after daily irradiation for 3 days (arrowhead). Unusual chromosomal arrangement is seen. Bar = 100 μm. (**f**) Resting stage in the dividing cell at 4 weeks after daily irradiation for 3 days (arrowhead). The nucleus is displaced to one side, and the cytoplasm contains a large vacuole. The chromosome in the neighboring cell is condensed (arrow). Bar = 100 μm. (**g**) Condensed chromosome in the dividing cell at 8 weeks after daily irradiation for 3 days (arrowhead). The size of the cell is relatively small. Bar = 100 μm. (**h**) Large nucleus in the large acellular area at 8 weeks after daily irradiation for 3 days (arrowhead). Bar = 100 μm.

8 weeks after irradiation (Figure 2a). In flat preparations of the equatorial epithelium at 8 weeks after weekly irradiation, irregular alignment of the end of the epithelium in the meridional direction and posterior dislocation of nuclei improved slightly (Figure 2b). Histologically, dark cells and swollen light cells were mixed in the epithelial cells in the equatorial area, and the bow configuration was considerably disturbed. Some nuclei were dislocated posteriorly from the bow area (Figure 2c). By electron microscope, it was confirmed that dark cells and light cells were mixed (Figure 2d). At higher magnification the light cells contained only a small number of organelles such as mitochondria and rough endoplasmic reticulum in the cytoplasm (Figure 2e), while the dark cells were filled with organelles such as a large number of mitochondria, developed rough endoplasmic reticulum, and free ribosome (Figure 2f). In flat preparations of the central epithelium at this stage, deformed nuclei and epithelial loss were observed (Figure 3a). Histologically, light cells and dark cells were found to be mixed in the central epithelium (Figure 3b).

Rats given three doses of daily irradiation. In flat preparations of equatorial epithelium at 1 week after daily irradiation for 3 days, there were no significant differences in the epithelium in the equatorial area between the daily irradiation and the control groups (Figure 3c). However, histological examination showed that dark, atrophied cells were mixed with epithelial cells in the equatorial area. Disturbed bow configuration and swelling of cortical fibers were clearly observed (Figure 3d).

In flat preparations of the equatorial epithelium at 4 weeks after daily irradiation for 3 days, the appearance of many acellular areas, irregular alignment of cells in the meridional direction, and posterior dislocation of nuclei were clearly seen in the equatorial areas (Figure 3e). Histologically, slight unevenness in the height of epithelial cells, slightly disturbed bow configuration, posterior dislocation of nuclei, and slight swelling of cortical fibers were observed (Figure 3f).

The whole lens at 8 weeks after daily irradiation showed slight opacity at the lens surface (Figure 4a). In the flat preparation of the equatorial epithelium, many acellular areas were still present at this stage. Deformed nuclei were detected (Figure 4b). Histologically, the uneven height of epithelial cells, the appearance of light cells, disturbed bow configuration, posterior dislocation of nuclei, and the swelling of cortical fibers were clearly observed (Figure 4c). By electron microscope, epithelial cells with different electron densities were visible (Figure 4d). At higher magnification of a light cell, mitochondria and a small number of rough endoplasmic reticulum existed in the cytoplasm. Organelle-derived degraded products were also observed (Figure 4e). In flat preparations

of the central epithelial cells at this stage, deformed nuclei and acellular areas were observed (Figure 4f). Histologically, cells with different degrees of staining were mixed, and the cortical fibers were slightly swollen (Figure 4g).

The effect of x-ray irradiation on dividing cells. The metaphase, anaphase, and telophase in the dividing cells of the controls are shown (Figures 5a and 5b). The chromosomes in these cells were evenly arranged.

The dividing cells at 1 week after weekly irradiation for 3 weeks showed an unusual chromosomal arrangement (Figure 5c). An acellular area was formed in the vicinity of the dividing cells at 8 weeks after weekly irradiation (Figure 5d).

The metaphase of the dividing cell at 1 week after daily irradiation for 3 days also showed an unusual chromosomal arrangement (Figure 5e). The nucleus of the cell at 4 weeks after daily irradiation for 3 days was displaced to one side, and the cytoplasm contained large vacuoles (Figure 5f). Condensed chromosomes were found at 8 weeks after daily irradiation (Figure 5g). Large acellular areas were often formed in the germinative zone at this stage (Figure 5h).

Discussion

In this study, repeated irradiation at a low dose of 2 Gy was performed three times. Few changes in the lens were observed in the samples collected 1 week after irradiation in the weekly irradiation group. In the samples collected 8 weeks after irradiation in the weekly irradiation for 3 weeks group, mild changes were observed in the entire lens such as swelling and uneven height of epithelial cells, disturbed bow configuration, and slight swelling of cortical fibers in the equatorial area, including the appearance of acellularity and dark cells in the central area.

In the daily irradiation group, mild changes were observed in the lens such as uneven height of epithelial cells, disturbed bow structures, and swelling of cortical fibers one week after the daily irradiation for 3 days. Eight weeks after daily irradiation, changes in the lens were much more clearly observed; there was loss of epithelial cells and appearance of deformed nuclei in the central area, and uneven height of epithelial cells, decomposition of bow configuration, and swelling of cortical fibers in the equatorial area.

It has been known that the lens epithelium in the unirradiated rat synthesizes α-crystalline.[12] However, it has been reported that exposure of the rat lens to an irradiated dose of 24 Gy produced nuclear fragmentation and nuclear condensation in the lens epithelial cells.[7,8] Moreover, some damaged cells became swollen.[7,8] These

swollen epithelial cells were similar to the light cells observed in the present study, suggesting that these cells were atrophic. On the other hand, it is likely that the dark cells found in the present study changed into metabolically abnormal cells that did not synthesize α-crystalline. These dark cells have been reported to be diseased, dense cells as seen in rats[13] and mice[14] with congenital cataract and in developing chick lenses.[15]

This study on repeated irradiation at a low dose indicated that cataract caused by three doses at intervals of 1 week was mild because the regeneration and repair of epithelial cells had occurred in the lens after irradiation. However, epithelial cells, which were synergistically damaged by daily irradiation, without time for proliferation and repair, showed severe damage in the lens.

Generally, 2–3 days are required for the repair of damaged cells by proliferation from the surrounding tissues. In the daily irradiation group, cells were damaged by repeated irradiation before the proliferation and repair of cells could occur, resulting in more severe damage to the lens. However, the damage to the lens was mild in the weekly irradiation group. The standard total dose for the treatment of choroidal hemangioma is considered to be 20 Gy[16] with daily irradiation of 2 Gy, 46 Gy[17] with daily irradiation of 2 Gy for retinoblastoma, and 30 Gy[18] with irradiation of 2 Gy for orbital MALT lymphoma.

Based on the damage to the lens of repeated irradiation, the risk of weekly irradiation to cells in the lens for the treatment of tumor and thyroid oculopathy is low, but its effects on the target tumor cells may also be low. Daily irradiation is effective in destroying target cells, but risk to cells in the lens is high. Therefore, it is not irradiation of the entire eye but local irradiation that should be employed for the treatment of diseases in the eye. However, sensitivity to x-ray irradiation is reported to be different depending on the animal species.[19,20] Von Sallmann et al[19] reported that inhibition of cell division in mice and rats persisted for 2–3 months after irradiation, while dogs, cats, and monkeys recovered in about 1 week, indicating that these animals have more developed repair systems.[19] The present study demonstrated that the lens in rats was easily damaged by x-ray irradiation, but we considered that there may be differences in the damage pattern between the rat and human lenses. Repeated irradiation of 2 Gy for treatment is widely performed in humans, suggesting that the human lens is more resistant to x-ray irradiation than the rat lens. However, the occurrence of cataract has not always been reported. Regardless of the safety of irradiation in a continuous dose for the human lens, it seems better to be careful in using a continuous dose.

Lipman et al[21] proposed the mechanism for the occurrence of radiation cataract as follows: x-ray irradiation generates active oxygen, by which epithelial DNA chains are destroyed, and the repair of cells is suppressed. As a result, glutathion and other SH residues are oxidized in the lens, and oxides such as H_2O_2 and peroxylipids are generated in the lens by oxidation stress, by which S—S bond protein is increased and coagulated. This increased insoluble protein causes turbidity. Merriam and Worgul[22] indicated that x-ray irradiation damages DNA in epithelial cells in the germinative zone, generates abnormal lens fibers, or Wedl cells, affects the metabolism of the lens, and may cause cataract. In the present study, DNA chains were damaged by low-dose irradiation in the early irradiation stage, and epithelial cells in the lens were degraded by higher irradiation doses of more than 6 Gy.[23] Cataract development with low-dose irradiation originates from damage to the DNA chain, and thereafter unusual cells are formed. On the other hand, with high-dose irradiation, the lens revealed characteristics of the mature cataract that might be due to degradation of the cell membrane.

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