THE EFFECT OF AGE ON THE RADIOSENSITIVITY OF RAT LENSES*

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INTRODUCTION

SINCE THE FIRST, AND NOW CLASSICAL STUDIES OF CHALUPECKY[1] IN 1897, an extensive literature on the effects of radiation on the eye has accumulated. A complete review of the subject can be found in Duke-Elder,[2] in the monographs of Haye et al,[3] in the text by Rubin and Casarett,[4] and in recent reviews by Bateman,[5] Merriam et al,[6] and Horn.[7]

The effect of age on the sensitivity of human tissue to ionizing radiation has long been recognized by radiotherapists. In experimental animals this feature was unrecognized for sometime and there were reports in which the age of the animals was not mentioned, or simply stated as young or adult. In this respect, the studies on the lens are rather unique, since as early as 1905, striking differences in the response to radiation of young and adult lenses were noted. The first report of this hypersensitivity of the young lens was that of Tribondeau and Récamier[8] in 1905. In their experiment, a 3-day-old cat was exposed to an unspecified dose of X-rays delivered in six fractions in two weeks. A severe lens opacity developed 4.2 weeks after irradiation.
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In the period from 1905-1928 approximately ten reports on this subject appeared in the literature.[8-17] The difficulty with these early studies was that, in general, adequate dosimetry was not available and

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the physical factors employed are not known. During one period, the dose was often expressed in terms of the skin erythema dose (SED). However, there are many uncertainties in defining the erythema reaction and the SED. The size of the irradiated area, the dose rate, the energy spectrum of the radiation all effect the SED.

From this early work, in spite of inadequate equipment and lack of accurate dosimetry, arose the hypothesis that young lenses are much more sensitive to radiation. The results of Tribondeau and his co-workers were confirmed by subsequent investigations. In 1931 when Desjardins[18] published the first extensive review of the effects of radiation on the eye and ear, he considered the evidence to be conclusive that young lenses are more sensitive to radiation than adult ones. He also noted that this difference was greater in the lens than in any other tissue.

There are several important factors which should be considered in an analysis of these early studies:

1) In most of the studies rather small groups of animals were used.
2) The length of observation was usually less than six months and not longer than nine months after irradiation.
3) Young and adult animals were not treated simultaneously under identical conditions.

Essentially the results in the early studies indicated that for a dose of the order of 1000 rads, lens opacities appeared sooner in young lenses. Considering the difficulties under which these early investigations were done, the reported findings were remarkably accurate, and have been confirmed by subsequent investigations. The only significant discrepancy noted in more recent work was the failure to observe radiation cataracts in adult animals with doses of 600-1000 rads. This may be explained by the short periods of observation and the small numbers of animals used in the experiments. Although the investigators were impressed with the high susceptibility of young lenses to radiation damage, no experiments with doses below 1000 rads were performed on young lenses.

From 1929 to 1969 numerous reports appeared in the literature on the minimum cataractogenic dose of radiation and the relative effect of age at the time of irradiation.[19-32] The investigation of Rohrschneider in 1929 marked the beginning of definitive studies on the effects of radiation on the eye performed under well defined conditions and with acceptable dosimetry. He listed the ocular structures in order of decreasing radiosensitivity as lens, conjunctiva, cornea, uvea, retina and optic nerve.

The first significant study on the effect of age was that of Cogan and Donaldson in 1951 in which rabbits from 3 weeks to 3 years of age were exposed to 1500 rads of 1200 kVp roentgen rays. They found that the length of time after irradiation when the first clinical lens opacities were observed was directly proportional to the age of the animal at the time of irradiation — thus the younger the animal at the time of exposure, the sooner the lens opacities appeared. They also reported that the minimum cataractogenic dose in a young adult rabbit that produced a clinical lens opacity in about six months was 250 rads.

The clinical study of Merriam and Focht[33] suggested, in a tentative statement, that the lenses of children under one year of age may be more sensitive than adult lenses. Children over one year of age appeared to have the same sensitivity as adults.

The report by Kimbeldorf in 1963,[28] at the Second International Congress of Radiation Research, was the first to indicate that under certain conditions older lenses may be more susceptible to radiation. Neutrons, with a spectrum close to that of fission neutrons, were used for irradiation. Only three age-groups of animals were used and one group consisted of only one animal at the completion of the observations. The youngest rats were from 94 to 101-days-old which corresponds to a young adult, since rats of this age are sexually mature. However, there was a definite suggestion that the radiosensitivity of mammalian lenses may not be a simple function of age.

In 1964 Bateman et al[29] presented a report on lens opacification in mice exposed to monoenergetic fast neutrons. The primary purpose of the paper was the development of a technique for the slit lamp examination of the lens which would allow an accurate evaluation of the opacities for comparative studies of neutron and X-ray induced changes as a function of dose. The report also contained a study of cataractogenesis as a function of age. The authors noticed "as a major point of interest the persistently lower incidence of opacities in the mice irradiated at lesser ages".

The most recent study on the relative sensitivity of young and adult lenses was that published in 1969 by Merriam and Focht.[32] This was a short progress report on experiments with two groups of rats, 3½ and 8½-weeks-old, given a single dose of 800 rads to one eye. As expected the onset of the early changes was sooner in the young animals. However, the rate of progression was faster and severe opacities developed sooner in the older animals.

In analyzing the available data, there appeared to be many aspects of the age sensitivity problem that remained unsolved. The studies reported since 1963 suggest that the relative sensitivity of young and adult lenses was not a simple function of age but could be dose dependent. However, this had not been definitely established. It was felt, therefore, that a series of experiment designed to investigate the problem more thoroughly would be worthwhile. Such experiments should include large enough groups of animals to insure statistical significance, use varying doses of X-rays — both single and divided — delivered to a wide range of ages, with suitable controls and followed for the lifetime of the animals. This report will cover only the results of the study using single doses of X-rays.

EXPERIMENTAL PROCEDURES

For these experiments, rats of the White, Columbia-Sherman strain were used since these animals had been employed in all of the previous studies. One to three rats were housed in each cage, depending on the age and sex, given water and Purina pellets ad libidum, and maintained in the animal care facilities of the Eye Institute. Both male and female rats were used originally. Since no differences between the sexes were detected in the development of radiation cataracts, female rats were used in most of the experiments.

Eight age groups were used — 2 days of age, 2 weeks, 3½ weeks, 6 weeks, 9 weeks, 14 weeks, 18 weeks and 28 weeks. For the radiation, X-ray of HVL 1.0mm Cu were used. Doses of 200, 400, 600, 800, 1200 and 1600 rads were given in a single exposure to one eye of each animal. The unexposed fellow eye was used as a control. There were, on an average, twenty rats in each group at the start of the experiment. Mortality from various causes gradually reduced these numbers. As can be seen from Table 1 several hundred animals were involved initially in this aspect of the investigation. For various reasons it was not feasible to include each age group at every dose level. Therefore, only at the dose levels of 400, 800, and 1200 rads were all age groups included. The distribution and numbers of animals in each group at the start and at the completion of the experiment is shown in Tables 1 and 2.

Just before radiation the animals were anesthetized with Sodium Pentobarbital (3mg/100gm of weight) given intraperitoneally. The control eye and the entire body of the animals were suitably shielded to protect them from direct and scattered radiation. The edge of the eye

TABLE 1. THE NUMBER OF ANIMALS IN EACH AGE/DOSE GROUP ONE WEEK AFTER IRRADIATION

AGE / DOSE (rads)	2 days	2 weeks	3.5 weeks	6 weeks	9 weeks	14 weeks	18 weeks	28 weeks
200	35			30			35	
400	25	27	22	20	20	20	23	23
600		17		15			18	
800	31	22		15	15	18	21	17
1200	33	21	11	15	16	15	20	16
1600				10			12	

TABLE 2. THE NUMBER OF ANIMALS IN EACH AGE/DOSE GROUP AT THE COMPLETION OF OBSERVATIONS

AGE / DOSE (rads)	2 days	2 weeks	3.5 weeks	6 weeks	9 weeks	14 weeks	18 weeks	28 weeks
200	10			6			5	
400	6	8	5	7	5	5	6	4
600		6		6			5	
800	21	8		6	7	5	8	8
1200	20	6	5	6	11	5	13	8
1600				9			8	

shield was coated with paraffin to reduce secondary radiation. After irradiation the rats were examined, without anesthesia, with a Haag-Streit slit lamp (corneal microscope) at weekly, biweekly, or at three to four week intervals depending on the rate of progression of the opacities. The pupils were dilated with 5% Homatropine Hydrobromide. At the times of examination the examiner had no knowledge of which eye had been irradiated or which group the animal represented.

The lens changes were graded from 0-4+ according to the method previously described.[33] Briefly zero represented no opacities, 1+ early posterior subcapsular vacuoles, 2+ additional changes posteriorly plus early, anterior subcapsular opacities, 3+ an extension of both the anterior and posterior changes plus some generalized cortical and nuclear sclerosis, and 4+ a complete opacity.

The animals were identified individually by a special ear-punch code and the results of each exmination for each eye were recorded. Each

animal was followed for his lifespan or until a 4+cataract developed. The incidence of any stage of opacity in a given group has been defined as the ratio of the number of lenses which reached a given stage of opacity or greater to the total number of lenses irradiated. The time after exposure at which the incidence equals 50% has been defined as the T50. The results were subjected to probit analysis[34] using a Fortran program written for the IBM 360-90 computer at the Columbia Computer Center, New York City. From this program the following information was obtained:

1) The time interval (T50) for the 50% incidence of each stage of cataract.
2) The 5% upper and lower fiducial limits (defining the range of values between which T50 lies with a probability of 95%).

Only those data were used in the analysis of age dependence which satisfied the Chi-square test of the goodness of fit (at a level of 0.05 to 0.95).

RESULTS

The detailed results of all the experiments are shown in Table 3 through 6. For each age/dose group, the time after irradiation for the 50% incidence (T50) of stages 1+, 2+, 3+and 4+is listed together with the upper and lower fiducial limits defining the range of values between which T50 lies with a probability of 95%.

THE PROGRESSION OF LENS CHANGES

200 RADS

Figure 1A shows the development of cataracts through the various stages in two age groups (2 days and 18 weeks old) after a dose of 200 rads. It is apparent that the older animals developed their opacities before similar changes appeared in the young and that the cataracts progressed to 3+faster in the older age group. As can be seen, the young animals did not progress beyond stage 2+during their lifetime.

400 RADS

With this dose, as shown in Figure 1B, stage 1+opacities appeared in the young animals several weeks before the onset of similar changes in the older ones. However, at stage 2+, the 50% incidence of cataracts occurred at the same time in the young and the older animals. From this point on, the opacities in the older group progressed to 4+more rapidly. In fact, the opacities of the young animals never reached 4+during their observable lifespan of 98 weeks after irradiation.

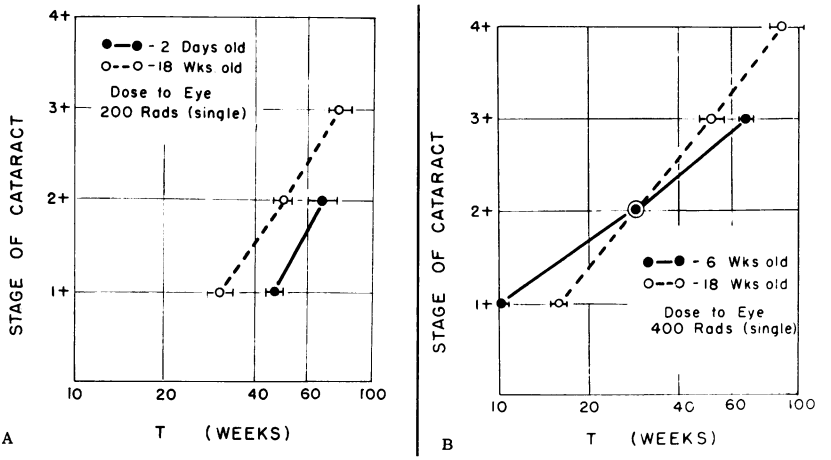


FIGURE 1

A: With this low dose the opacities appeared sooner and progressed more rapidly in the older animals.

B: The opacities started sooner in the young but progressed more rapidly in the older animals. Note that the 50% incidence of stage 2+ occurred at the same time after irradiation in both groups.

600 AND 800 RADS

When a single dose of 600-800 rads was used, the young animals developed 1+and 2+cataracts before similar changes in the lens appeared in the older age group. As can be seen in Figures 2A, 2B, 50% of the 6 week old rats showed 2+opacities slightly before 50% of the adults showed 1+opacities. However, beyond stage 2+development of the lens changes was more rapid in the older animals. Whereas the T50 was the same for the two groups at 2+with 400 rads, the crossing point occurred between stages 2+and 3+with doses of 600 and 800 rads.

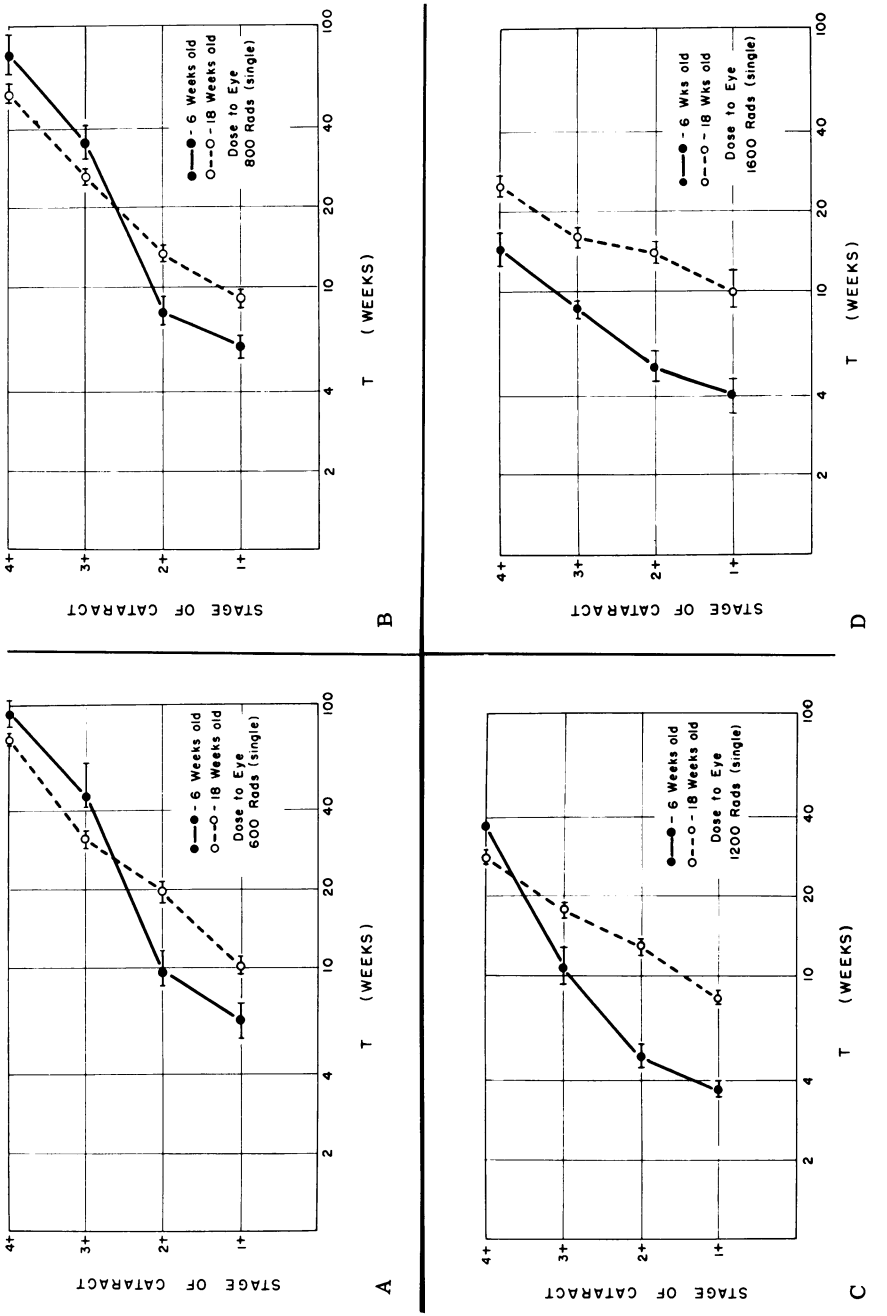
FIGURE 2

A: As can be seen with a higher dose the opacities appeared earlier in both groups. Stage 2+ to 3+ was reached at the same time after irradiation in both groups.

B: This is essentially the same as Figure 3 but the progression from early to complete opacities was more rapid.

C: With this dose, stages 1+, 2+ and 3+ appeared sooner in the young animals. However, the 50% incidence of 4+ opacities occurred in the adults ten weeks before the young animals.

D: With a dose of this magnitude all stages of opacities appeared sooner in the young animals. Note that this is the reverse of what was shown in Figure 1A with a low dose of 200 rads.


STAGE OF CATARACT
4+
3+
2+
1+
2
4
10
20
40
100
T (WEEKS)
●—● - 6 Weeks old
O--O - 18 Weeks old
Dose to Eye
600 Rads (single)
A
●—● - 6 Weeks old
O--O - 18 Weeks old
Dose to Eye
800 Rads (single)
B
●—● - 6 Weeks old
O--O - 18 Weeks old
Dose to Eye
1200 Rads (single)
C
●—● - 6 Wks old
O--O - 18 Wks old
Dose to Eye
1600 Rads (single)
D

1200 RADS

As can be seen in Figure 2C, the same pattern of earlier development of opacities in the young but more rapid progression of the lens changes in the older animals is evident. However, with this high dose, the same incidence of opacities occurred in both groups between stages 3+ and 4+. From this it would appear that as the dose is increased the values of T50 become equal at a more severe stage of cataract development. Thus with 400 rads the T50 was the same at stage 2+, with 600-800 rads between stages 2+ and 3+, and with 1200 rads between stages 3+ and 4+.

1600 RADS

At this dose (Figure 2D), the young animals developed their opacities sooner than the adults and progressed to 4+more rapidly. In fact, 50% of the 6 week old rats were at 4+ when 50% of the adults were at stage 2+.

It is evident that there are significant differences in the temporal development of radiation cataracts between young and adult lenses. Figure 2 illustrates the fact that with doses of from 600-1200 rads to young lenses, there is a significant interval during which the progression of the cataract slows down and the opacity may appear stationary. The stage of this "pseudostationary" level increases with increasing dose. The changes in the adult lenses appeared to progress more uniformly.

These observations are apparent when one examines the dependence of the incidence of early (1+) and complete (4+) opacities on time after irradiation in young and adult animals. This is shown in Figure 3 for a dose of 800 rads. While the sigmoid curves are steep for both ages for stage 1+, a significant difference is apparent for stage 4+ where the changes in the young lenses progress more slowly.

T50 AS A FUNCTION OF AGE AT IRRADIATION

The dependence of T50 on age at the time of irradiation for the four stages of cataract is illustrated in Figures 4A, 4B, 5 for doses of 400, 800 and 1200 rads respectively. With a dose of 400 rads (Figure 4A), the T50's for stages 1+and 2+are maximum for the two-day old animals. They are minimal at 2 to 4 weeks of age after which they increase up to 9 weeks of age. Beyond this the T50 remains fairly constant with increasing age.

The value of T50 for stage 3+remains fairly constant up to 9 weeks of age and then decreases with age at the time of irradiation. It is higher in the young animals than in the adults.

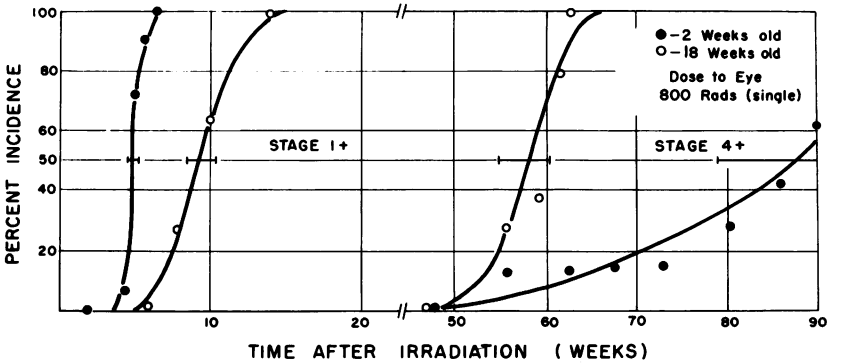


FIGURE 3

As can be seen the incidence of early opacities increases rapidly in both groups with time after irradiation. However, although the onset of stage 4+ opacities was approximately the same in both groups, the incidence increased much more rapidly in the older animals.

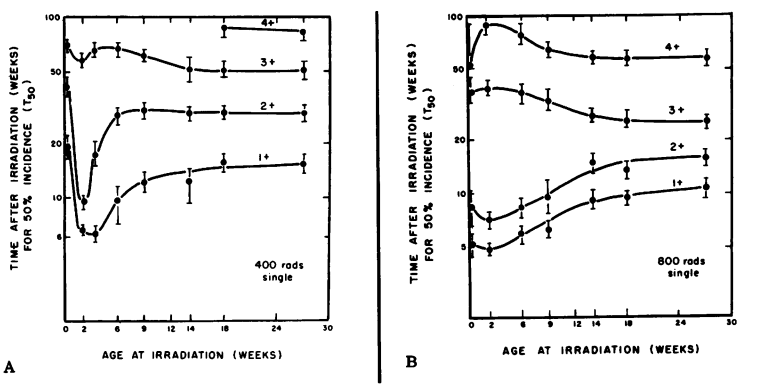


FIGURE 4

A: A composite graph showing the time after irradiation for the 50% incidence of a given stage of cataract when 400 rads was delivered to the eyes of animals ranging in age from 2 days to 28 weeks. Note the peak of sensitivity (lowest T50) for stages 1+ and 2+ at age 2-4 weeks.

B: With 800 rads the peak of sensitivity occurred at about 2 weeks of age for stages 1+ and 2+. Note the reversal of this pattern for stages 3+ and 4+.

As has been stated previously, the younger animals did not develop complete opacities within their observable lifespan of 98 weeks after irradiation.

TABLE 3. TIME AFTER IRRADIATION FOR 50% INCIDENCE OF STAGE 1+ CATARACT

AGE / DOSE	200 rads	400 rads	600 rads	800 rads	1200 rads	1600 rads
2 days	50[1] 47 44[2]	22 19.7 17	12 10 8	6.1 5.3 4.4	4.5 4 3.1	
2 weeks		7 6.6 6.1		5 4.8 4.6	3.4 3.2 2.9	
3.5 weeks		7 6.2 5.1			4.7 2.6 1.9	
6 weeks	33 31 29	12 9.9 6.8	7.4 6.4 5.4	6.7 6 5.1	4 3.7 3.5	4.6 4.1 3.6
9 weeks		14.5 12.5 10.5		6.8 6.3 5.8	7.1 6.6 6.3	
14 weeks		14 12.2 8.2		12 9.3 8.6	10.2 9.5 8.6	
18 weeks	32.5 30.6 28.5	16.8 15.8 14.7	11.1 10.3 9.9	10.4 9.4 8.5	9.9 9.1 8.3	12 9.9 9.3
28 weeks		17.2 15.5 13.6		12 10.5 9.5		
56 weeks	EXPERIMENT IN PROGRESS					

[1] Upper fiducial limit
[2] Lower fiducial limit

With a dose of 800 rads (Figure 4B) the T50 for stages 1+ and 2+ showed a less distinct minimum at about 2 weeks of age, and then increased with increasing age at irradiation. A noteworthy feature is the reversal of the pattern for stages 3+and 4+. The data suggest a maximum of T50 at 2 to 4 weeks for stages 3+ and 4+and there is a definite decrease in the value of T50 for severe opacities with increasing age at the time of irradiation.

With a dose of 1200 rads (Figure 5) the minimum T50 would appear to be at about 2 weeks of age for stages 1+ and 2+. It is also near minimal at this age for stage 3+ but becomes maximal for stage 4+.

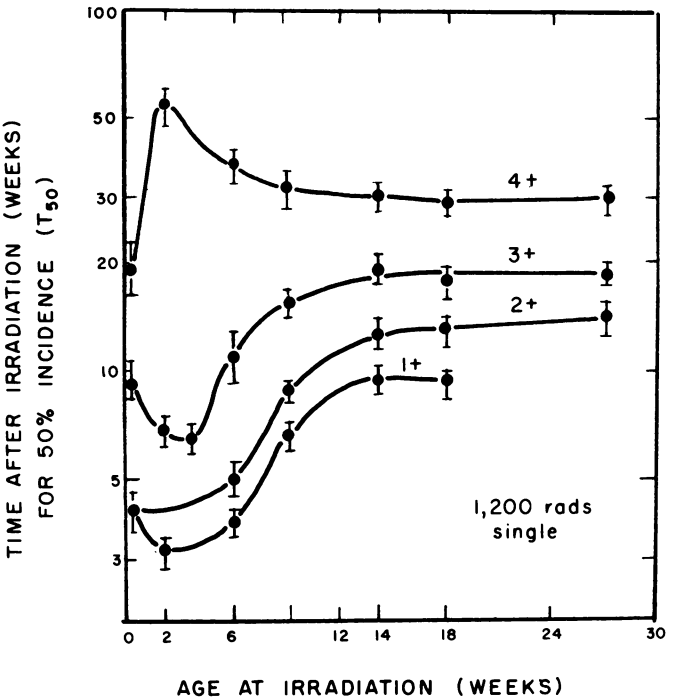


FIGURE 5

The greater sensitivity of lenses 2 to 4 weeks old for stage 1+ through 3+ is apparent. The pattern is reversed for stage 4+.

DEPENDENCE OF T50 ON DOSE LEVEL

It has long been observed that the time of onset of lens changes after irradiation is an inverse function of dose. This was apparent in these experiments. The dependence of T50 on the dose to the lens is shown in Figures 6A, 6B for the two age groups (6 weeks and 18 weeks) most completely studied. It is evident that for all stages of opacification above certain dose levels, increasing the dose further had a relatively small effect on the time for 50% incidence of opacities, (T50). The definite leveling off of the dependence of T50 on the dose suggests that there is a minimum period necessary for the clinical appearance of a cataract. It was not possible to definitely determine this time interval from the data.

TABLE 4. TIME AFTER IRRADIATION (WEEKS) FOR 50% INCIDENCE OF STAGE 2+ CATARACT

AGE / DOSE	200 rads	400 rads	600 rads	800 rads	1200 rads	1600 rads
2 days	60 67 76	47 40 35	12.6 14 15.2	10.5 8.5 6	4.5 4 3.1	
2 weeks		10.3 9.3 8.5		8 7.1 6.4	3.4 3.2 2.9	
3.5 weeks		21 17 16				
6 weeks	65 60 57	32 29 27	11.7 9.7 8.6	9.4 8.1 7.2	5.4 4.9 4.2	5.7 5.1 4.6
9 weeks		33.7 30.8 28.5		12.3 9.1 7.4	9 8.4 7.9	
14 weeks		32.2 28.9 26.3		17 15 13	14 13 12.3	
18 weeks	52.2 50 47	31 29.5 28	21.5 19.7 18	14.2 13.5 12.8	14 12.8 11.7	15 14 13
28 weeks		31.8 29 26.6		17.2 15.8 14.4	15.7 14.2 12.9	
56 weeks		EXPERIMENT IN PROGRESS				

TABLE 5. TIME AFTER IRRADIATION (WEEKS) FOR 50% INCIDENCE OF STAGE 3+ CATARACT

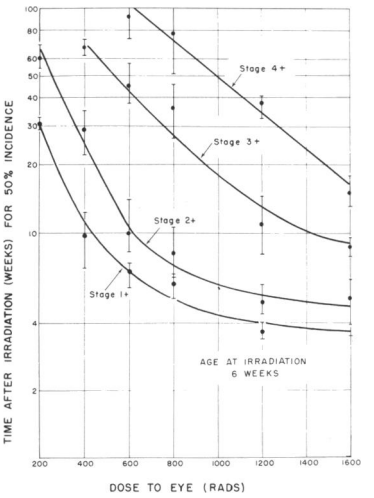
AGE / DOSE	200 rads	400 rads	600 rads	800 rads	1200 rads	1600 rads
2 days	[3]	81 73 64		45 36 31	10.4 9.1 7.8	
2 weeks		66 64 60		41 38 35	7.2 6.7 6.3	
3.5 weeks		72 65 62		40 33 27	7.2 6.1 5.2	
6 weeks	121 98 93	70 67 64	51 45 41	41 36 31	13 10.8 9.4	9 8.6 8.2
9 weeks		68 62.1 60		39 33 29	17 15.2 13.7	
14 weeks		61 51 45		30 27 25	20 19 18	
18 weeks	81 77 72	57 51 47	35 31 29	28.4 26.5 25	18.8 17.8 16.6	16.7 16 15.5
28 weeks		58 50 46		28 26 24	19.4 18 16.4	
56 weeks		EXPERIMENT IN PROGRESS				

[3] 0% incidence at 98 weeks after irradiation

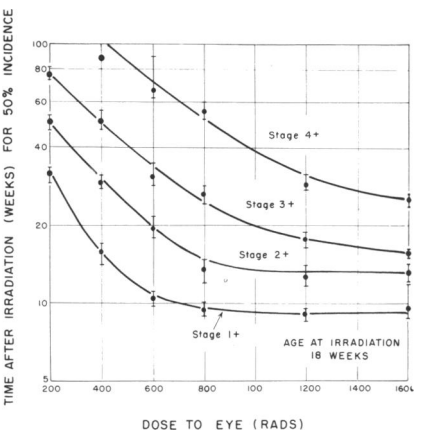
TABLE 6. TIME AFTER IRRADIATION (WEEKS) FOR 50% INCIDENCE OF STAGE 4+ CATARACT

AGE DOSE	200 rads	400 rads	600 rads	800 rads	1200 rads	1600 rads
2 days		[3]		88 51 39	23.2 18.2 16.2	
2 weeks				108 87 79	57 53 49	
3.5 weeks				94 79 63		
6 weeks		[3]	108 93 83	92 76 63	39 38 34	16.1 14.6 13.4
9 weeks				73 65 59	34.8 32.8 30.8	
14 weeks				68 60 56	32 31 29	
18 weeks		106 89 80	110 76 64	61 55 52	30 28.7 27.5	26.1 25 24
28 weeks		146 84 75		64 59 54	34 32 30	

[3] 0% incidence at 98 weeks after irradiation



A



B

FIGURE 6

A: This illustrates the time after irradiation for the 50% incidence of each stage of cataract as a function of the dose delivered to one group of young lenses.

B: The dependence of time for the 50% incidence of cataracts on the applied dose to 18 week old lenses is shown.

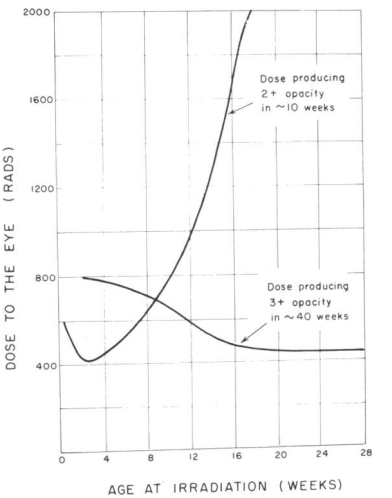


FIGURE 7

This illustrates the variation in radiosensitivity with age and demonstrates the importance of the definition of radiosensitivity.

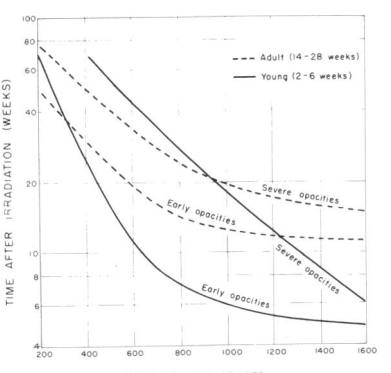


FIGURE 8

This shows the time for the 50% incidence of early (up to 2+) and severe (3+ or above) opacities as a function of dose in young and adult animals.

DISCUSSION

Before analyzing the results, a more exact definition of the term radiosensitivity, as applied to the mammalian lens, seems indicated. In the comparative studies of radiation cataractogenesis the following criteria could be used:

1) At a given dose level, the time interval necessary for the development of early opacities (stages 1+ and 2+).
2) At a given dose level, the time interval necessary for the development of severe (stage 3+) or complete opacities (stage 4+).
3) The dose level required for the production of incipient opacities (stage 1+and 2+) at a specific time after irradiation.
4) The dose level required for the production of severe (stage 3+) or complete opacification (4+) at a specific time after irradiation.
5) The minimum cataractogenic and the maximum non-cataractogenic dose levels.

These criteria become more meaningful if each of the effects listed above is defined at the 50% incidence level for a given stage of cataract. If these criteria are applied to an analysis of the effect of age on the radiosensitivity of the rat lens it is readily apparent that no single generalized statement can be made. The age dependence of T50 for all four stages of clinical radiation cataract at dose levels of 400, 800, and 1200 rads is not a monotonic function (Figures 4, 5).

In the dose range of 400-800 rads, the 2 to 4 week old lenses appear to be more radiosensitive if the first criterion is used, that is the time of development of early opacities. However, if one considers the time of development of severe opacities, the adult lens is more radiosensitive. The results at a dose level of 200 rads indicate that with low doses the relative radiosensitivity, as defined by criteria 1 and 2, increases with increasing age at the time of irradiation. Conversely, at a dose of 1600 rads, all stages of radiation cataract appeared sooner in the younger animals. Thus at higher doses, the relative radiosensitivity appears to increase with decreasing age. However, since only two age groups were used, any conclusions must be tentative, but it would appear that at high dose levels the young lenses are more radiosensitive, as defined by criteria 1 and 2.

To illustrate the use of criteria 3 and 4 defined by the dose required to produce a given stage of opacity in a given time, the doses necessary for the production of a stage 2+cataract in 10 weeks and stage 3+in 40 weeks are shown as a function of age at irradiation in Figure 7. As can be seen, if a 2+ opacity is considered, a relatively low dose of 400

rads is necessary for its production in a 2 to 4 week old animal. A dose of about 2000 rads would be required to produce a 2+ cataract in 10 weeks in an 18 week old animal. However, if the development of a 3+ opacity in 40 weeks is the standard, the maximum dose necessary to produce this effect is about 800 rads in a 2 to 4 week old animal, and decreases with age to about 450 rads at approximately 16 weeks of age. Therefore the conclusions reached using the third criterion are the reverse of those obtained by applying the fourth.

The possibility of a threshold minimum cataractogenic dose was not determined definitely in these experiments. There was evidence to suggest that below a certain dose level, severe opacities (stages 3+ and 4+) will not develop within the lifespan of the animal. Thus, with a dose of 200 rads, severe opacities were not observed in young animals up to 2 years after irradiation.

The minimum dose level necessary for the induction of severe opacities appears to be lower in the adult than in the young animals. Whether or not this is true for early opacities as well was not determined. In reviewing the available data on radiation cataracts in man, the lowest cataractogenic dose recorded was 200 rads.[25] This occurred in two patients — 53 and 54 years of age at the time of treatment who developed small, stationary opacities.

If all the young animals from 2 to 6 weeks of age are grouped together and similarly the adult animals from 14 to 28 weeks, the results can be readily compared if the opacities are classified into two categories — early (up to stage 2+) and severe (stage 3+ or above), as shown in Figure 8. Thus for a single dose of below 300 rads both early and severe opacities would be expected to develop earlier in the adult animals. At an intermediate dose range of 300-900 rads, early opacities would be anticipated sooner in the young but severe opacities should develop earlier in the adults. With a dose above 900 rads both early and severe opacities would be observed earlier in the young.

If one compares the observations reported above with the earlier reports in the literature, it is evident that there is general agreement. In the majority of the previous investigations, the time of onset of the early lens changes served as the criterion for defining the radiosensitivity. Thus at the rather high dose levels, the time of onset for the development of the initial opacities was shorter in the younger animals. The later and limited observations that there may be a dose level at which severe opacities appear sooner in the adults than in the young have been confirmed.

The apparent hypersensitivity of the rat lens for the development of early opacities, at 2-4 weeks of age which was observed particularly with a dose of 400 rads (Figure 4A) is interesting and warrants further investigation. A similar observation has been noted in the studies of acute radiation mortality in mice where the LD 50/30 (dose necessary to kill 50% of the animals in 30 days) was minimal at 2 to 4 weeks of age.[35]

SUMMARY

Experimental evidence has been presented to show that the effect of age on the radiosensitivity of the rat lens is dose dependent and is a more complex problem than previously stated. From the data compiled it would appear that there is a dose level below which all stages of lens opacification appeared sooner and progressed faster in the adult than in the young animals. Conversely, there would appear to be a dose level above which all stages of radiation cataract develop faster in the young than in the adult animals. In the intermediate range of doses, while the initial opacities appeared earlier in the young animals, the opacities in the adults progressed at a faster rate and the adults developed severe opacities before the young.

The underlying mechanisms for this varied response are not apparent at this time.

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DISCUSSION

DR S. RODMAN IRVINE. First, I want to congratulate the authors. They have shown in very well controlled experiments, with their results adequately analyzed by sophisticated statistical methods, that the experimental production

of cataracts in rats, by X-rays, is dose dependent. This is expected. It is also age dependent, but only within certain limits.

The generally accepted assertion has been that the younger the animal, the more radiosensitive its tissues. This concept was stated in 1906, in the Law of Bergonieu and Tribondeau, "Radiosensitivity of tissue is proportional to its reproductive capacity and inversely proportional to the degree of differentiation." Theoretically then, young immature animals should develop cataracts sooner and with smaller doses than older animals. The authors have in their review of the literature, pointed out that under certain circumstances, the reverse is true. Reese, among others, noted some time ago that, "Radiation cataracts were less likely to develop in younger than in older patients." He stated that "In treatment of retinoblastoma, cataract is a rare occurrence."

The authors have shown that, with minimal doses of X-ray (200 rads), cataracts have developed sooner and progressed more rapidly in the older rats.

With high doses (1600 rads), younger rats developed opacities sooner and these progressed more rapidly than in older rats. However, with intermediate doses (400 to 1200 rads), young rats developed stages 1 and 2 vacuolization of the subcapsular regions sooner than did the older animals. Although the older animals showed opacities, they developed later and progressed more rapidly to complete opacification.

The fact that younger rats did not show progress of cataractous changes with minimal doses, indicates three possibilities: (1) that damage to the germinal epithelial cells may have been only partial, destroying some, but with enough surviving or being unaffected, that subsequent growth of lens fibers takes place, (2) that there may be partial or complete recovery of damaged cells, (3) that the aging process itself has brought the older animal closer to development of cataract and it takes less radiation to produce an opacity. We certainly see such repair or limitation of damage clinically. When a minor injury to the lens occurs in a young individual, an opacity may develop which subsequently becomes buried in clear cortex. In an older person, a similar injury would cause complete cataract.

Another clinical correlation is seen when iridectomy is performed in a young person. There is no fear of cataract developing, whereas, in an older individual iridectomy is frequently followed by cataract.

When we consider these factors of repair and the normal aging process, the results reported here are not as contradictory as might have been predicted from our earlier understanding of the relationship of the radiosensitivity of the lens to the age of the irradiated animal.

DR WALTER H. BENEDICT. In 1962 I presented my thesis to this Society, the subject of which was the development of X-ray induced lamellar cataract in the newborn mouse in relation to age at the time of irradiation. I realize the subject of this paper was rats, but I am talking about mice.

My study revealed that a lamellar cataract is produced in lenses of newborn mice when irradiated with 300 rad. This was consistent and the first stages of lens opacification were visualized at the first examination after the eyes were

opened, generally two or three weeks after treatment. This opacification progressed to complete cataract in most of the eyes within a period of several months. The most sensitive age of the mouse for consistent complete cataract formation was two days of age. Mice treated at a later age did not show this form of cataract consistently, and not at all after four days of age.

[Slide] This is a Grade I cataract in a mouse, taken with a slit lamp.

[Slide] This is another Grade I cataract with a little anterior subcapsular vacuole. These vacuoles will disappear after several weeks.

[Slide] This shows a little more extensive peripheral subcapsular anterior vacuolization. This also disappears with time.

[Slide] This shows a Grade 2 or 2+ (in ranges up to 6). This is focused on the posterior surface of the nuclear opacity.

[Slide] This shows the focus on the anterior nuclear suface of the lens opacity. You see the good zone of discontinuity.

[Slide] This shows further advance. Look at the one on the right and you can see the anterior Y suture, for example, and there is more opacification of the anterior fibers.

[Slide] This shows what I call a Grade 6, a very ripe cataract with extrusion of the nucleus. The nucleus is on the left and the empty capsular sac is on the right.

In the last several years these experiments have been repeated using a dose of 200 to 250 rad. Work has also been done, which is the subject of a further report, in which the exposure of the mice has been done in a low oxygen environment, that is 95 per cent helium and 5 per cent oxygen at the time of exposure. The results have statistically shown a lower cataract production and density rate under these conditions.

Dr George R. Merriam, Jr. I would like to thank Dr. Irvine for his kind and considered remarks. We do not know much about the possible variations in the mechanism of the development of a cataract as a function of dose. It is felt that radiation cataracts result from injury to the lens epithelium; but it may well be more complicated than that, and we hope to look into this in the future.

I would like to thank Dr. Benedict for his remarks. We know that different species can behave quite differently. I mentioned in my talk that other tissues have shown a curve similar to the one we found for incipient opacities at the 400 rad dose level. I was particularly thinking of the LD50/30 in mice — (the whole body dose that will kill 50 percent of the animals in 30 days). It is almost identical with the curve found for lens opacities.

Again, I would like to thank the discussers for their remarks.