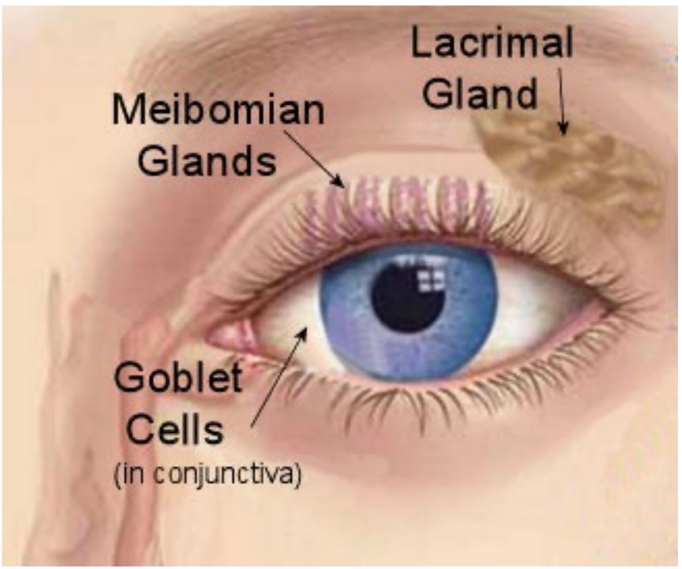
Chapter 13 – Radiation Cataractogenesis

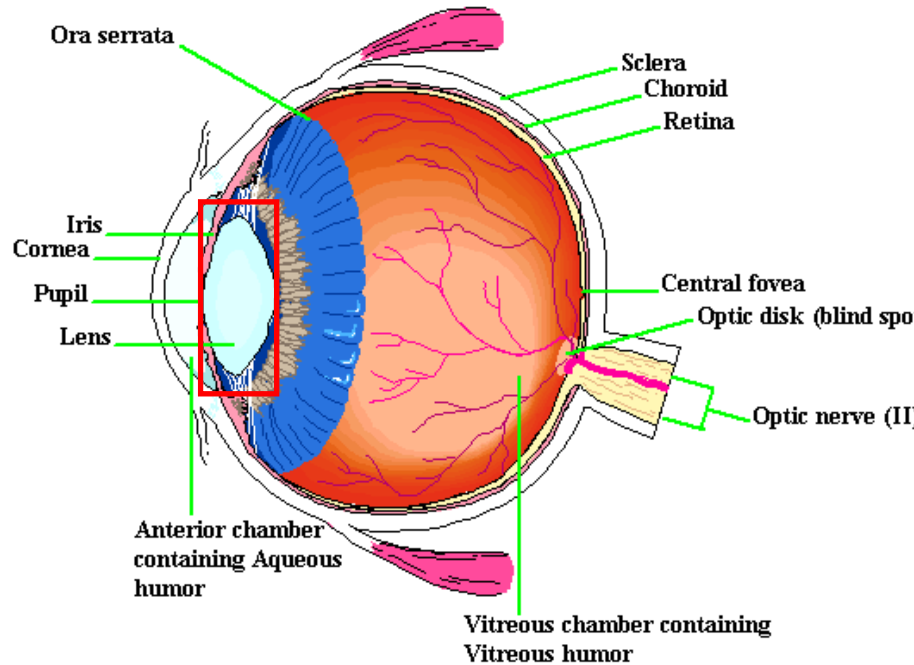
11/7/2024

Radiation-Induced Cataracts

- 1905 – first mention of a human radiation cataract in an x-ray laboratory worker
- Post-WWII – reports of lens opacities in cyclotron workers and A-bomb survivors published
- These studies stimulated much interest and research into this phenomenon

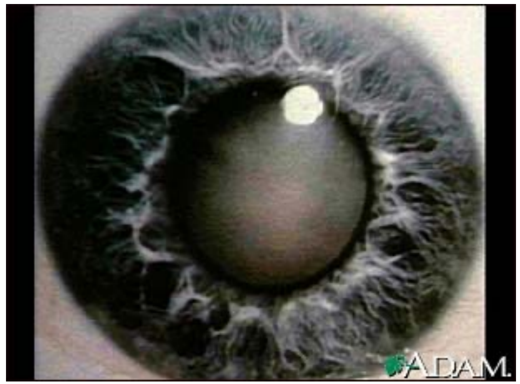
Anatomy of the Eye





Cataract

Cataract is an opacity of the normally clear lens which may develop as a result of aging, metabolic disorders, trauma or heredity



It is well established that ionizing radiation may also cause cataract

Types of Cataract

Cortical cataract

Cortical Cataract

Involves spoke or wedge-like opacities that often start around the **periphery** of the lens

Nuclear cataract

Nuclear Cataract

Involves a yellowing of the **central** lens

Sometimes cause a shift in prescription, leading to a temporary improvement in near vision

Posterior capsular cataract

Posterior Subcapsular Cataract

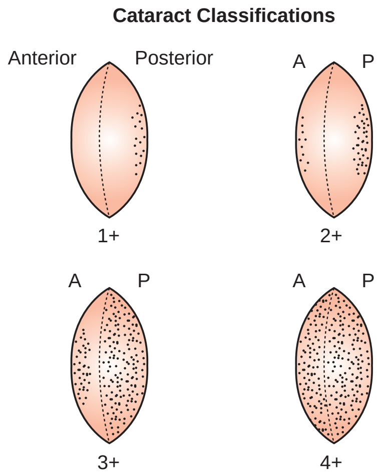
Involves a hazing of the **back** of the lens.

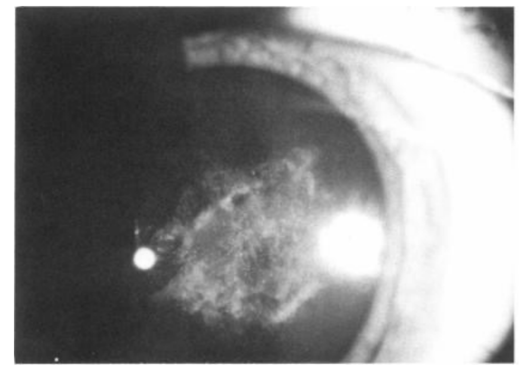
Progress more rapidly and affect vision more significantly

Seen more frequently with diabetes, steroid use, and s/p vitreoretinal surgery;

Closely associated with ionizing radiation exposure

Radiation-Induced Cataracts

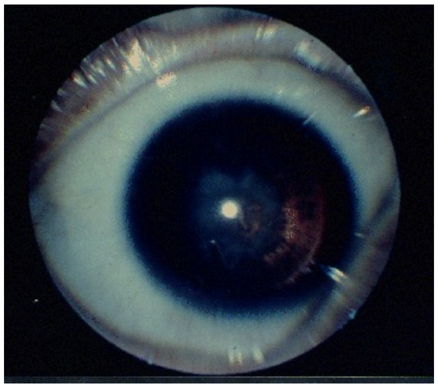


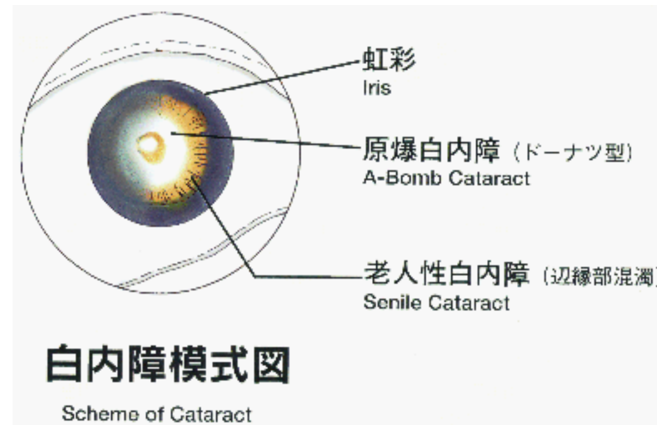


Characteristically, the opacities initially appear centrally in the **posterior subcapsular region** of the lens and consist of small granules and vacuoles that tend to form a roughly circular opacity

As posterior changes increase, granular opacities and vacuoles may appear in the anterior subcapsular region, usually centrally

Radiation-Induced Cataracts





A female exposed to A-bomb at age 21 on the street 805 m from the hypocenter

The progression of opacities as previously described is **not unique** to radiation, but in most instances, a careful history and ocular examination will allow a differential diagnosis to be made with considerable accuracy

Radiation-Induced Cataracts

- There are 3 possible clinical outcomes, depending on the dose and other factors
  - The opacities may remain stationary in the early stage with little effect on vision
  - May develop slowly to an intermediate stage and remain stationary for years
  - May progress to a fully mature cataract, resulting in blindness

The Effect of Radiation

Questions

1) What is the minimum dose to the lens that would produce a cataract **(threshold)**

2) What is the percent incidence of cataracts at increasing dosage level? **(probability)**

3) What is the effect of dose on the timing of onset of a cataract? **(latency)**

4) What is the effect of dose on the incidence of stationary or progressive opacities? **(severity)**

5) What are the relative effects of single and divided treatments on the above? **(fractionation)**

6) What is the relative sensitivity of young and adult lenses? **(age)**

The Work of Marriam and Focht

Radiation charts from Memorial and Columbia-Presbyterian in New York city were reviewed

A total of **233 cases** were identified which had detailed radiation plans available.

These included patients being treated for hemangioma or carcinoma of the head and neck region

Of those 128 patients developed radiation cataracts, 105 patients did not.

The Work of Marriam and Focht

Fig. 2. The phantom used in the radiation studies was a human skull covered with a mixture of paraffin and beeswax and filled with bolus. Provision was made in the plastic eye to place a small Baldwin-Farmer Condenser ionization chamber in the position of the lens. Reproduced by permission from Merriam, G. R., Jr., and Focht, E. F.: A clinical study of radiation cataracts and the relationship to dose. *Am. J. Roentgenol.* 77:759-85, 1957.

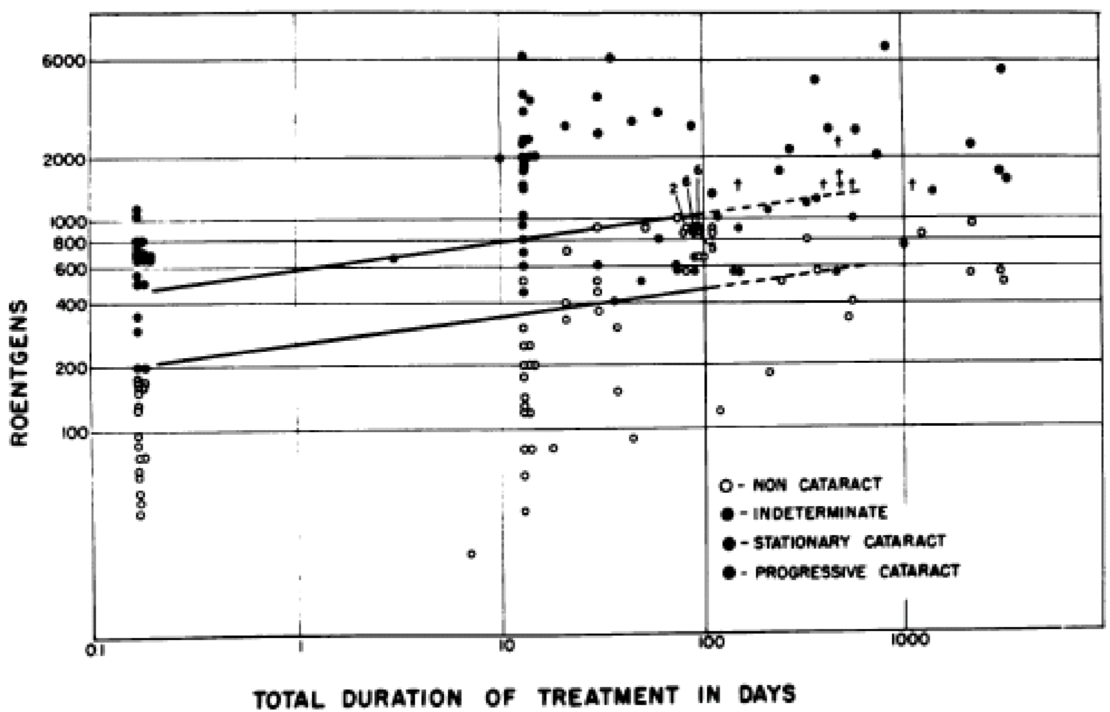
In each case, the actual amount of radiation to the lens was determined by employing a paraffin and beeswax phantom

A small condenser **ionization chamber** was inserted into the position of the lens

In each case, the radiation factors, shielding, and positioning were reconstructed as closely as possible from data available in the chart

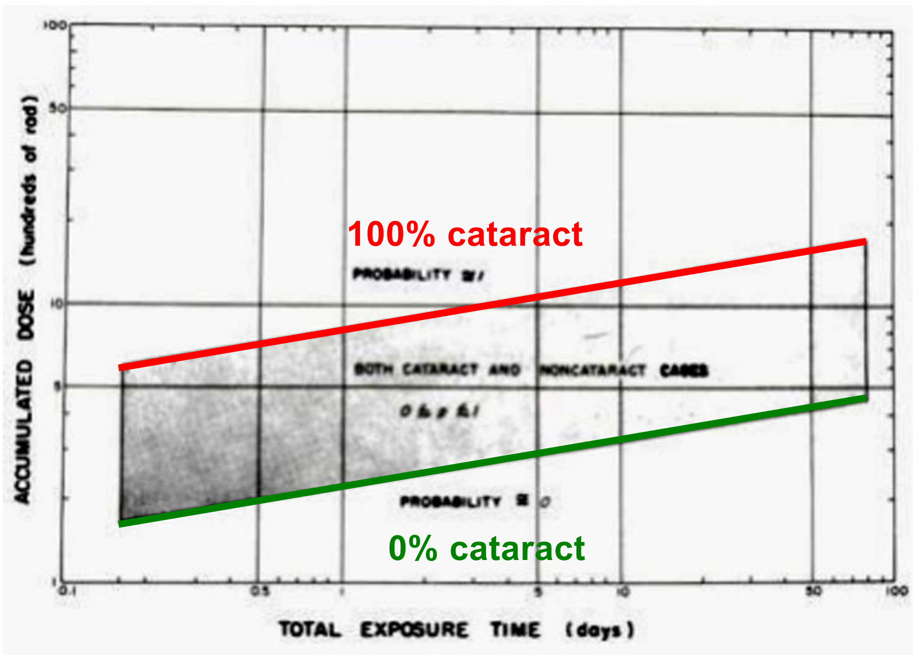
For analytic purposes, the cases were arranged in **3 groups** representing the most frequent courses of therapy: ***_single treatments_**, ***_multiple treatments from 3 wks-3 mo_**, ***_multiple treatments over a period > 3 mo_**

The Work of Marriam and Focht



Dose for cataract and noncataract cases vs. the overall treatment time

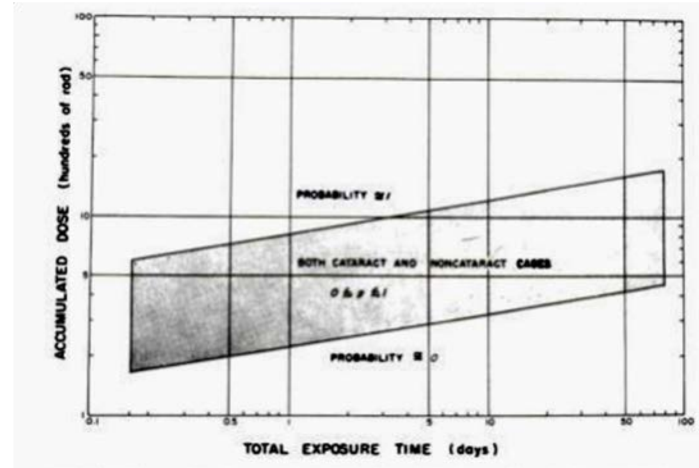
Dose-Response



As the dose increases, the probability of developing a cataract increases

There is a clear **time-dose relationship** – the lens were able to tolerate a higher dose with increased fractionation and overall duration of treatment

Dose-Response



Relation between Overall Exposure Time and the Radiation Dose Needed to Produce a Cataract

Duration of Treatment	Minimum Cataractogenic Dose, Gy		Maximum Noncataractogenic Dose, Gy
Single	2.0	threshold	2.0
3 weeks–3 months	4.0	"Deterministic effect"	10.0
Over 3 months	5.5	"Tissue Reaction"	10.5

The Degree of Opacities

Of patients who received low dose levels to the eye (2.2 - 6.5 Gy), only 12% developed progressive opacities

Of patients who received higher dose (6.5 - 11.5 Gy), only 12% had stationary opacities

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As dose increases, the severity of the cataracts increases

Remember, radiation cataractogenesis is a deterministic effect (tissue reaction)!

The Latent Period

- The latent period estimated to be from 6 mo to more than 50 years
- In RT patients received 2.5 to 6.5 Gy, the average latent period was 8 years
- At higher doses 6.5 to 11.5 Gy, the average latent period was 4 years
- The latent period is therefore an inverse function of the dose

Quality of Radiation

10 of 11 physicists exposed to cyclotron **neutrons** developed cataracts over periods of 10-250 wks
The estimated total accumulated doses at lens averaged 1 Gy

During the Apollo 11 flight, astronauts reported seeing “light flashes and streaks”, which were believed to be due to particles passing through the retina

Subsequent experiments with 1,000 rats exposed to accelerated ^{40}Ar ion showed that the **heavy ions** in space can be from 3.5 – 100+ times more cataractogenic than conventional x-rays

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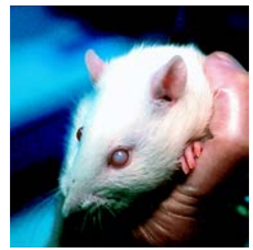
Neutrons and other densely ionizing radiations are very effective at inducing cataracts

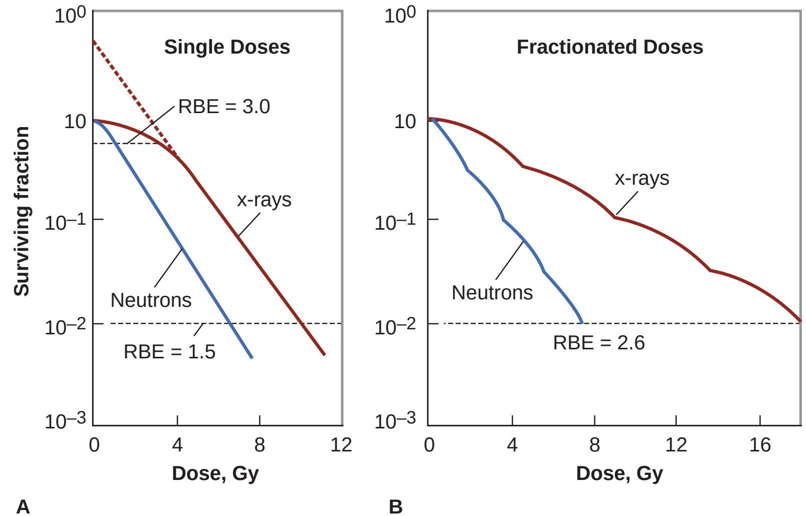


Quality of Radiation

Consider **cataract induction** as a biologic endpoint

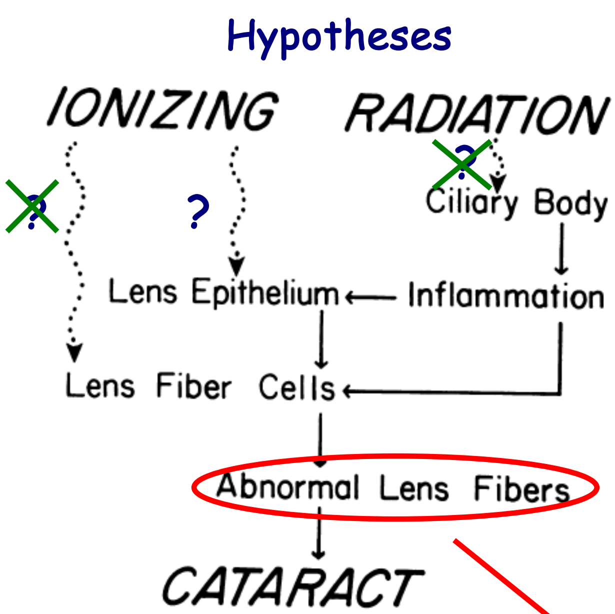
The RBE of fast neutrons relative to x-ray is **10** at **high dose level** (several Gy)

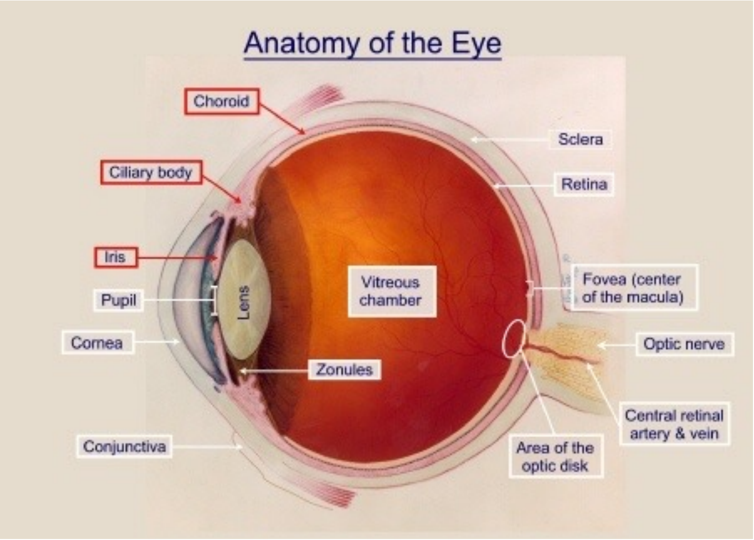
The RBE increases to **50+** for **small doses** of a fraction of a cGy



The increase in RBE at low doses is caused largely by the sharply declining effectiveness of x-rays with decreasing dose, rather than an increasing in effect per unit dose of neutrons or charged particles

Mechanism of Radiation Cataractogenesis





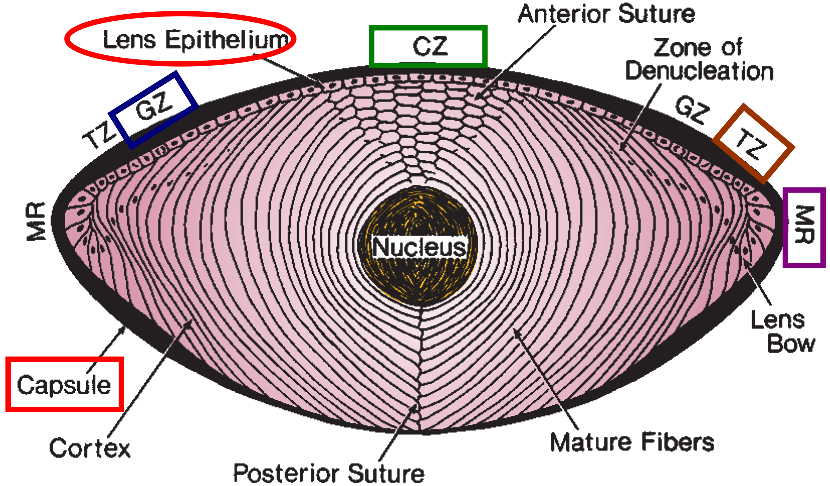
It was clear that abnormal lens fibers are the first cytopathological correlates to clinically detectable opacities

Anatomy and Physiology of Human Lens

Germinative zone is the primary site of **mitotic activity** of the lens epithelium

The ocular lens is enclosed in a capsule

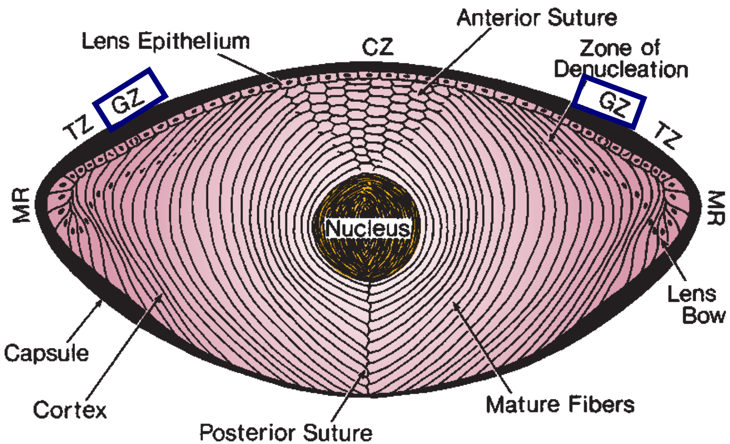
Central zone cells are nonmitotic



Terminal zone where progeny of GZ undergo a terminal cell division

Cells begin differentiation and form the meridional rows where cells queue up in precise register, forming ordered columns of nuclei

Mechanism of Radiation Cataracts



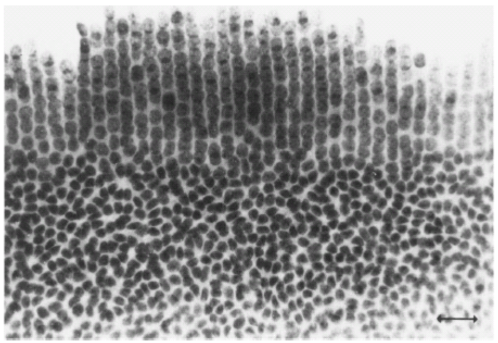
Many investigators have shown that the germinative zone must be irradiated for a cataract to develop

A marked depression of mitotic activity occurs soon after irradiation, followed by an overshoot with a gradual return to normal

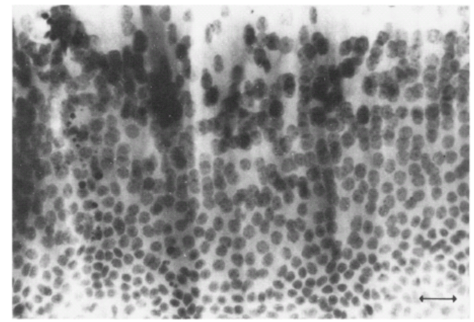
This post-irradiation proliferative activity is absolutely essential for cataract formation

Mechanism of Radiation Cataracts

Meridional rows in rat lens



MR **2 wks** after 10 Gy x-ray



Cells are highly ordered in the MR

This precise alignment of elongating epithelial cells is important to the maintenance of normal cytoarchitecture and, therefore, transparency

Moderate doses of x-ray causes disorganization of the MR

Note the cells occupying the row were in the GZ at the time of irradiation

The higher the dose, the more severe the disorganization and the earlier it will appear

Mechanism of Radiation Cataracts

Initial injury is suffered primarily by epithelial cells in the germinative zone

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When these cells resume mitosis, their progeny are displaced into the meridional rows; altered differentiation causes disorganization of the MR

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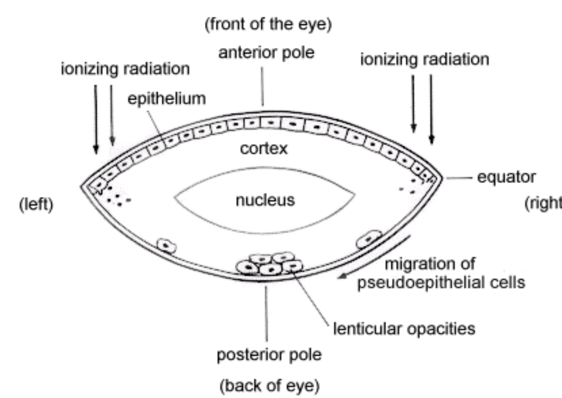
Nucleated, abnormally shaped fibers begin to accumulate beneath the posterior capsule; in the **posterior subcapsular region** these cells assume a rounded, bladderlike appearance and are known as “Wedl” cells



Mechanism of Radiation Cataracts

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Wedl cells may rupture, leaving eosinophilic material and cellular debris strewn between apparently intact cells
Since lens has no blood supply and is enclosed in a capsule, there is no mechanism for removing cellular debris

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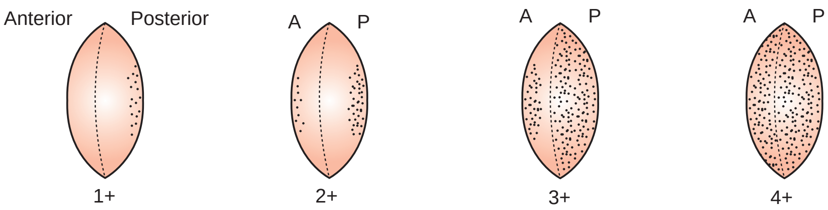
When the superficial cortex becomes enclosed by the newly formed abnormal fibers, normal metabolic activity is disrupted and the deeper cortex and eventually the entire lens opacifies



NCRP and ICRP Dose Limits to Lens

TABLE 17.5 Summary of Recommended Dose Limits

	NCRP	ICRP (If Different)
Occupational Exposure:		
Stochastic effects: effective dose limits		
Cumulative	10 mSv × age	20 mSv/y averaged over 5 years
Annual	50 mSv/y	50 mSv/y
Deterministic effects: dose equivalent limits for tissues and organs (annual):		
Lens of eye	150 mSv/y	150 mSv/y
Skin, hands, and feet	500 mSv/y	500 mSv/y
Embryo/Fetus Exposure:		
Effective dose limit after pregnancy declared	0.5 mSv/month	Total of 1 mSv to abdomen surface
Public Exposure (annual):		
Effective dose limit, continuous or frequent exposure	1 mSv/y	No distinction between frequent and infrequent—1 mSv/y
Effective dose limit, infrequent exposure	5 mSv/y	
Dose equivalent limits; lens of the eye	15 mSv/y	15 mSv/y
Skin and extremities	50 mSv/y	50 mSv/y
Education and Training Exposure (annual):		
Effective dose limit	1 mSv/y	No statement
Dose equivalent limit for lens of eye	15 mSv/y	No statement
Skin and extremities	50 mSv/y	No statement
Negligible Individual Dose (annual):	0.01 mSv/y	No statement

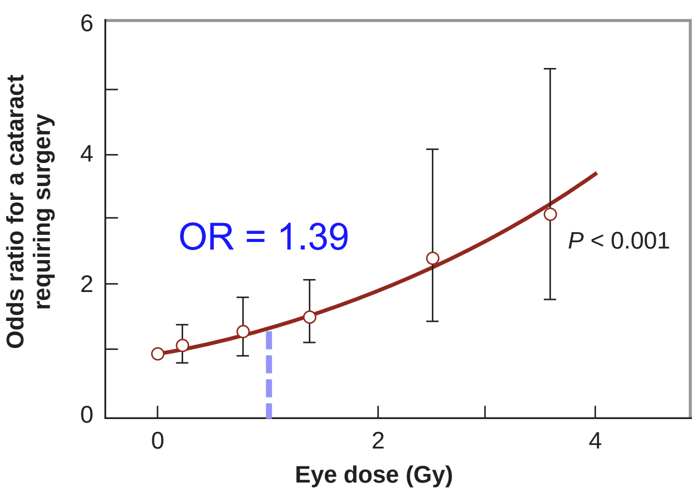
Based on National Council on Radiation Protection and Measurements: *Recommendations on Limits for Exposure to Ionizing Radiation.* NCRP Report No. 116. Bethesda, MD; 1993; and International Commission on Radiation Protection: *Recommendations of the ICRP.* ICRP Publication 103. New York, NY: Pergamon Press; 2007.

Definition of Deterministic Effect (Tissue Reaction)

- A threshold in dose below which visually disabling cataracts do not form
- The severity of the effect increases with dose above the threshold
- Visually disabling cataracts may require damage to a population of cells rather than to a single cell

Updated Data from A-Bomb Survivor

1990 – Threshold of **1.5 Gy** (based on data collected in the 1960s and principally involved those irradiated as adults)



Radiat Res 2007; 168:404-408

- Included individuals **exposed at earlier ages** with longer follow up
- Prevalence of cataracts requiring surgery (vision-impairing cataracts) increases significantly with radiation dose, with little sign of a threshold in dose, certainly not 2 Gy
- Odds Ratio = 1.39 @ 1 Gy

Is cataract a deterministic effect?

Dose-Response Relationship Re-Examined

- The updated A-bomb survivor data call into the question of the classification of an ocular cataract as a tissue reaction or deterministic effect
- This view is supported by the unexpected appearance of cataracts in astronauts, clean-up workers from Chernobyl, and radiation technologists, all of whom received doses well below the old threshold dose of 2 Gy

ICRP & NCRP Updated

2016 2011

Table 16.5 Summary of Recommended Dose Limits

	NCRP	ICRP
Occupational exposure		
Stochastic effects: effective dose limits		
Cumulative	10 mSv × age	20 mSv/y averaged over 5 y
Annual	50 mSv/y	50 mSv/y
Tissue reactions (deterministic effects): dose equivalent limits for tissues and organs (annual):		
Lens of eye	50 msV/y	20 mSv/y averaged over 5 y not more than 50 mSv in any year
Skin, hands, and feet	500 mSv/y	500 mSv/y
Embryo/fetus exposure		
Effective dose limit after pregnancy declared	0.5 mSv/mo	Total of 1 mSv to embryo/fetus
Public exposure (annual)		
Effective dose limit, continuous or frequent exposure	1 mSv/y	No distinction between frequent and infrequent—1 mSv/y
Effective dose limit, infrequent exposure	5 mSv/y	1 mSv/y
Dose equivalent limits; lens of the eye	15 mSv/y	15 mSv/y
Skin and extremities	50 mSv/y	50 mSv/y
Education and training exposure (annual)		
Effective dose limit	1 mSv/y	No statement
Dose equivalent limit for lens of eye	15 mSv/y	No statement
Skin and extremities	50 mSv/y	No statement
Negligible individual dose (annual):	0.01 mSv/y	No statement

Based on National Council on Radiation Protection and Measurements. *Limitation of Exposure to Ionizing Radiation*. Bethesda, MD: National Council on Radiation Protection and Measurements; 1993. NCRP report no. 116; and International Commission on Radiological Protection. *The 2007 Recommendations of the International Commission on Radiological Protection*. New York, NY: Elsevier; 2007. ICRP publication 103.

Lower the threshold dose of cataract from 2 Gy to 0.5 Gy

Review Questions

Question 1

Which of the following statements concerning radiation-induced damage to the eye is TRUE?

A. The threshold radiation dose for cataract formation is approximately 10 Gy
B. It is often possible to distinguish between a radiation-induced cataract and an age-induced cataract
C. The neutron RBE for cataract formation is about 5 for low total doses
D. The tolerance dose for the development of blindness is lower than the tolerance dose for cataract formation
E. The length of the latency period for cataract formation is independent of radiation dose