RADIATION CATARACT

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Introduction

Lens damage arising from exposure to ionizing radiation was reported soon after the discovery of x-rays. Isolated cases of radiation cataract appeared among the early x-ray technicians and later among patients who had received radiation therapy to the head. These early cases were reported from time to time in the literature but occasioned scant interest outside ophthalmological circles.

Cyclotron Victims

Early in December 1948, it became known that at least 5 nuclear physicists of average age 31 had developed incipient cataracts. These scientists had a common history of radiation exposure from the cyclotron which was known to produce high fluxes of fast neutrons and hard gamma rays. Since it was probable from past experience that relatively high doses of gamma rays were needed to produce lens damage, the presumption was that fast neutrons might be the primary cause of cataract among these cyclotron workers. Accordingly, an "ad hoc" committee set up by the Division of Medical Sciences of the National Research Council arranged to have questionnaires sent to most of the major laboratories in the country where comparable exposures might have occurred. This procedure uncovered a possible six additional cases of incipient cataract.

A meeting was held in Washington in January 1949 under the auspices of the National Research Council and the United States Atomic Energy Commission to discuss the problem. Some of the known cataract victims were present and on the succeeding day 11 of these cyclotron scientists were examined in Baltimore at the Wilmer Ophthalmological Institute. Ten of them showed opacities of the lens and three of them were grossly handicapped. The victims made every effort to estimate their exposures but no great reliance could be placed on laboratory records several years old and on pocket dosimeters and film badges designed primarily to detect gamma rays. Abelson and Kruger reported the results of this initial survey. Duration of exposures ranged from ten weeks to 250 weeks and estimates of total neutron dose varied from eight reps to 270 reps. It should be emphasized that these doses represent little more than educated guesses by physicists who were well qualified to estimate their exposures but who were handicapped by incomplete laboratory records and faulty instrumentation insofar as neutron dosimetry was concerned.

Since that time, four additional cases of radiation cataract have shown up among cyclotron workers in America, while Dollfus reported, in May 1950, a possible seven additional victims among workers on the cyclotron in Paris, France. This makes a total of 21 scientists who, presumably, have received lens damage from cyclotron irradiations.

Atom Bomb Victims

The Committee on Ophthalmology of the National Research Council sent a team to Japan during the summer of 1949 to investigate the incidence of radiation cataract among the survivors of the atomic explosions at Hiroshima and Nagasaki. This original survey, under the leadership of Cogan, found ten radiation cataract victims among the survivors. All were within 3,000 feet of the hypocenter at the time of the explosion. Subsequent investigations have disclosed well over 100 radiation cataract cases among the bomb survivors. The farthest distance from the hypocenter at which lens damage has been definitely established is about 3,600 feet.

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Estimates of the fast neutron exposure at this distance from the so-called nominal bomb of 20 KT vary between three and 15 reps; the corresponding gamma ray exposure would be about 600 r.

Donaldson has re-examined 70 radiation cataract cases among the Japanese whose clinical histories had been recorded by other ophthalmologists prior to his investigation during the summer of 1951. Seventy percent of these victims had suffered complete epilation following their exposures; another 20 to 30 percent had undergone partial epilation. He found moderate regression of opacities in two percent of these patients, slight regression in 17 percent, no change in 36 percent, slight progression in 15 percent, moderate progression in 26 percent, and evidence of marked progression in four percent. This was six years after exposure to the bomb.

Accidental Nuclear Reaction Victims

Accidental nuclear reactions which injured ten scientists occurred at the Los Alamos Scientific Laboratory in August 1945 and May 1946. Two of the survivors have developed radiation cataracts. Hempelmann, Lisco, and Hoffman have reported the case histories of nine of these ten victims. The radiations responsible for biologic damage in these patients were primarily moderately fast neutrons and hard gamma rays emitted by a fast fission process. The data given below is taken with minor modifications from the report of Hempelmann et al.

Victim	Age	Whole Body Neutron Dose in Reps	Neutron Dose to Eye in Reps	Whole Body Gamma Ray Dose in Roentgens	Remarks
1	26	18	54	110	Touching assembly; died in 24 days.
2	29	1.2	4	1	12' from assembly; lenses normal 4 years after exposure.
3	32	74	222	114	Touching assembly; died in nine days.
4	34	15	45	26	3' from assembly; left side closest; cataract left eye, 3 years after exposure; cataract right eye, 5 years after exposure.
5	54	7	21	11	6' from assembly; lenses normal 3 years after exposure.
6	21	5	15	9	8' from assembly; lenses normal 3 years after exposure.
7	23	2	6	4	8' from assembly; lenses normal 3½ years after exposure.
8	36	1.6	5	3	16' from assembly; lenses normal 3 years after exposure.
9	23	1.3	4	2	16' from assembly; lenses normal 3½ years after exposure.

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The neutron doses to the whole body given in column 3 above were estimated from the Na^{24} and P^{32} content in the blood serum of the patients. While the absolute magnitude of the whole body neutron dose may be in considerable error by this method, it does afford a rather accurate criterion of the relative doses received by the victims. Radioactive assay of the blood serum necessarily provides an estimate of the integrated dose to the whole body and not the surface tissue dose incident on the victims. Snyder's calculations by the Monte Carlo method show that fast neutrons incident on tissue are rapidly thermalized in their passage through tissue. For example, neutrons of average energy 0.48 Mev, incident on tissue, have a half-value-layer of roughly 4 cm. The fast fission neutrons to which these scientists were exposed probably were concentrated mainly in the energy range below 1 Mev, so that the great majority were thermalized in passing through their bodies. A consideration of the depth dose curve in tissue for moderately fast neutrons makes it probable that the surface dose was considerably larger than the whole body dose, so that the lens of the eye must have received a much larger dose than would be indicated by the whole body dose. The estimated doses to the eye given in column 4 were obtained by multiplying the whole body dose by a factor of 3, a conservative estimate under the circumstances applying here.

These estimates of fast neutron dose to the eye may be subject to errors of large magnitude but they, at least, allow some conclusions to be drawn as to what constitutes a cataractogenic dose of fast neutrons for man. Victims 1 and 3 died from whole body radiation exposure before lens anomalies could have been expected to develop. Victim 2 received an estimated dose of six reps of fast neutrons to the eye; examinations up to 4 years after exposure have failed to disclose any lenticular abnormalities. Victim 4, on the other hand, received about 45 reps to the left side of the head and an unknown but certainly smaller dose of fast neutrons to the right side. Epilation was pronounced on the left side of this patient's head. It is significant that examination of patient 4 about 28 months after the accident failed to disclose any clinical manifestations of lens damage in either eye but when he was re-examined 32 months after the exposure, the left eye exhibited haziness in the posterior cortex which developed within 6 months into a moderately advanced radiation cataract. It was not until 58 months after the exposure that the right eye began to display clinically observable opacities. It is reasonable to infer that the cataractogenic dose of fast neutrons for this individual was considerably less than 45 reps. The other survivors of this accidental exposure have experienced no lens abnormalities up to the present time (Feb. 1952), or rather, no lens changes were on record at the time of their last examination. If some allowance is made for the age of victim 5 who received an estimated dose of 21 reps, it seems probable that the cataractogenic dose of fast neutrons must lie somewhere above 15 reps and considerably below 45 reps for men in their twenties and early thirties.

Cataract From Exposure to X-Rays and Gamma Rays

There is diversity of opinion as to what constitutes a cataractogenic dose of x-rays or gamma rays. Estimates run all the way from several hundred to several thousand roentgens. According to Hunt, the minimal dose for 100 to 200 kilovolt x-rays lies between 500 and 1000 r. Merriam, on the other hand, concludes that at least 1500 r are needed to produce cataract. These estimates are based on clinical data collected on patients who received radiation therapy to the head. There is great need for a further investigation of available clinical data along these lines. Up to the present, there is no evidence that x-ray or gamma ray doses of a few hundred roentgens cause lens damage in man; indeed, it seems probable that

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the cataractogenic dose is well above the LD-50 in humans. However, recent exposures on mice and rabbits have shown that x-ray doses between 100 and 250 r can cause lens damage in these species. Christenberry and his co-workers have been able to demonstrate lenticular abnormalities in mice with x-ray exposures as low as 32 and even 16 r. Cogan states categorically that the human lens is a relatively susceptible organ to x-irradiation with energies used in therapy (200 to 1000 KV) and that the threshold for production of cataract is less than that for any other gross abnormality of the eye or periocular tissue. In view of the low threshold doses found experimentally in other species and the wide variation in clinical data among humans, it seems wise to regard 500 r of x-rays or gamma rays as potentially dangerous to the human lens.

Conference on Radiation Cataracts, February 1950

In February 1950, the Committee on Radiation Cataracts held a meeting in Washington to assess the present status of the problem and to plan a definitive research program. Funds were provided by the United States Atomic Energy Commission with the request that they be administered by the National Research Council. At this time, there were 14 known cases of radiation cataract among physicists who had been associated with research employing the cyclotron.

A report by Evans in 1948 had shown that mice receiving small daily doses of fast neutrons and gamma rays from the cyclotron developed cataracts in many instances. Comparable exposure to x-rays failed to produce cataracts. His data on the chronic exposure of mice, whole body, to the radiations from the cyclotron, when compared to x-ray exposures, made it probable that fast neutrons were between 10 and 20 times more effective in producing cataracts in mice than x-rays. These findings and the unfortunate experiences of the cyclotron victims aroused much interest in military and civilian circles. Scientists engaged in the development of nuclear weapons, nuclear power, civilian defense, and health physics were concerned, not to mention those engaged in nuclear research and in the medical and biological sciences.

Although a great deal of fundamental nuclear research had been going on among the physicists, it was apparent that little was known about radiation fluxes, energy spectra, and angular distribution of the neutrons and gamma rays emanating from cyclotron targets bombarded by protons and deuterons. For example, the fast neutron flux emitted by a beryllium target bombarded by deuterons had not been appreciated generally. A current of 100 microamperes of 16 Mev deuterons hitting a beryllium target produce about 20 reps/min of fast neutrons having energies above 3 Mev as determined with sulphur detectors. This is in the forward direction of the dauteron beam at a distance of 90 cm from the target; at right angles to the beam the dose rate is approximately 5 reps/min. A common laboratory procedure among physicists consisted in shimming the magnetic field of the cyclotron while watching the glow from the target to determine the efficacy of the operation.

Radiation dosimetry for mixed beams of neutrons and gamma rays was not well developed at this time. Biologists and physicists, lacking suitable instrumentation, employed commercially available 25 r and 100 r Bakelite thimble chambers to determine fast neutron doses in tissue. When exposed to fast neutrons, the ionization reading of the 25 r chamber is called the large "N" unit of fast neutron dose in tissue, while the reading of a 100 r chamber is called the small "n" unit. These units were estimated originally to correspond to about 2.5 reps of energy absorption in tissue by fast neutrons. Recent determinations indicate that the

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ionization reading should be multiplied by 2 rather than 2.5 to obtain the tissue dose in reps. It has been pointed out that such bakelite thimble chambers do not agree among themselves with any accuracy when exposed to the same beam of fast neutrons. Moreover, when these thimble chambers are exposed to a mixed beam of fast neutrons, thermal neutrons, and gamma rays there is no reliable method of interpreting the results in terms of tissue dose. The radiations emitted by cyclotrons and nuclear reactors always consist of neutrons and gamma rays.

One objective of the Committee on Radiation Cataracts was to stimulate research on radiation dosimetry and to encourage intercomparisons between different laboratories so that the biological effects of ionizing radiations might be determined in terms of a common denominator. There have been several promising developments along the lines of mixed radiation dosimetry. One method, developed at Oak Ridge by Hurst and his associates, utilizes a proportional counter surrounded by polythene and filled with an hydrogenous gas. The counter is designed on the Bragg-Gray principle; recoil protons engendered in the polythene radiator are counted as ionization pulses. An ingenious electronic method of pulse integration has been described by Glass and Hurst. One major advantage of this type of instrument is that it may be used to measure fast neutron doses in the presence of a gamma ray radiation field. Since the ionization pulses from gamma rays are smaller than those arising from proton recoils, the former may be biased out without sacrificing any appreciable efficiency in the counting of proton recoils. Failla and Rossi have developed another approach to the dosimetry of mixed beams of radiation. Their instrument consists of an ionization chamber with walls of a tissue-like plastic and containing a gas which is also similar to tissue in composition. This ionization chamber will measure the energy absorbed in tissue regardless of the nature or mixture of the radiations concerned. When placed in a mixed beam of neutrons and gamma rays, the tissue-wall, tissue-gas ionization chamber records the total energy absorbed in tissue without differentiation as to the type of radiation depositing the energy. Within the past few months, Hurst and Rossi have performed some preliminary checks with both types of instruments exposed to the same beam of mixed radiation. The results, to date, are most encouraging. It is possible by a process of subtraction to measure, accurately and separately, the fast neutron and gamma ray doses so that the relative biological effectiveness of each component can be taken into account. Mixed beam dosimetry is still a formidable problem for the health physicist but these two instruments used in conjunction make it possible to measure the radiation components emanating from a cyclotron or a nuclear reactor.

There were two primary objectives to be kept in mind while planning a research program on radiation cataracts: first, the immediate and practical problem of attempting to ascertain the cataractogenic fast neutron dose in humans to a higher degree of accuracy than was known from the scanty data on cataract victims; secondly, the need of promoting basic research on the biologic effects of ionizing radiation as applied to the lens of the eye. The practical philosophy underlying the first objective was to determine the cataractogenic fast neutron dose in at least 3 species of animals, with the hope that if no large scale variation among species were found, an extrapolation might be made to man. Also, if the relative biological effectiveness (RBE) between x-rays or gamma rays and neutrons for the production of cataract should prove to be relatively constant for several widely differing species, it should be possible to infer the toleration dose of neutrons in man on the basis of a critical evaluation of the clinical records on patients having received radiation therapy to the head with subsequent development of cataract.

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A problem needing resolution was the capacity of tissue to recover after exposure to ionizing radiation. The practice of fractionation in radiation therapy is based on the demonstrated ability of tissue to recover partially from x-ray damage. Was this true for neutron irradiation? Were the effects of neutron irradiation completely irreversible or only partially so? Questions of this nature indicated a need for data on animals subjected to both acute and chronic exposures of neutrons and x- or gamma rays. Many experiments in radiobiology had indicated a possibly large scale difference between x-rays and neutrons when delivered in small, fractionated doses. The fact that chronic doses of neutrons seemed highly additive was primary evidence of some difference in biologic effect between x-rays and neutrons. Current thinking in radiobiology stresses the role of heavily ionizing particles like high speed protons in producing cell damage. Some of the effects of the spatial distribution of ion pairs in tissue (specific ion density) are discussed briefly in the appendix to the Proceedings of the first conference on radiation cataracts. Was lens damage the result of direct hits on vulnerable material within the cell (so-called target theory) or the result of indirect effects (chemical changes brought about by the production of H and OH radicals in aqueous media)? There is a growing tendency among radiobiologists to think of cell damage in terms of chemical changes induced by oxidative or reductive radicals engendered in solutions by ionizing radiation. Support for this thesis is to be found in experiments demonstrating the protective effect of certain chemicals and in the production by chemicals of cellular damage similar to that resulting from radiation exposure. Most of the experiments on aerobic vs. anaerobic irradiation seem to be best interpreted in terms of some form of indirect mechanism involving chemical radicals.

Another problem needing investigation was the possible effect of neutron energy on lens damage. Dose for dose, were 14 Mev neutrons and 300 Kev neutrons equally effective in producing cataract? The possibility of systemic effects in the production of cataract (whole body irradiation vs. irradiation of the eye or head alone) could not be ruled out. Was radiation cataract a purely local effect or were there contributing causes from other sites in the body? Age was another variable which had to be considered in attempting to determine susceptibility to cataract. All available data indicate that the young and still actively growing lens is more sensitive to radiation damage than the mature lens and both the latent period before onset and the severity of the lesion seem to be definite functions of age as well as magnitude of dose. A fascinating problem was whether the slow growth rate of the lens could be related to the long latent period between exposure to radiation and the development of cataract. Poppe's experiments in 1942 first suggested that some of the pecularities of radiation induced cataract might arise from the fact that, in the lens, new fibers are continually being laid down throughout life by slow proliferation of the epithelial cells. Little was known in 1950 regarding the growth rate and mitotic index of lens epithelium. Some investigators were of the opinion that mitosis was too infrequent to allow an accurate determination of cell division.

In the remainder of this paper, an attempt will be made to discuss some of the experiments which have helped to clarify the problems facing the Committee on Radiation Cataracts in 1950. Many of these problems still await solution but definite progress has been made in the interim.

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Cyclotron Irradiation vs. X-Rays in Mice

Evans has confirmed some of his earlier data on mice exposed to x-rays and to fast neutrons from the cyclotron. For acute exposures, using the LD-50 as the biological criterion, he finds that neutrons from the cyclotron are 2.5 times more effective in producing death than x-rays. Complete opacification in 50 percent of the mice within one year was produced by 80 reps of fast neutrons delivered as an acute dose. This same dose produced visible opacities in all his mice within one year. Comparable lens effects by means of whole body x-irradiation were not feasible because most of the mice die before the onset of cataract; this problem was solved by shielding the body of the mice and delivering x-rays to the head alone. Thus, Evans compares whole body neutron irradiation from the cyclotron with x-irradiation to the head alone. Preliminary data on acute exposures under these conditions result in an RBE of about 9 for the production of visible opacities. That is, 700 r to the head alone corresponds to 80 reps of neutrons in producing visible opacities in 100 percent of the mice. Evans is experimenting currently with chronic exposures in an attempt to define more accurately the RBE for cataract. There is little doubt that RBE ratios in excess of 10 will be obtained, since some recovery between x-ray exposures is to be expected on past experience, whereas repeated small doses of neutrons are highly additive.

Cyclotron exposures employing an internal beam of deuterons on a beryllium target produce large quantities of hard gamma rays as well as fast neutrons with energies extending from 15 Mev down to epithermal and thermal energies. The energy spectrum of the fast neutrons has a broad peak at about 5 Mev. It has been shown by means of sulphur detectors that roughly 50 percent of the total tissue dose in the forward direction of the deuteron beam is composed of fast neutrons with energies above 3 Mev. As a first approximation, it is usual to assume that fast neutrons contribute the major portion of the tissue dose; lead shielding can be used to reduce the gamma ray exposure without affecting appreciably the fast neutron beam. The efficiency of deuterons on beryllium in producing fast neutrons makes the cyclotron an excellent accelerator for acute exposures. About 1 fast neutron is produced for every 1000 deuterons striking the target and it is not uncommon in modern laboratory practice to obtain deuteron beams of several hundred microamperes. However, the mixed nature of the radiation beam introduces dosimetry problems which complicate the experiment of the radiobiologist. More elegant from the standpoint of pure neutron beams and exact dosimetry are some of the available reactions with the Van de Graaff and Cockcroft-Walton accelerators. The efficiencies of the D-D (deuterons bombarding deuterium) and the D-T (deuterons bombarding tritium) reactions are sufficient for biologic exposures. These reactions can be used to provide a monoenergetic neutron beam of almost any desired energy and have the advantage of being uncontaminated with gamma rays and slow neutrons. Rather lengthy exposure times are required for acute radiation studies but the method is ideal for chronic exposure studies. As an example of this type, the Cockcroft-Walton accelerator at Los Alamos requires about 1½ hours to deliver a dose of 250 reps of 14 Mev neutrons at an irradiation distance of 10 cm from the target, using the D-T reaction.

Allen and his co-workers at the University of Pittsburgh have succeeded in bringing a beam of 15 Mev deuterons out of their cyclotron and allowing it to impinge on an outside target which is well shielded and far removed from the cyclotron proper. This procedure provides an excellent source of fast neutrons with a much smaller percentage of gamma rays in the beam than can be obtained with a target situated within the cyclotron. An experimental animal's head can be placed close to the outside target in a manner to take full advantage of the inverse square law

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to minimize whole body irradiation. Acute exposures of several hundred reps of fast neutrons can be delivered to the head without sacrificing the animal to lethal doses of whole body radiation. Moses and Linn are using this arrangement to study the production of radiation cataract in dogs.

Exposures of Mice to X-Rays and Slow Neutrons from the Thermal Column

Furth, Christenberry, Upton and Sheppard have exposed mice to x-rays and to thermal neutrons produced in the nuclear reactor at Oak Ridge. Before discussing their findings, it is necessary to describe their method of grading lens damage in mice. By using the slit lamp they are able to detect lens changes which are not ordinarily observable with the ophthalmoscope. Ophthalmologists are in general agreement that it is difficult, if not impossible, to define a true threshold value for radiation cataract; the tendency is to regard lenticular abnormalities which do not affect visual acuity or, at least, are not observable with the ophthalmoscope, as representing negligible damage from a practical standpoint. However, sensitive criteria of lens damage are desirable, especially as an early indication of radiation injury to the lens. The Oak Ridge group recognize 4 grades of lens damage in mice. Apparently, a grade I lesion is observable only with the slit lamp, whereas grade II can often be seen with the ophthalmoscope but does not constitute necessarily a visible opacity which would interfere with vision; grade III seems to be equivalent to a visible opacity which would interfere with vision and grade IV constitutes a mature radiation cataract with partial if not complete opacification.

At Oak Ridge, the LD-50 of mice exposed to slow neutrons from the thermal column of the nuclear reactor was compared with whole body x-ray exposures. Eighty minutes exposure to a thermal neutron flux of 9×10^8 n/cm^2/sec, plus an estimated 4 to 8 r of hard gamma rays, was found to be equivalent to an 80 minute exposure to 250 KVP x-rays at a dose rate of 6.4 r/min. A rough calculation indicates that about 300 reps of slow neutrons produced the same lethal effect as 512 r of x-rays, or an RBE of approximately 1.5 for lethality. During these experiments, cataracts made their appearance 70 to 80 days after exposure; the incidence of lens damage at all dose levels was greater for the mice exposed to the thermal column than for those exposed to a comparable dose of x-rays. Sufficient data have not been made available to allow any quantitative estimates of the RBE for x-rays vs. thermal neutrons in the production of cataract and about all that can be judged is that thermal neutrons are more effective than x-rays in producing lens damage. Grade I lens abnormalities were observed in mice exposed to 30 and even to 16 r of whole body x-irradiation. Grade III and grade IV lens damage was seen only in animals receiving 120 r or more of x-rays.

Brennan et al have made an exhaustive study of the experimental conditions accompanying the exposure of mice within the thermal column attached to the homogeneous reactor (water boiler) at Los Alamos. Female Swiss mice were exposed to x-rays from a 250 KVP machine and to the mixed radiation in the thermal column. Correction factors were applied for (1) inherent gamma ray contamination in the column, (2) inter--mouse gamma ray dose due to hydrogen capture gamma rays and (3) attenuation of the thermal neutron flux in the exposure cavity by the "sink" effect of the mass of mice. The RBE for x-rays vs. thermal neutrons was found to be 1.7, using the LD-50 (death in 30 days) as the biological criterion and employing acute exposures.

Storer et al have exposed white female Swiss mice under the same general experimental conditions outlined above in the Brennan report with the objective of studying the incidence of lens opacities and of determining an RBE for exposures to 250 KVP x-rays and to thermal neutrons from the thermal column of the homogeneous

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reactor. They define as "lens opacities" all lens abnormalities characteristic of radiation damage and visible with the ophthalmoscope; the first examination at which an opacity which subsequently persisted was seen is taken as the end point of the latent period for its production. The mice were observed for 30 weeks and the incidence and latent period of radiation-induced lens opacities determined as a function of radiation dose. X-ray doses of 200 r or more produced opacities in 100 percent of the animals. It was found that the higher the dose the shorter the latent period before the appearance of opacities; this was true for both types of radiation exposure. The data showed that 4.7 seconds of thermal column exposure was equivalent to 44.4 seconds of x-ray exposure in producing lens opacities in 50 percent of the animals 30 weeks after exposure. Taking the rep as 93 ergs/gm of tissue and expressing all radiation doses in terms of reps, it appears that 2.9 reps of thermal neutrons plus 1.7 reps of inherent gamma rays (approximate energy 4 Mev) plus 0.5 reps of inter-mouse gamma rays (energy 2.2 Mev) was equivalent to 39.4 reps of 250 KVP x-rays. Any calculation of a RBE ratio necessarily involves a knowledge of the RBE of 4 Mev gamma rays and 2.2 Mev gamma rays vs. 250 KVP x-rays for the production of lens opacities. On the assumption that the RBE ratios for these gamma rays are the same as for LD-50 studies determined by Brennan, Storer concludes tentatively that thermal neutrons are roughly 15 times as effective as 250 KVP x-rays in producing lens opacities. Even if these hard gamma rays are assigned a RBE of 1 in comparison to x-rays, the RBE of x-rays vs. thermal neutrons for lens opacities comes out to be of the order of magnitude of 13 or 14. It is difficult to understand how thermal neutrons can be more effective presumably than fast neutrons in the production of lens opacities. Practically all the energy dissipated in tissue by fast neutrons goes into the production of proton recoils, whereas only those thermal neutrons captured by nitrogen or possibly by traces of boron produce heavily ionizing particles in tissue. It is admittedly difficult to calculate the energy dissipated in a small mouse by thermal neutrons because of the uncertainty as to what proportion of the hard gamma rays (2.2 Mev) engendered by hydrogen capture of thermal neutrons is deposited in the body of the mouse. Making allowances for possible errors in the calculation of the tissue dose deposited by thermal neutrons would not alter the RBE materially. Mice display a congenital tendency towards lens opacities as shown by the fact that controls which have received no radiation exposure often develop opacities. It is more likely that some biologic variation of this type might explain these high RBE ratios for x-rays vs. thermal neutrons. It should be pointed out that no definitive studies comparable to those of Storer have been made on the production of lens opacities by fast neutrons in mice. It may well be that the RBE for initial lens damage in mice as a result of fast neutron exposures in in considerable excess of that found for thermal neutrons.

Exposures of Mice at Operation Greenhouse

LeRoy and the group at Oak Ridge (Furth, Christenberry, Upton and Sheppard) collaborated in a study concerning the incidence of lens damage among mice exposed to atomic bomb radiations at Operation Greenhouse. To insure relatively pure gamma ray exposures, mice enclosed in bomb-proof aluminum containers were placed at various distances from the explosion where the fast neutron exposure should be relatively unimportant in comparison to the gamma ray dose. Forty-five hundred mice were exposed to gamma ray doses ranging from 1300 to 180 r. The LD-50 for gamma rays from the bomb was found to be 750 r. At the distance from the bomb where 750 r was received, the fast neutron exposure was estimated to be less than 1 rep. While this estimate may be low, it seems probable that the fast neutron dose was under 10 reps. Mice surviving the LD-50 exposure of gamma rays developed lens damage by the end of the third month; mature radiation cataracts developed eventually in all of these mice. Mice experiencing the lowest gamma ray dose, 180 r, developed observable lens changes (grade I and grade II lesions).

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Relatively pure neutron exposures were obtained by placing mice in special bomb-proof containers shielded by 7 inches of lead. Fast and thermal neutron doses within the containers were estimated from sulphur and gold detectors. Six hundred and forty mice were placed at various stations where the fast neutron dose varied from about 600 reps down to about 1 rep. Even at the farthest station where the mice were estimated to have received somewhere between 1 and 10 reps of fast neutrons and about 1 r of gamma rays, grade I and grade II lens changes developed. The unavoidable dosimetry problems encountered on these bomb exposures make it difficult to assess the results but the experiments are in general accord with those of others and support the conclusion that neutrons are much more effective in producing lenticular damage than gamma rays.

Exposures of Rabbits to Hard X-Rays and to Fast Neutrons

Cogan and Donaldson have studied lens damage in Chinchilla rabbits after acute exposures to 1200 KV (constant potential) x-rays. Radiation cataracts appeared with a latent period that was an inverse function of the dose. The threshold dose was estimated to be 250 r or less for 10 week old rabbits and the latent period for the development of radiation cataracts was much less, the younger the animal. The body of the rabbits was shielded and for dosesof less than 1000 r, cataracts were the only biologic abnormality produced.

As a complement to the hard x-ray exposures of rabbits, Cogan, Goff and Graves exposed 10 week old, French Silver rabbits to pure neutron beams of 14 Mev produced by bombarding tritium with deuterons from the Cockcroft-Walton accelerator at Los Alamos. Duplicate exposures to 300 Kev neutrons were performed on the so-called fast reactor. The purpose here was to determine any differences in the cataractogenic properties of fast neutrons having widely different energies. Gamma rays were completely negligible in both of these types of exposures. The animals were positioned in a manner to take full advantage of the inverse square law to reduce whole body exposure to a minimum and no animals died as a result of whole body exposures. Either 4 or 5 rabbits were exposed simultaneously to acute doses which took anywhere from 6 hours to 1 hour, depending on the total dose delivered. The course of events following neutron irradiation was basically similar to that following x-ray exposures. The degree of lens damage after exposure to 8×10^9 n/cm^2 of 14 Mev neutrons corresponded to that after 30×10^9 n/cm^2 of 300 Kev neutrons; this damage was comparable to that produced by 500 r of 1200 KV x-rays.

Calculations of first collision neutron tissue dose based on Mitchell's work and the more elaborate investigations involving multiple scattering by Snyder make it possible to estimate the tissue dose in reps from Cogan's and Donaldson's data. Thus, 8×10^9 n/cm^2 of 14 Mev neutrons corresponds to about 40 reps, while 30×10^9 n/cm^2 of 300 Kev neutrons corresponds to about 50 reps. Thus, the dependence on neutron energy does not appear to be critical in the production of lens damage, being a factor of about 1.25 between 14 Mev neutrons and 300 Kev neutrons. When the dose of 40 reps of 14 Mev neutrons is compared to 500 r of 1200 KV x-rays for comparable lens damage, a RBE of about 11 results; similarly, for 300 Kev neutrons, the RBE is about 9. These RBE ratios compare favorably with Evans' data on mice exposed to the neutron beam from the cyclotron and to 250 KVP x-rays. However, they are somewhat lower than the RBE for x-rays vs. thermal neutrons obtained by Storer et al at Los Alamos. An experiment similar to Cogan's on mice using the Cockcroft-Walton accelerator at Los Alamos would help to determine whether thermal neutrons are really more effective in producing lens damage than fast neutrons. Cogan estimates that the threshold dose for production of lens damage which is detectable with the ophthalmoscope in rabbits is less than 2×10^9 n/cm^2, or about 10 reps for 14 Mev neutrons. The corresponding threshold for 1200 KV

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x-rays is about 250 r. Thus, the RBE for detectable threshold damage is roughly 22 in rabbits, a value which is considerably higher than Storer's RBE for thermal neutrons. This is in accord with modern radiobiological thinking regarding the role of heavily ionizing particles in tissue damage. It seems quite likely that both Cogan's and Storer's RBE ratios in rabbits and mice are much larger for threshold evaluations of lens damage, whereas, if more extensive damage is used as the biological criterion, the RBE ratio between neutrons and x-rays becomes correspondingly smaller.

Gross Anatomy of the Eye

Before discussing some of the more recent experiments on biological mechanisms leading to radiation cataract in the mammalian lens, it will be helpful to describe the gross features of lens anatomy for the benefit of those who do not have an ophthalmological background. The cornea in man is about 0.6 to 0.8 mm thick. Behind the cornea is the anterior chamber filled with aqueous humour. The maximum depth of the anterior chamber is along its central axis, being about 3 to 3.6 mm, so that the maximum distance from the anterior surface of the cornea to the anterior surface of the lens is about 4 mm. The iris separates the anterior chamber from the posterior chamber which is also filled with aqueous humour. The vitreous body, a clear transparent gel of semi-solid consistency, fills the chamber of the eyeball behind the lens. The lens has no direct blood supply and must rely on the nutrient fluid bathing its surface for metabolism. The aqueous may be regarded as a dialysate of the blood serum, containing oxygen in solution and many of the metabolites needed by the lens.

The lens is a transparent structure having a bi-convex shape with a rounded border, the equator. The anterior surface is curved as a flattened ellipsoid, the curvature culminating in a central anterior pole. The posterior surface is more highly curved as a parabaloid, culminating in a central posterior pole. The central axis, from pole to pole, is about 4 mm in diameter while the equatorial diameter is about 9 mm. The average weight of a mature human lens is about 0.2 gm and the average volume about 0.2 ml; the water content is about 65 percent by weight and the protein and hence the nitrogen content of the lens is high compared to other tissues, being a little better than 4 percent nitrogen by weight. Structurally, the lens is divided into three parts: the capsule, the epithelium, and the lens substance. The capsule is a tough, clear membrane entirely surrounding the rest of the lens; it has a thickness of about 12 to 14 microns at the anterior pole. The epithelium extends as a single layer of highly viable cells under the anterior capsule as far as the equator. There are no epithelial cells on the posterior subcapsular surface of the lens beyond the equator. Towards the equator, in the anterior peripheral zone, the epithelial cells become smaller and more cylindrical. This is the germinative zone where mitotic activity is pronounced compared to the relatively static, anterior central area. Near the equator, the epithelial cells tend to become arranged in meridional rows and their inner parts become elongated and orient themselves obliquely to run up underneath the epithelium of the anterior capsule. At this stage, the epithelial cells are more correctly characterized as young lens fibers.

There is a constant laying down of new lens fibers at the equator; going into the lens substance, the older and older fibers are encountered, so that at the center of the nucleus are found those oldest fibers which were laid down in fetal life. The interior of the lens is stratified into zones which can be distinguished with the aid of the slit lamp. There is an embryonic and fetal nucleus

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composed of the oldest fibers, an adult nuclear zone composed of fibers formed during early life, and the cortex which is composed of those younger and more superficial fibers which lie between the nucleus and the capsule. The lens is rather unique among mammalian organs in that it grows very slowly but continuously throughout life without being able to slough off old cells because of the lens capsule. This is not to say that the lens is not in a dynamic state with regard to metabolites according to the concept first clearly enunciated by Schoenheimer; on the contrary, some of the metabolic turnover rates have been explored by means of radioactive tracers. However, other generative tissues like skin and bone marrow are continually shedding old cells whereas the epithelial cells behind the capsule differentiate into lens fibers which remain within the nucleus or cortex throughout life. There is no mechanism whereby the lens can rid itself, on a cytological scale, of abnormal, damaged, or non-viable cells. This may be a primary reason for lens susceptibility to radiation damage, as pointed out by Poppe in 1942.

Effect of X-rays on Lens Epithelium in Rabbits

Von Sallmann has conducted some interesting investigations regarding the effect of x-rays on the mitotic activity and nuclear fragmentation of the lens epithelium in normal and cysteine-treated rabbits. He has applied a technique perfected by Howard for the preparation of total flat mounts of lens epithelium attached to the capsule. This method provided a means of obtaining reliable estimates of the mitotic index in normal rabbits and suggested the possibility of studying the influence of ionizing radiation on cell division, as well as the possible protection afforded by chemical substances like cysteine. The Feulgen-positive staining technique was used for counting cells in mitosis and for detecting signs of early nuclear damage in cells which had been irradiated. Chinchilla rabbits, 12 to 16 weeks old, were used for an analysis of cell division; von Sallmann employed 100 rabbits and examined 200 preparations of lens epithelium.

The number of cell elements was estimated to be approximately 790,000 in the normal, mature rabbit on the basis of cell counts for preparations of the entire epithelium. The mitotic index for the total preparation of epithelium ranged between 18:100,000 and 27:100,000 in the rabbits examined. The distribution of dividing cells varied characteristically in the several anatomic zones of the epithelium. The highest index (60:100,000) was found in the germinative zone; this contrasted with an index of 0.11:100,000 in the spacious central area, and with the apparent absence of dividing cells in the nuclei of the lens bow.

Irradiation with 1500 r of x-rays was followed by almost complete disappearance of dividing cells 30 minutes after exposure. Total inhibition lasted from 3 to 4 days to be followed by recovery of mitotic activity within the next 4 days. This, in turn, was followed by a period of overcompensating increase in the proportion of dividing cells which persisted for at least another week. Nuclear fragmentation and extrusion of Feulgen-positive material was observed after irradiation. Since those cells which have entered mitosis at the time of exposure to x-rays presumably complete the cycle, the cessation of mitosis 30 minutes after irradiation indicated that the time required for mitosis was about 30 minutes. There was a steep rise in the incidence of nuclear damage when the inhibition of mitosis terminated, particularly when the overshooting phenomenon had developed fully. Among the pathologic reactions observed were clumped chromosomes, translocation of chromosomal material with a tendency to form bridges, and nuclear fragmentation. A drastic depletion of cellular elements in the germinative zone was observed 3 months after irradiation. This observation confirmed the common radiobiological experience that nuclear destruction is encountered predominantly in

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regions of active cellular proliferation and may be considered a precursor of subsequent depletion of viable cells.

The injection of cysteine prior to irradiation prolonged the inhibitory effect of x-rays on mitosis, slowed the speed of recovery, and reduced the extent of overshoot in cell division. The protective action of pre-treatment with cysteine was demonstrated by a lower incidence of nuclear fragmentation in all zones as compared with the incidence of this type of damage in the eyes of untreated rabbits which had been irradiated and of rabbits injected with cysteine after irradiation. Follow-up studies over a long period of time on those rabbits receiving pre-treatment with cysteine have not been reported as yet. It remains to be seen whether permanent or merely transitory protection was afforded.

Von Sallmann's painstaking research demonstrates clearly that cytological damage from ionizing radiation can be detected in the lens epithelium prior to clinical manifestations of lens damage. Similar findings by Poppe in 1942 and Cogan in 1951 are amply confirmed and emphasize the growing conviction among ophthalmologists that the primary site of radiation damage leading eventually to radiation cataract is in the lens epithelium. Von Sallmann is the first to obtain convincing mitotic indices for the different regions of the epithelium and to show the influence of ionizing radiation on the mitotic index. His research indicates that the maximum damage from x-rays occurs where the cells are proliferating most actively, namely, in the germinative zone, and his demonstration of the protective action of cysteine stimulates hope that eventually some type of chemical protection against ionizing radiation may be perfected to the stage where personnel undergoing radiation exposure in line of duty may be given pre-exposure treatment with palliative results. It is to be hoped that techniques similar to von Sallmann's can be used to uncover possible differences in the biologic actions of x-rays and neutrons.

Cogan and Donaldson also have contributed convincing evidence of cytological damage to the lens epithelium of rabbits exposed to 1200 KV x-rays. After exposures of 1500 to 2000 r they have observed such phenomena as cells with abnormally large amounts of cytoplasm and cells with multiple nuclei and striking karyorrhexis. Flat preparations of the posterior capsules of rabbit lenses 100 days after a dose of 2000 r were found to have aberrant cells affixed to the capsule. In the early stages of cataract formation at the posterior pole and before the subjacent cortex undergoes changes leading to opacification, these abortive cells may be rubbed off prior to fixation with a spatula, leaving a clear capsule beneath.

Pathogenesis of Radiation Cataract

A puzzling problem is how manifestations of radiation cataract first appear clinically at the posterior pole of the lens when the truly viable cells are located entirely on the anterior surface of the lens beneath the capsule. Cogan has presented some fruitful observations regarding the pathogenesis of radiation cataract based on his observations of 20 cases among bomb victims, cyclotron physicists, and others receiving radiation therapy to the head. He was able to collect 26 human lenses which had been removed from cataractous patients for histologic examination. The cytological changes in the epithelium, preceding the opacification of the lens, suggest a disturbance of cell differentiation and are compatible with the hypothesis that radiation disrupts normal cell division. Some epithelial cells are killed by the radiation dose; others undergo metamorphosis --

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aberrant mitosis -- whereby they become monster cells with abnormal cytoplasmic content and multiple nuclei. Whether these monster cells die or develop further does not seem to be known. Other cells are damaged by the radiation and show their abnormality when they come to differentiate at the equator. These cells survive and perhaps divide but they can no longer fulfill their destiny of becoming young lens fibers at the equator; rather, they remain globular or ellipsoidal and form at best abortive processes. Then, apparently, they migrate or are pushed toward the posterior pole between the cortex and the capsule, where they form the characteristic opacity of early radiation cataract. Whether this migration is active or passive is not clear but they move beneath the only potential space available and come to lodge finally in the central area around the posterior pole of the lens. This seems to be the place of least mechanical resistance to the piling up of damaged cells. What relation these cells have to the later opacification of the subjacent cortex is conjectural; it seems reasonable to assume that it is the degeneration of these damaged cells, with liberation of their intracellular enzymes, that causes the lysis of the cortex. The most characteristic observation in early radiation cataract is the migration of these aberrant cells while the lens appears otherwise perfectly normal.

There is disagreement among ophthalmologists as to whether early manifestations of radiation cataract can be seen first at the equator or at the posterior pole of the lens. In man, the equator is not readily visible on clinical examination and this may explain why opacities are observed first at the posterior pole. In rabbits, on the other hand, lens damage is seen often at the equator before it can be observed at the posterior pole according to Leinfelder.

Permeability Studies on Normal and Cataractous Lenses

Radioactive tracer techniques have been employed by von Sallmann to study the permeability of normal and cataractous lenses. Radioactive indicators (Na^{24}, K^{42}, I^{131}, and P^{32}) served as tools. Specific activities in the serum, in the aqueous, and in normal and x-irradiated lenses were measured by standard counting techniques or by densitometry on radioautographs. There was no difference in the uptake of radioactive sodium by normal and by irradiated lenses immediately after exposure but the uptake was greater in irradiated lenses after cataract had set in, and this uptake increased with the progress of opacification. Radiopotassium penetrated well in the normal lens; there appeared to be a slight decrease in the exchange of radiopotassium with the potassium of the cataractous lens. The accumulation of radioiodine in irradiated lenses showing initial cataractous changes exceeded the accumulation in normal lenses. This was not true for irradiated lenses prior to the onset of cataractous changes. Radiophosphorus accumulated in normal lenses principally at the equator and in the surface layers of the cortex. The differences between the cortical and deeper portions vanished in lenses with total radiation cataract but the autographs of normal lenses and lenses with initial radiation damage were the same. These investigations do not lend support to the theory that changes in the permeability of the lens are caused by ionizing radiation and that this results in initial changes leading to radiation cataract. They suggest rather that changes in permeability accompany and perhaps influence the progress of opacification.

Biochemistry of the Mammalian Lens

Kinsey and Merriam have contributed valuable data on the biochemistry of the mammalian lens. Their studies demonstrate that the Schoenheimer concept of the dynamic state of body constituents applies equally well to the avascular lens

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as to other tissues having a direct blood supply. A modified Warburg technique was developed to culture the lens "in vitro". The synthesis of glutathione which is concentrated highly in the mammalian lens was studied. Radioactive glycine was added to the culture medium and rabbit lenses were cultured for 24 hours. The tagged glycine was taken up in the various portions of the lens and some of it was incorporated into glutathione which is a tri-peptide containing glycine as one of its constituent amino acids. Half of the glutathione content of the lens was turned over within 24 to 28 hours. The average rate of turnover of glycine in lens glutathione was 2.35 percent per hour, and the turnover rate of glycine in protein was of the same order of magnitude. These observations suggest that glutathione and protein in the lens are being continuously synthesized from their constituent amino acids. The rates of turnover of glutathione in lenses removed from animals which were fed naphthalene were greatly reduced. Naphthalene is known to produce cataract when fed to experimental animals. The reduced concentration of glutathione known to be associated with the cataractogenic process is thought to result primarily from an inhibition of glutathione synthesis, probably through poisoning of either the enzyme systems directly responsible for synthesis or those responsible for providing energy for the synthetic processes.

The more recent studies of Kinsey and Frohman on the enzyme systems operating in the lens give biochemical support to the belief that the lens epithelium may be the initial site of radiation injury. They investigated the sources of energy available to the lens for synthesis. Cytochrome C was isolated in relatively pure form from the epithelium of 40 bovine lenses. Previous attempts by others to demonstrate the presence of the cytochrome system in appreciable amounts within the mammalian lens had met with little success because whole lenses had been used for the analysis. Kinsey and Frohman separated the epithelium and capsule from the rest of the lens before performing their analysis and found almost 200 milligrams of cytochrome C per 100 grams of epithelial tissue on the assumption that the capsule contained negligible amounts of this enzyme. They also found that riboflavin was present in the epithelium in concentrations 100 times greater than in the cortex. These findings demonstrate the existence of a respiratory system which is confined almost entirely to the epithelium of the lens.

The cytochrome and riboflavin systems in the epithelium appear to function in the oxidation of carbohydrate and not solely in the oxidation of amino acids or fats. This deduction comes from a consideration of the concentration of lactate and pyruvate in the epithelium, cortex, and nucleus of the rabbit lens. The data indicate that the epithelium contains an unusually high concentration of pyruvate and a low concentration of lactate, whereas the cortex and nucleus contain a high concentration of lactate and a negligible concentration of pyruvate. Two hydrogen atoms are released in the overall process involving the oxidation of glucose to pyruvic acid. In the absence of a cytochrome system, it is difficult to understand how these hydrogen atoms can combine with oxygen to form water; accordingly, they must combine with pyruvate to form lactate if metabolism is to continue. In tissue lacking the cytochrome system, as seems to be the case for the cortex and nucleus of the lens, the amount of lactate formed would be greater than in tissue where this enzyme system is functioning to oxidize carbohydrate. The deficiency of lactate in the epithelium is taken to mean, therefore, that the respiratory enzyme system functions, at least in part, in the breakdown of carbohydrate.

The lens epithelium appears to have a strictly aerobic type of metabolism, and the cortex and nucleus seem to have a strictly anaerobic type. The rate of oxygen consumption by the epithelium is extremely high in comparison to most other

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tissues. Since by far the greater amount of energy derived from the breakdown of carbohydrate is obtained aerobically, the fundamental differences in metabolism in the various parts of the lens suggest that an important function of the epithelium may be to furnish energy for the maintenance of the entire lens. Presumably, the only oxygen available to the lens is that which is dissolved in the aqueous. Nature seems to have provided a highly efficient process for the utilization of this limited supply of oxygen and has located the factory close to the source of supply.

Tissue usually derives its energy from energy-rich phosphate bonds. When adenosine triphosphate (ATP) is broken down to adenosine diphosphate (ADP), the energy available in the phosphate bond can be used in the presence of suitable enzymes for protein synthesis. The lens consumes about 3 milligrams of glucose daily and if only the anaerobic glycolytic process were available, there would not be enough energy available to account for synthesis in the lens. Kinsey has shown that the supply of ATP is highly concentrated in the epithelium but falls off rapidly in the interior of the lens. Von Sallmann also found that radiophosphorus accumulated principally at the equator and in the surface layers of the cortex. ATP is not available in sufficient quantities within the interior of the lens to supply its energy requirements but phosphocreatine which acts as a storage house for high energy phosphate has a concentration gradient in the opposite direction, being more abundant in the cortex than in the epithelium. Just how the epithelium can transfer energy to the cortex and nucleus for protein metabolism has not been determined but Kinsey postulates some type of diffusion mechanism. He is continuing his studies on irradiated lenses.

It is tempting to postulate that the inactivation by ionizing radiation of the enzyme systems functioning in the epithelium might account for von Sallmann's observations concerning the inhibition of mitosis. Cellular division requires the production of large amounts of desoxyribonucleic acid (DNA), for example. Perhaps cellular division ceases temporarily because the epithelium can no longer supply the energy needed for synthesis. In vitro experiments indicate that it requires large doses of ionizing radiation to inactivate enzymes in aqueous solution but it has been shown in at least one case that when the enzyme is spread out as a thin layer on the substrate that surprisingly small doses of radiation can cause inactivation. X-rays are more efficient than heavily ionizing particles like proton recoils or alpha particles in inactivating enzymes in solution. Undoubtedly, several types of biologic damage may be occurring simultaneously when cells undergo irradiation but it would be interesting to know whether neutrons are as effective as x-rays in causing the inhibition of mitosis noted by von Sallmann. Enzyme inactivation by ionizing radiation is a reversible process or at least a process capable of repair with time, whereas nuclear damage like fragmentation or extrusion of Feulgen-positive material is regarded generally as a completely irreversible process. A comparison of the inhibition of mitotic activity and nuclear damage to the cell structure as a function of comparable doses of x-rays and neutrons might uncover interesting phenomena regarding the role of these radiations in producing biologic injury and might help to explain why the damage caused by neutrons is seemingly more irreversible than that caused by x-rays. It seems probable that high specific ion densities are more effective in producing nuclear damage of the irreversible type than low density ion tracks, it being postulated by some radiobiologists that more than 1 ion pair is needed within a given area to cause the effect. In the case of enzymes, however, it is believed that 1 ion pair is generally sufficient to inactivate the molecule. Certainly, the production of H and OH radicals in aqueous media must be operative in producing chemical changes in the capsule and epithelium as well as in the aqueous humour. The possibilities for further research on lens injury by ionizing radiation present a fertile field of investigation to the radiobiologist.

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Comments

Referring back to the status of knowledge in 1950 concerning radiation cataract, it can be seen that notable progress has been made, though many problems are still unresolved. Surveying the human cases such as atomic bomb victims, cyclotron victims, and victims of nuclear reactor accidents, it is apparent that 10 to 20 reps of fast neutrons must be regarded tentatively as a sufficient dose to induce lens opacities which might interfere with eyesight. Additional data are needed badly to determine the cataractogenic x-ray or gamma ray dose in humans; until such data are forthcoming, it seems wise to consider 500 roentgens of x-rays or gamma rays as potentially dangerous to the human lens.

Variation in susceptibility among species needs further exploration, especially among additional species like dogs and simians. In mice and rabbits, the cataractogenic dose level for x-rays lies somewhere between 100 and 250 r for acute exposures and the fast neutron dose level seems to be between 1 and 10 reps. There is insufficient data on chronic exposures to form any definite conclusions beyond the expectation that the RBE of x-rays vs fast neutrons will be found to exceed that for acute exposures by a considerable factor. The severity of lens damage and the latent period of development are inverse functions of both dose and age. The incidence of lens opacities does not seem to be a critical function of fast neutron energy. Thermal neutrons in acute doses are from 12 to 15 times more effective in producing visible opacities in mice than x-rays. Systemic effects as a contributing cause to radiation cataract have not been shown to be important; in fact, the evidence to date indicates that radiation cataract is primarily a lens phenomenon. Progress in neutron dosimetry, especially for mixed beams of neutrons and gamma rays, has been made but this instrumentation is not widely available to radiobiologists.

Cytological and biochemical research on the lens suggest strongly that the lens epithelium may be the initial site of biologic injury leading eventually to radiation cataract. Clinical observations and cytological data on cellular damage as a result of exposure to ionizing radiation have led to a better understanding of the pathogenesis of radiation cataract. It is postulated that the long latent period between exposure and the development of clinically observable abnormalities at the posterior pole of the lens is the consequence of the slow migration of injured cells from the equator to the posterior pole. Inhibition of cellular division and the occurrence of an overcompensating increase in the mitotic rate after recovery from inhibition have been demonstrated for epithelial cells of the lens in rabbits after exposure to large doses of x-rays; abnormal forms of cellular division and nuclear fragmentation were observable in the epithelial cells of these rabbits.

Metabolic studies on rabbit lenses cultured in vitro show that glutathione and protein are being continuously synthesized from their constituent amino acids. There is no conclusive evidence that initial changes in permeability of the lens or lens capsule immediately after irradiation are contributing factors to lens damage; changes in permeability do accompany the process of opacification. A respiratory enzyme system is active in the lens epithelium but not in the cortex. The lens epithelium appears to have a strictly aerobic type of metabolism, while the cortex and nucleus seem to have a strictly anaerobic type. It is proposed that one of the major functions of the lens epithelium may be to provide energy for metabolism in the cortex and nucleus. Inactivation of the enzyme systems in the epithelium after irradiation may be a contributing cause to mitotic inhibition.

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Gray, in a recent survey of radiobiology, has pointed out that "when all the information concerning mammalian generative tissues is considered, the remarkable fact emerges that the cells which go to form generative tissues, whether in animal or plant, adult or embryo, all require comparable doses of x-irradiation to damage them grossly when they are actively proliferating. It is noteworthy that all these tissues have in common the fact that they are more easily damaged by neutron radiation than by an equal dose of x or gamma radiation. The relative effectiveness of the two radiations is, in fact, much the same in the different tissues". It seems likely that the relative effects of neutrons and x-rays on the generative tissue of the lens, the epithelium, are also similar to the effects in other generative tissues but that, because of the unique structure of the lens, the toleration dose of ionizing radiation is smaller than in other tissues. When bone marrow, for example, is injured by radiation, the damaged cells may be sloughed off and after various metabolic changes, removed or excreted from the biologic system; eventually, the bone marrow recovers its biologic function if the dose of radiation is not overwhelming. The lens, on the other hand, appears to have a "memory" for cellular damage, so that cells which are abnormal but still viable, remain within the lens for life because of the lens capsule and eventually collect around the equator or posterior pole, where they attempt unsuccessfully to differentiate into normal lens fibers. This capacity of the lens to "store-up" damaged cells could account for its susceptibility to chronic doses of radiation. In a sense, it becomes a question of how many damaged cells the lens can tolerate before the clinical manifestation known as radiation cataract interferes with vision.

Both x-rays and neutrons cause nuclear damage to proliferating cells but most of the evidence available suggests that heavily ionizing particles are more efficient in producing nuclear damage than x-rays or gamma rays. On the other hand, there is some cause for believing that x-rays are especially efficient in inactivating enzymes and interfering with metabolic processes which are often reversible with time. In view of the above observations, it is not surprising that experiments have shown neutrons to be more effective in producing lens damage than x-rays.

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