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BIOELECTRIC SENSITIVITY TO IRRADIATION OF THE RETINA AND VISUAL PATHWAYS

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C. T. Gaffey and A. K. Kelley

September 9, 1963

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BIOELECTRIC SENSITIVITY TO IRRADIATION OF THE RETINA AND VISUAL PATHWAYS

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September 9, 1963

ABSTRACT

A study has been made of the acute effects of ionizing radiation on the visual pathways of the cat, as revealed by electrophysiological techniques. Irradiation sources were: 910 MeV alpha particles from the Lawrence Radiation Laboratory's 184-inch cyclotron, 40-MeV alpha particles from the Heavy Ion Linear Accelerator, and 250 kV x rays. Rotational procedures restricted irradiation to the eye, optic tract, or optic chiasma. The b-wave amplitude of the electroretinogram served as an index of the functional sensitivity of retinal cells to unilateral irradiation. Photically evolved responses from chronically implanted bipolar electrodes in the optic tract provided a quantitative means of evaluating the influence of unilateral optic-tract irradiation. Midline irradiation of the optic chiasma was performed, and blockage of interocular transfer was used as a measure of the effectiveness of irradiation. Ophthalmoscopic examinations were performed on irradiated cats.

Using 40-MeV and 910-MeV alpha particles, we carried out tests to determine if ionizing radiation effects the functional state of excitable systems in a manner analogous to electrical stimulation. Efforts were made to evoke with ionizing-radiation action potentials from frog sciatic nerve and internodal Nitella cells. Attempts were made to induce pupillodilation in the nucleus perifornicalis of the hypothalamus of cats, by means of focused ionizing, radiation.

INTRODUCTION

The relative importance of vision for vertebrate activity is disclosed by the fact that of all the nerve fibers that enter or leave the central nervous system, 38% are optic-tract fibers (Bruesch and Arey, 1942). The visual system is normally credited with being the most important channel for information about the world. According to Ackerman (1962) the rate of visual information entering the conscious part of the brain is 10^7 time the rate of auditory information. It is not surprising that vision has been investigated intensively and that there is now a large mass of significant data of visual perception and the influence of radiation on the receipt of visual information. However, the relative radiation sensitivity of the components of the visual system is still unknown. The purpose of this endeavor has been to study by electrophysiological techniques the acute effects of ionizing radiation on visual pathways.

A principal concern of this study was the harmful effects of x rays and cyclotron-accelerated α particles on the cat's retina, optic tract, and optic chiasma. Several studies have reported that high dosages of x rays decrease the amplitude of the b wave of the electroretinogram (ERG). Baily and Noell (1958) found that 6 000 to 8 000 rad of 100-kV x ray caused a reduction in rabbit's ERG to light stimuli. Most of the studies on the influence of irradiation deal with histological changes. Brown (1956) and Cibis and Brown (1955) studied the ocular pathology of γ radiation in monkeys. Cogan, Goff, and Graves (1952), Evans and Leinfelder (1954), Jacobson and Krohn (1961), and Moses, Linn, and Allen (1953) investigated the role of neutrons on the physiological changes of the eye. Hughes and Iliff (1946), Iliff (1947), Merriam (1955, 1956), and Von Sallman et al. (1955) reported the effects of β radiation on the eye. Von Sallman et al. (1955) described the effects of deuterons and α particles on the rabbit's lens.

The results of optic-tract irradiations in cats led us to test the hypothesis that there is a direct stimulation of excitable systems by ionizing radiation (Hug, 1960; Hunt and Kimeldorf, 1962). High-energy α particles have been used to see if this radiation acts in a manner analogous to electrical stimulation in the cat's pupillodilation center, the frog's sciatic nerve, and internodal Nitella cells.

METHODS

X Ray Irradiation of the Eye

Baily and Noell (1958) recognized the problem of the distribution of the absorbed dose when irradiating rabbits' eyes. In their x ray dosimetry they considered the influences of backscattering, bone structure, soft tissue, and the peculiar geometry of the eye. When possible, the method of solution of Baily and Noell (1958) has been applied to our studies of the cat. However, in our procedure there are specific differences that should be mentioned.

Before irradiation a lucite phantom of a cat's head was locked in a stereotaxic head holder (Lab-Tronics Instruments) and positioned under a circular opening (25.4 mm diameter) in a 63.5-mm iron shield. In the lucite phantom, a removable Victoreen r-meter (Glosser-Seitz, Model 70) was located at the estimated center of the eye and was placed in a hole drilled along the visual axis. A light beam that passed through the opening in the protective shielding facilitated the positioning of the probe. A Philips x ray machine, operating at 250 kV and 15 mA, and equipped with a one-mm aluminum filter, replaced the light beam. Dosimetry was carried out on the phantom, and exact positions were recorded. This operation was repeated after substituting for the lucite phantom in the head holder an ophthalmectomized cat with the Victoreen r-meter probe located in the center of the eye cavity. The extraorbital space was packed with cotton. Because of these preliminary steps, the phantom, empirically corrected to match the cat, could be used as a convenient reference in determining the absorbed dose in test animals. All the animals were anesthetized and immobilized in the stereotaxic head holder. The dose rate was 260 ± 10 r/min, and the beam passed perpendicularly to the visual axis of the cat. Irradiation of the cat was restricted to the 25.4-mm circular opening in the shielding that housed the cat. In pilot experiments one half of the head was exposed to irradiation, and the rest of the cat was shielded. This technique was eliminated in order to reduce to a minimum the volume of tissue being irradiated.

Alpha-Particle Irradiation of the Eye

The Lawrence Radiation Laboratory's 184-inch frequency-modulated cyclotron served as a source of high-energy α particles. The specifications of the beam particles from the synchrocyclotron have been summarized by Gaffey (1962). By appropriate magnetic focusing techniques, particles moving at 59% of the speed of light were made to travel in parallel, approximately monoenergetic beams. The maximum beam energy for α particles was 915 MeV. An ionization chamber placed in front of the experimental animal monitored the delivered dose (Birge et al., 1956). The α particles were generated with pulse averaging 500 μsec in duration, of 64 pulses/sec. In eye-irradiation experiments, the dose delivered was about 500 rad/min, whereas in optic-tract irradiations the dose rate was about 1 000 rad/min one rad is 100 ergs absorbed per gram of tissue).

An aluminum head holder that was designed to lock into the precision-machined alignment bench at the 184-inch cyclotron positioned the cat in the cyclotron beam (Welch and Tobias, 1961; Born et al., 1959). By micrometer screw-type adjustments of the alignment bench, one eye of the cat was placed in the center of the circular beam of α particles. The diameter of the beam was 25.4 mm, and its path was normal to the visual axis of the eye. The linear-energy transfer of the α particles was 15 MeV-cm^2 per gram (Born et al., 1959), and their range in aluminum was 7 in.

Ophthalmoscopic Examination

It was expected that ophthalmoscopic examination of the fundus of the cats irradiated in one eye with either x rays or α particles would reveal vasolabile characteristics associated with the time course of ERG changes.

The study of the retinal vessels started at the optic disc (papilla) from which arteries and veins issue and spread over the fundus or eye ground. The retinal artery was followed along its entire course to its disappearance at the periphery; then the arterioles and the terminal capillaries were examined. A venous study followed this same routine. Some of the circulatory disturbances looked for were vasospasms, focal constriction, occlusion, dilation, hemorrhage, exudates, and edema.

Alpha-Particle Irradiation of the Optic Tract

In optic-tract irradiations with cyclotron-produced α particles, the cat was immobilized in the same head holder and positioned with the same alignment bench described in the section on α particle irradiation of the eye. Previous to irradiation, bipolar electrodes were implanted in the optic tract and visual cortex of both left and right hemispheres. Using the tips of the bipolar electrodes as markers at which to aim, we aligned the cat by means of horizontal and vertical x rays so that the terminals of the implanted electrodes were at the focus of rotation in the center of the α-particle beam. A multiplane rotation technique (Tobias et al., 1952; Tobias et al., 1958) was used to irradiate a sphere 0.25 in. in diameter. The recording tips were in the approximate middle of this irradiated volume (Fig. 1). In actual practice an ellipsoid was the configuration resulting from the procedure, because only five rotational planes were employed.

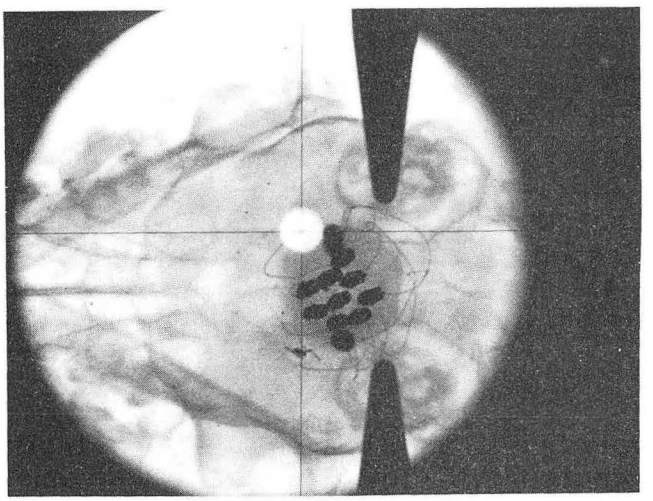
Alpha-Particle Irradiation of the Optic Chiasma

Transection of the optic chiasma in cats was attempted by passing a narrow beam of 910-MeV α particles through the midsagittal plane of the head. In the majority of the cases, the dimensions of the sectioning cyclotron beam were restricted to 0.5×25.4 mm (Fig. 2a); in later studies bisection of the optic chiasma was carried out with a cyclotron beam 2×10 mm (Fig. 2b). The head holder and alignment bench referred to previously were essential in this work. The most important landmarks for the alignment of the cat were the interaural line connecting the center of eadh external auditory meatus, and the center of the inferior orbital ridge. The sutures of the skull seen by the x ray served as secondary reference points in positioning the cat's head in the cyclotron beam. An α-particle dose rate of approximately 1 000 rad/min was used in these experiments.

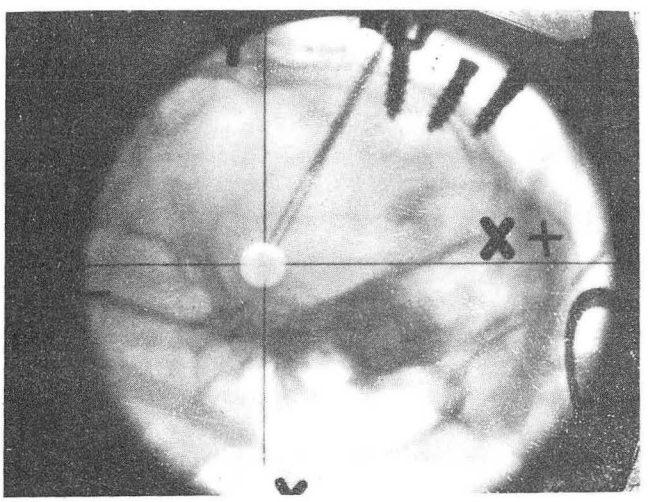
Electrophysiological Procedure

(a) Electroretinogram (ERG)

In ERG studies, cats were anesthetized by intraperitoneal injections of 20 to 30 mg/kg of Na pentobarbital in sterile water, and their pupils were dilated by administering to each eye 2 drops of 1% atropine sulfate in 0.5% methylcellulose. The cats were placed in a Lab-Tronics stereotaxic head holder within a dark, electrically shielded room. A photostimulator (Grass Model PS-2) triggered a flash of blue-white light (duration/flash = 10 μsec; the distance from the photolamp to the cat's eye was 10 inches. The data reported in this paper are concerned with the response to an intensity of 1.0 lumen-sec per ft^2, although intensities from 0.25 to 22 lumen-sec per ft^2 were used. The ERG was recorded on an eight-channel electroencephalogram



(a)

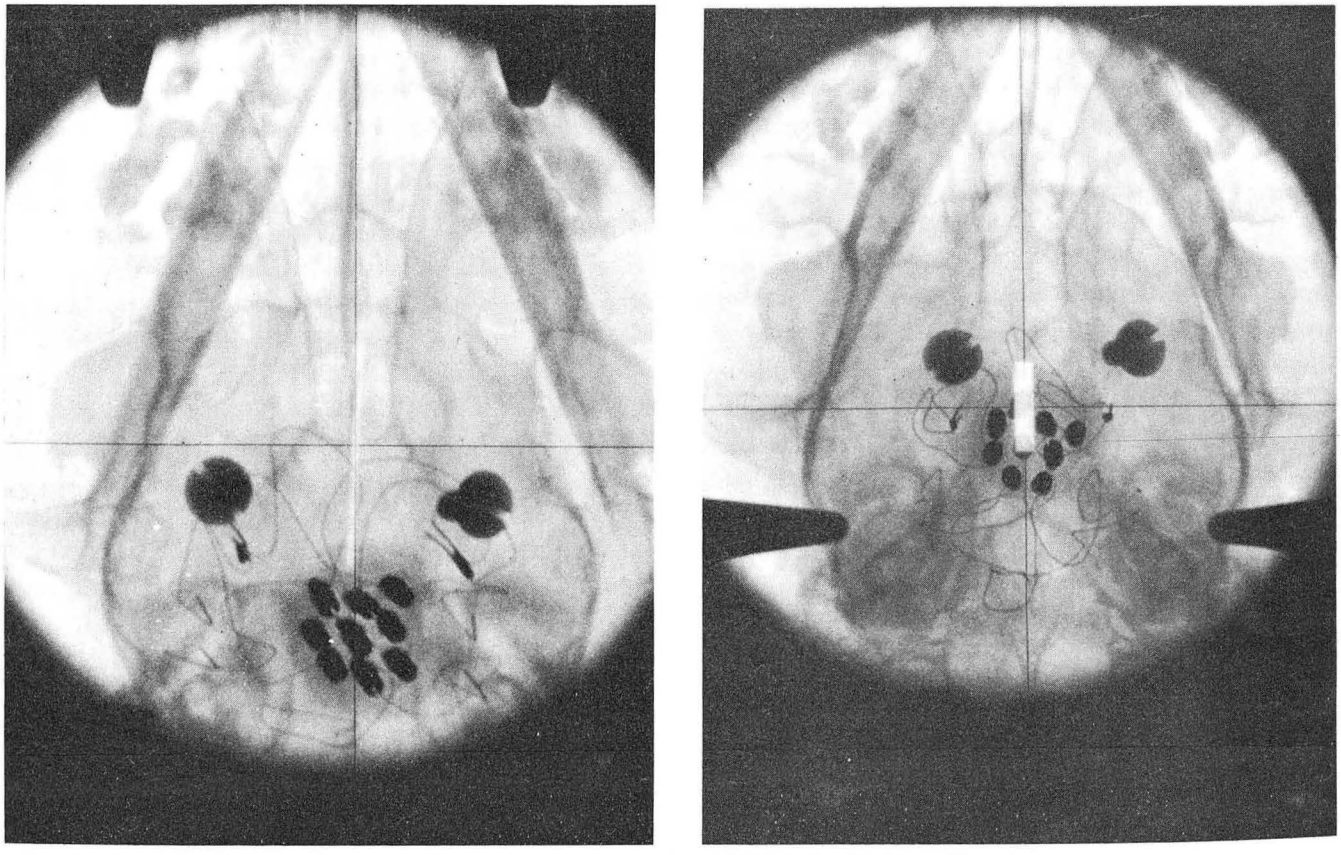


(b)

ZN-3985

Fig. 1a. Horizontal x-ray photograph of the dorsal view of a cat's head in the alignment procedure. A 1/4-in.-diameter 910-MeV α-particle beam is centered on the right optic-tract electrode.

Fig. 1b. Vertical x-ray photograph of a lateral view of a cat's head. Regardless of the angle of tilt, the tips of the optic-tract electrode remain at the focus of rotation of the high-energy α-particle beam.



(a) (b) ZN-3984

Fig. 2a. Horizontal x-ray photograph of a dorsal view of a cat's head. A 0.5×25.4-mm slit of 910-MeV α-particles is aligned along the midsagittal plane.

Fig. 2b. Horizontal x-ray photograph of a dorsal view of a cat's head. A 2.0×10.0-mm slit of high-energy particles is being adjusted along the midsagittal plane.

(Grass, Model III) by using the method of Groppel, Haass, and Kolrausch (1938) and Hairline (1925). The reference electrode was located in the scalp at the sagittal crest. In addition, the photic responses were produced by delivering the potential difference to a push-pull ac preamplifier (Grass, Model P-5), which then fed the signal into a Tektronix oscilloscope (Model 532) with a high-gain differential input amplifier (Tektronix type 53/53 D). The displaced potential differences were photographed with a Fairchild oscilloscope camera (Model F-286).

(b) Electroencephalogram

The Grass electroencephalograph was used to monitor the cortical electrical activity in cats studied for retinal sensitivity to irradiation by x rays and by 910-MeV α particles. Platinum alloy needle electrodes (Grass, E-2) were inserted intradermally, and bipolar and monopolar recordings were taken at symmetrical positions of the head. In monopolar recordings the reference electrode was located at the sagittal crest. The animals were anesthetized and fixed in a stereotaxic head holder, and the pupils were dilated with atropine prior to photic stimulation in the darkened, shielded room.

(c) Optic Tract

Contact with the optic tract (OT) was made by insertion of a bipolar needle electrode through a burr hole in the skull of an anesthetized cat, immobilized in a stereotaxic head holder. Accurate anatomical placement of the electrodes was achieved by using the coordinates detailed in the contributions of Jasper and Ajmone-Marsan (1958) and Snider and Niemer (1961). Bipolar needle electrodes were constructed of straight nichrome wire (0.226 mm o.d.) of which all but the 1 mm at the tip was insulated with Formvar. Twin wires were attached with varnish (Epoxylite 6001) to straight steel tubing that separated the wires by 2 mm and served as a mechanical support. During the implanation procedure (Hess, 1957; Horsley and Clarke 1908; Delgado, 1961) the cat was photically stimulated. The bipolar electrode was located where the optic-tract responses were maximal. Both left and right optic tracts were implanted, as were both sides of the visual cortex. The bipolar cortical electrodes were located on a strip along the marginal gyrus adjacent to the striate area, as this area yielded the highest evoked response to visual stimulation (Doty, 1958). The four optic-tract leads and the four visual-cortex leads were soldered to a nine-pin radio socket (Ampheno Corp.). A current lead from the sagittal crest served as a grounding electrode on the ninth socket pin. The current lead wires and socket were held securely by dental plastic (a mixture of Kadon resin powder and liquid methyl methacrylate monomer from the L. D. Caulk Company) anchored to the skull by stainless steel screw (Fig. 3). Control and postirradiation photically evoked OT recordings were obtained from the alert cat constrained in a Lawrence cat box. The pupils were dilated with two drops of 1% atropine sulfate. The photolamp-to-eye distance was 10 in. Mirrors were placed beside and directly above the cat's head. Both monopolar and bipolar recordings were taken under these conditions with an eight-channel electroencephalograph.

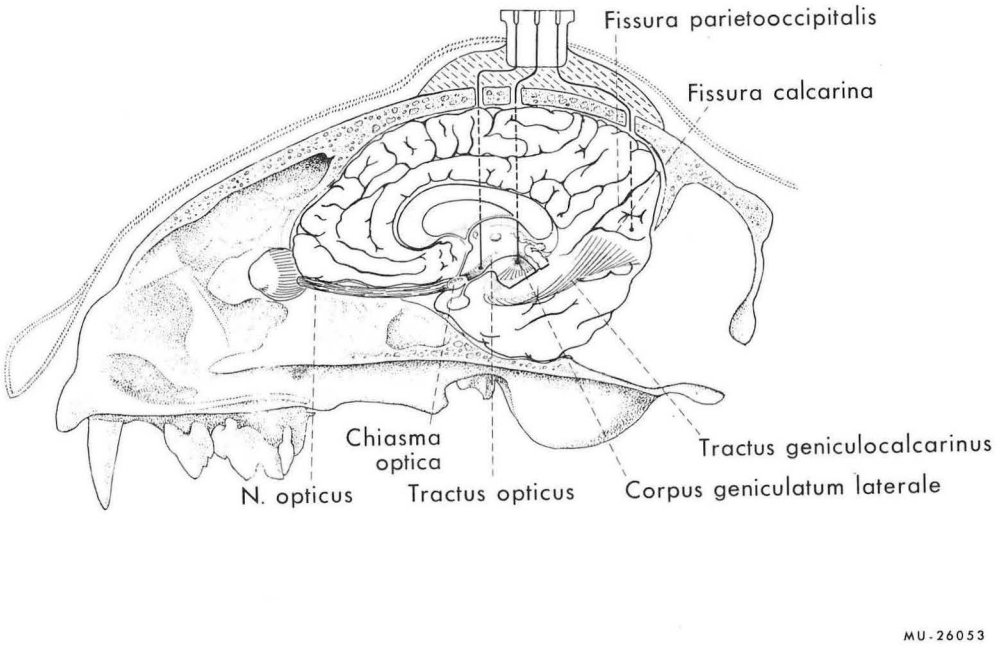


Fig. 3. Schematic diagram of a cat with electrode chronically implanted in some of the visual pathways.

(d) Optic Chiasma

Myers and Sperry (1953) have shown that following midsagittal division of the optic chiasma (OC), interocular transfer no longer occurred. This observation prompted us to try to produce chiasma-sectioned cats by means of a slit of 910-MeV α particles. Transecting the crossed retinal fibers at the optic chiasma would restrict the excitation from two separate eyes to the separate hemisphere through the preserved, uncrossed afferent pathways (Barris et al., 1935).

Electrophysiological techniques permitted indirect assaying of the efficiency of α particles in producing a functional midline bisection of the chiasma. Prior to irradiation, bipolar electrodes were implanted chronically in the left and right optic tracts. OT-evoked responses to photic stimulation were recorded after one eye was masked. If radiation proved successful in splitting the chiasma, only homolateral retinal stimulation would influence the amplitude of the optic tract discharge, as the contralateral retinal fibers would be blocked. In a chiasma-irradiated cat, if one eye is masked and the homolateral optic tract does not show a bioelectric response to photic stimulation from the contralateral eye, it may be assumed that optic chiasma irradiation was sufficient to block transmission.

RESULTS

ERG and X Rays

The potential difference evoked by a light stimulus and recorded as the ERG is an index of the functional state of the retinal cells (Noell and Baily, 1956; Baily and Noell, 1958; Noell, 1962). In this study the measurement of the amplitude of the b wave of the cat's ERG provided a quantitative means of evaluating irradiation damage.

In pilot experiments, 10 cats had one half of their heads irradiated in order to administer x rays to one eye. Figure 4 demonstrates a drastic reduction in the magnitude of the electrical retinal response to photoflashing in an eye exposed to 2 000 r. This attenuation of the ERG occurred within 15 minutes, the time the first postirradiation ERG could be recorded. The photically evoked electrical activity of the nonirradiated retina is normal. Electroencephalographic (EEG) activity recorded in the occipital and parietal areas reveals no alteration resulting from irradiation. In three of the cats the cortical activity from the parietal area showed high-voltage transients on the irradiated hemisphere (Fig. 5). In one cat the EEG in the parietal region of the irradiated side had a nonstable base line (Fig. 6).

The persistence of high-voltage transients in the resting EEG records was roughly related to the administered dose. These high-voltage irregularities were detected as much as 8 hours after irradiation with 1 200 r, and for about 24 hours after doses from 2 000 to 2 500 r. This transitory phenomenon was difficult to study as it was not common after all irradiations, and as considerable lengths of resting EEG records had to be procured in order to note its appearance. When the field of x rays was limited to a size 6% greater than the eye, these asymmetrical irregularities in the EEG no longer occurred.

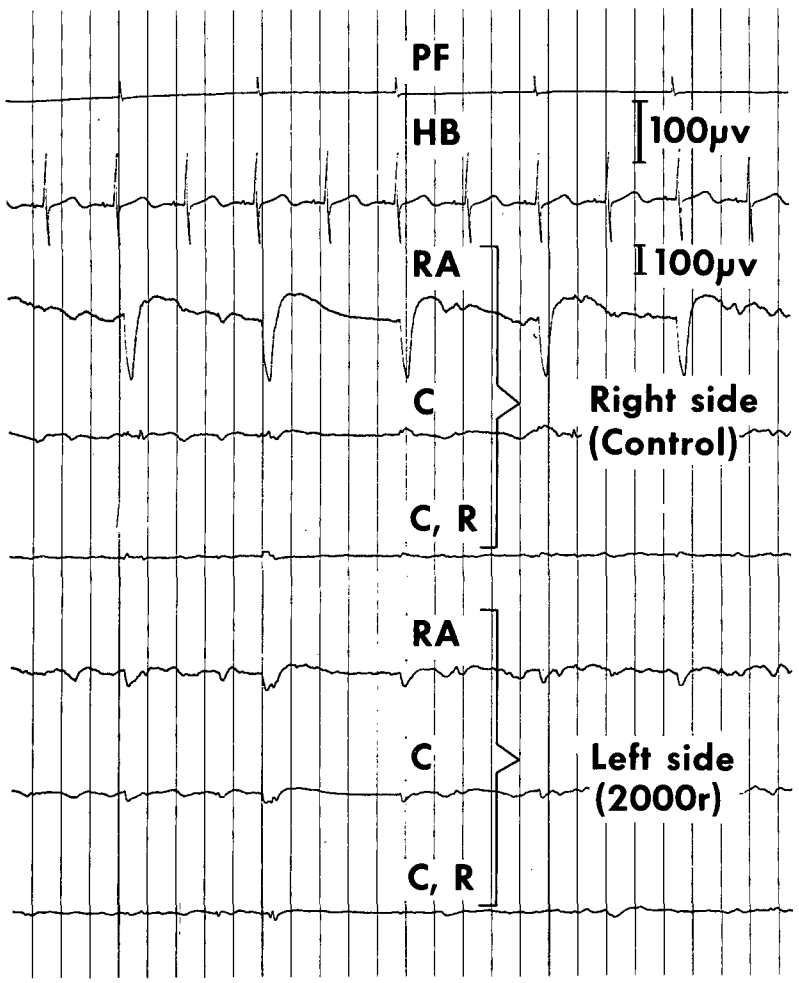


Fig. 4. Photoflashes (PF) are presented at the rate of 1 flash/sec to an anesthetized cat. The retinal activity (RA) of the eye exposed to 2,000 r of 250-kV x ray is drastically reduced, but the nonirradiated eye produces a normal response to light stimuli. The heart beat (HB) is regular, and the occipital activity (C) and parietal activity (C, R) are of low voltage. (Positivity is downward.)

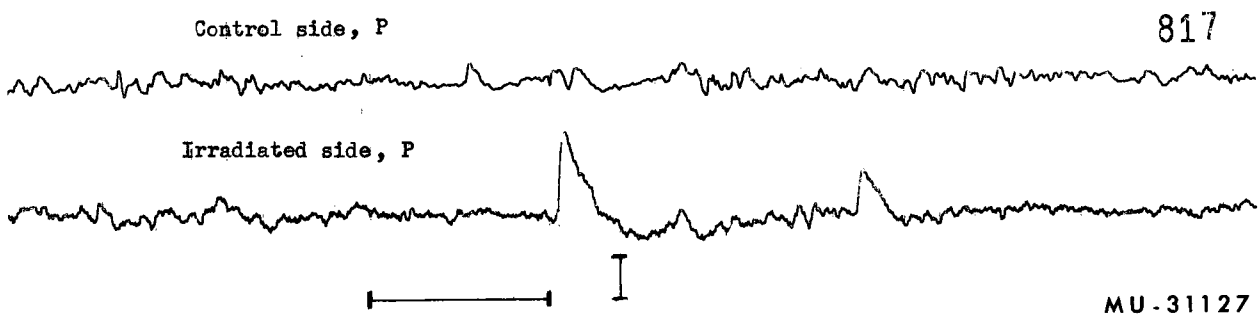


Fig. 5. Parietal activity (P) during a nonstimulating period. Irregular, high-voltage activity is confined to the side of the head that received 2,000 r x ray. The horizontal bar is 1 sec; the vertical bar is 100 μV.

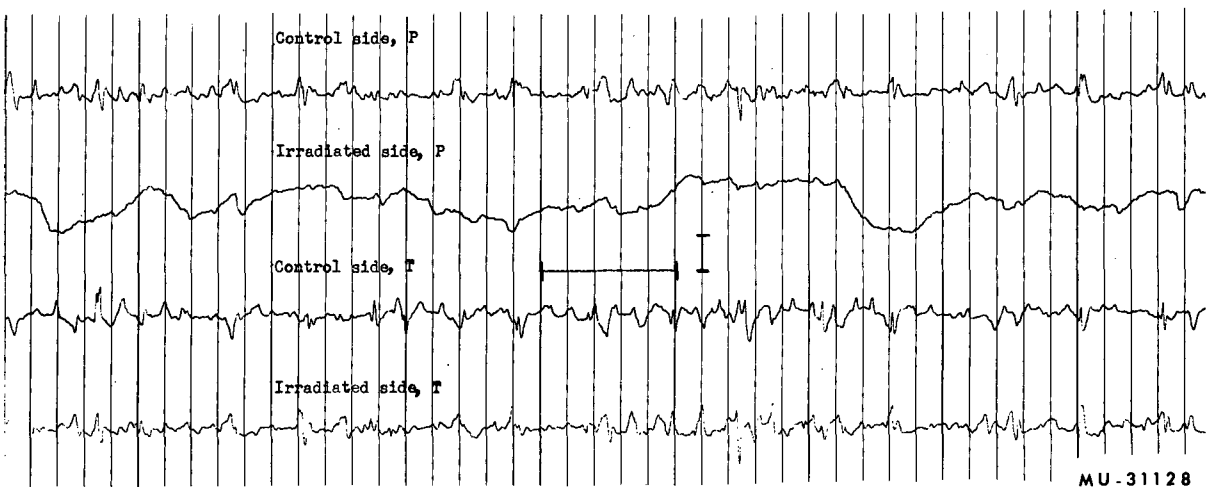


Fig. 6. Parietal activity (P) and temporal activity (T) during a resting period. A base line drift, not an artifact, is restricted to the parietal area of the irradiated hemisphere. The horizontal bar is 1 sec; the vertical bar is 100 μV.

Using a procedure that restricted x rays to a 25.4-mm circular beam, we irradiated one eye in each of 23 cats. Dosages from 600 to about 1 500 r produced for a period an ERG with a b wave larger than the pre-irradiation value. The maximum duration of the enhanced ERG occurred with doses near 1 200 r, but doses greater than 1 500 r produced no enhancement response. The enhanced phenomenon ultimately subsided, and an attenuated ERG was left. The biphasic action of irradiation is illustrated in Fig. 7. In this figure the time course of the b wave response ratio of the irradiated eye to the control eye is presented for a cat given 1 200 r. After a temporary enhancement phase, the response ratio was about 0.83. In another cat given the same dose, the steady-state b wave response ratio of the irradiated/control was 0.74 (Fig. 8). Hence, the b wave was reduced 17% in one case and 26% in a similar case. The exact cause for this variation is not known. Since the retinal cells are distributed over a section of a spheroid, differently positioned retinal cells receive varying doses of x rays. This variation in dose received, as well as anatomical and age differences, partially accounts for the variability of the radiation response. A 2% variation would be expected as a consequence of the accuracy limits of the dosimetry calibration. In Fig. 9 the steady-state values for the b wave irradiated/control response ratio are plotted as a function of the absorbed x ray dose. The dose-effect curve is clearly nonlinear.

ERG and High-Energy Alpha Particles

Six cats were irradiated in one eye with a 25.4-mm circular beam of 910-MeV α particles generated by the Lawrence Radiation Laboratory's 184-inch cyclotron. In Fig. 10 the steady-state amplitudes of the b-wave irradiated/control ratio are plotted as a function of the delivered dose. It appears that the effectiveness of x rays (Fig 9) and the effectiveness of α particles (Fig. 10) are approximately the same in blocking the ERG in the cat. The enhancement of the b-wave response with α-particle irradiation is not as prominent a feature as the enhancement induced by x irradiation.

Ophthalmoscopic Findings

The retina is unique in that it is the one part of the body in which blood vessels can be observed directly. It is known (Trevor-Roper, 1955) that closure of the central artery, which is the source of all retinal arteries appearing in the ophthalmoscopic field, can be accompanied by a sudden onset of irreversible blindness. The retinal arteries and veins of cats given x rays or α particles were carefully examined after ERG recording sessions.

Irradiation that inhibited the photically evoked ERG did not produce changes in any of the ophthalmoscopic signs investigated. After doses of 2 000 rad constriction of arterioles in the irradiated eye was followed by vein-diameter reduction to one third normal size. What is significant is that this vasoconstriction was not associated with the loss of evoked retinal activity because this change in the caliber of the retinal vessels occurred 6 to 10 hours after ERG criteria indicated blindness.

The external effects of eye irradiation were similar to the inflammatory response described by Cibis, Noell, and Eichel (1955), i.e., edema of the conjunctiva and lids, lacrimation, and lid closure. To prolong the period of observation the irradiated eye was cleaned and treated with antibiotics.

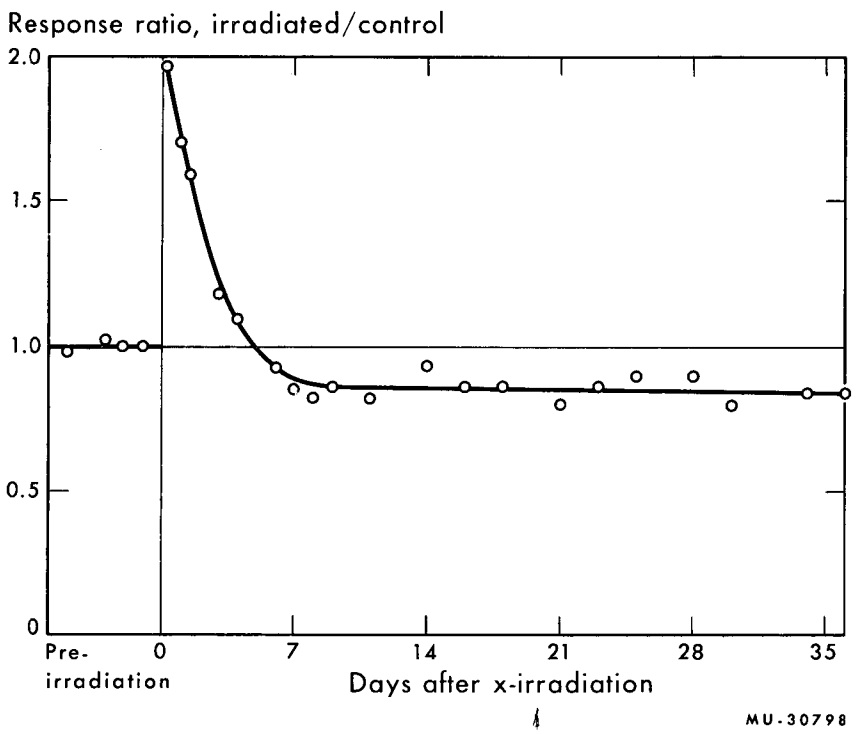


Fig. 7. The b-wave amplitude of the electroretinogram is plotted as the irradiated/control ratio against time. The irradiated eye received 1,200 r of 250-kV x ray.

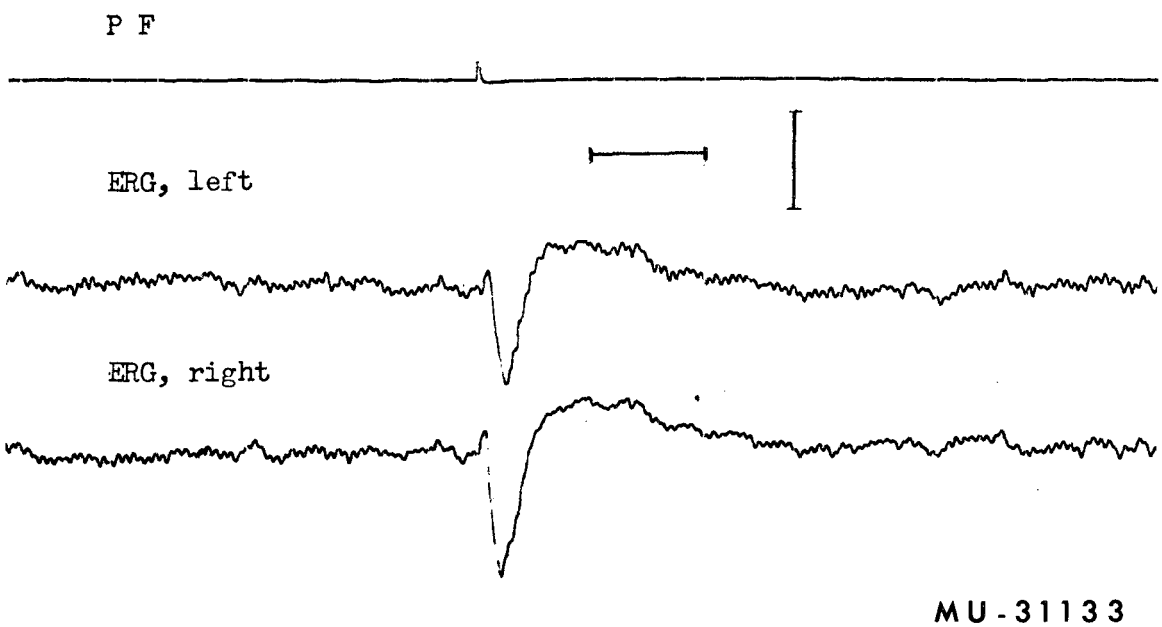


Fig. 8. Electroretinograms of the left (1,200 r of x ray) and right (control) eye of a cat. The photoflash (PF) trigger is given on a separate channel. The horizontal bar is 0.25 sec; the vertical bar is 200 μV. (Positivity is downward.)

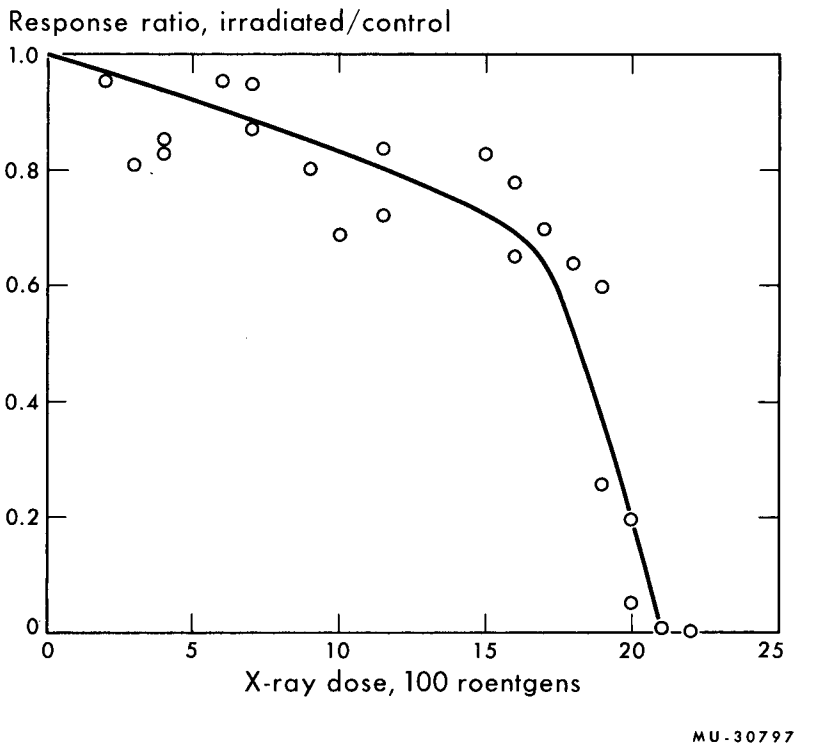


Fig. 9. ERG's b-wave irradiated/control response ratio is plotted against the x ray dose absorbed by the eye.

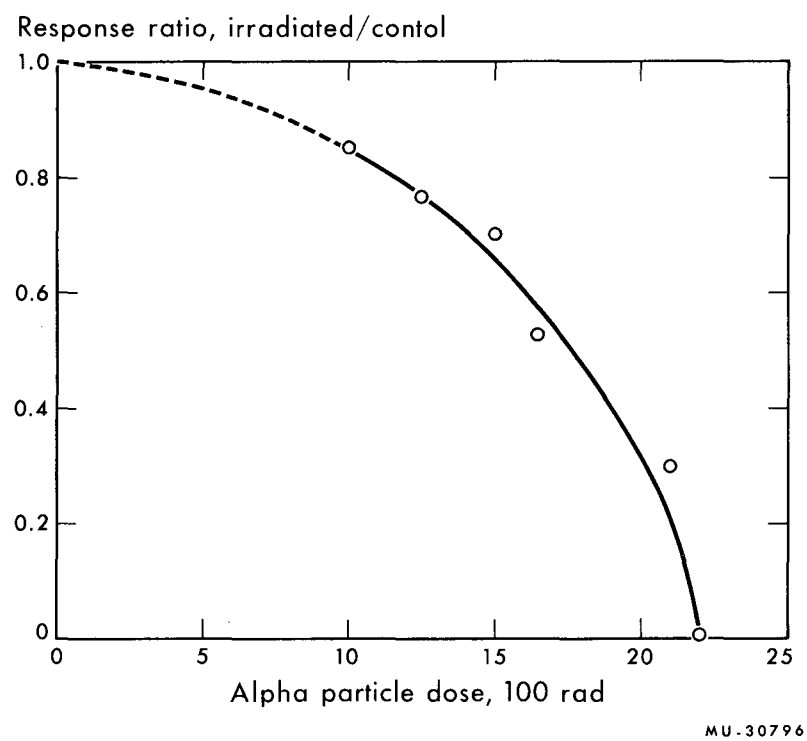


Fig. 10. The ERG's b-wave irradiated/control response ratio is plotted against the 910-MeV particle dose delivered to the eye.

Optic-Tract Irradiation

The radiosensitivity of the optic tract (OT) to 910-MeV α particles was investigated. Light-evoked bioelectric responses that were recorded from chronically implanted bipolar electrodes (Fig. 3) provided a means for evaluation effects of ionizing radiation. Monopolar and bipolar OT responses to photoflashing were studied (Fig. 11). In the majority of cases, bioelectric responses of the optic tract and visual cortex were recorded simultaneously. In other instances the optic tract, lateral geniculate nucleus, and visual cortex were monitored (Fig. 12).

The terminals of the OT bipolar electrodes in one hemisphere were irradiated with high-energy α particles. The tips of the electrodes were positioned at the focus of rotation in the center of a beam 1/4 in. in diameter (Fig. 1). The cat's head was rotated about this focal point in order to pile the radiation in a spherical volume. The photically evoked responses of the bombarded OT were compared with the OT responses in the nonirradiated hemisphere.

Unfortunately, the combination of α-particle ionizing irradiation and Nembutal anesthesia is hazardous to cats. A time-course study of irradiation effects in anesthetized cats was abandoned after the loss of nine cats.

Alert cats were used in studies of the time course for the abolition of the OT response to photoflashing. In Fig. 13 the irradiated/control ratio of the response to light stimuli is plotted against time after irradiation with 35 000 rad of 910-MeV α particles. A maximum enhancement is exhibited 44 h after irradiation. The results of 10 000 to 40 000 rad of high-energy α particles on seven alert cats are presented in Fig. 14. The survival time for the evoked response to light stimulation of the OT was within limits, a logarithmic function of the delivered dose. Extrapolation of the linear portion of this dose-survival curve for the OT is of special interest. It appears from Fig. 14 that to promptly block the OT's response to light stimulus would require a massive dose of irradiation, i.e., about 200 000 rads of 910-MeV α particles. Since this is 100 times the dose that blocks the ERG, it appears that the relative sensitivity of the retina to the optic tract is 100:1. A special effect caused by optic-tract irradiation will be treated separately.

Induced Pupillodilation during Alpha-Particle Irradiation

In testing the radiosensitivity of the optic tract of cats to 910-MeV α particles, we were surprised to find that the homolateral pupil was dilated maximally after radiation (Fig. 15), while the contralateral pupil (control side) was normal size. A multiple-plane rotation technique had been employed in irradiating the optic tract, and the expected volume of irradiated tissue was a spheroid 1/4 in. in diameter. This pupillodilation phenomenon seemed remarkable, as it occurred during irradiation and was evidenced at the termination of the delivered dose. Fixed far-vision and ophthalmoplegia accompanied permanent pupillodilation.

Attempts were made to reduce both pupils to the same diameter by using 0.5% isoptoeserine, but enlarged pupil was resistant to this agent.

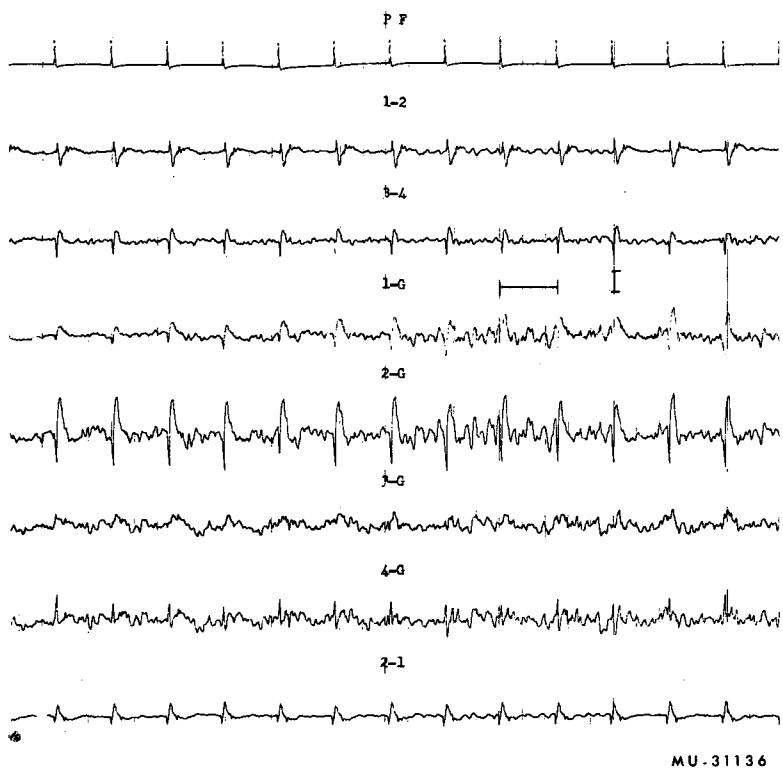


Fig. 11. Photoflashes (PF) are delivered to an alert cat at the rate of 1 flash/sec. Bipolar evoked responses to light stimuli in the left (1-2) and right (3-4) optic tracts are compared with monopolar responses. G is the indifferent electrode located in the sagittal crest. The horizontal bar is 1 sec; the vertical bar is 100 μV.

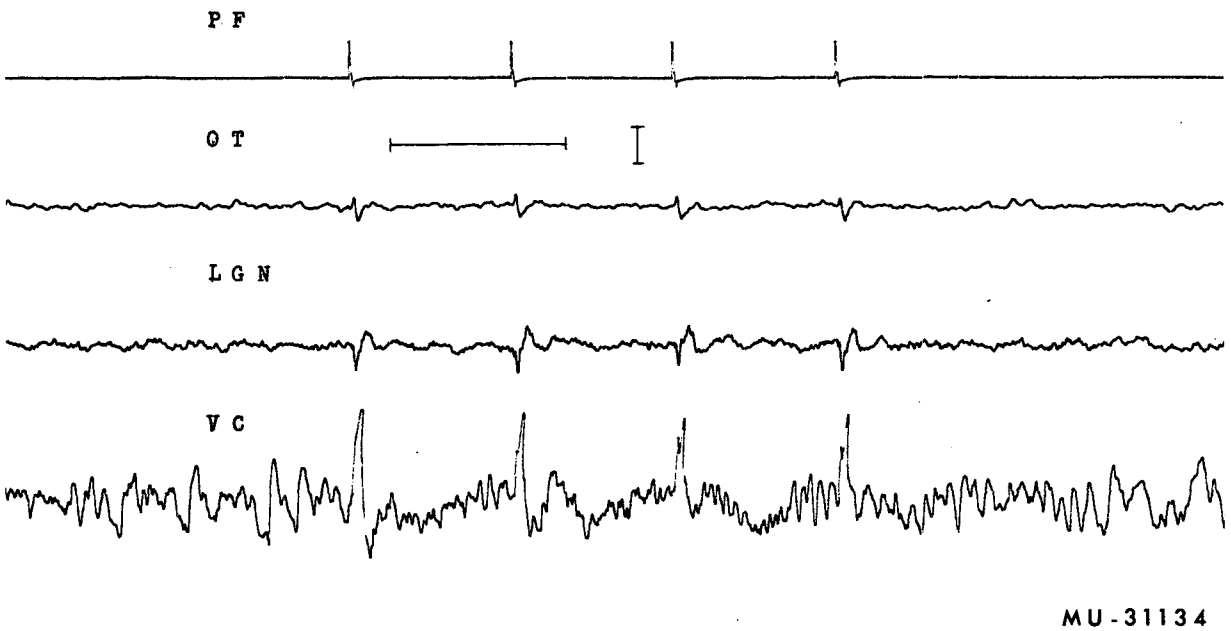


Fig. 12. Photoflashes (PF) are presented to an alert cat at the rate of 1 flash/sec. Bipolar responses to light stimuli are recorded from the optic tract (OT), the lateral geniculate nucleus (LGN), and the visual cortex (VC). The horizontal bar is 1 sec; the vertical bar is 100 μV.

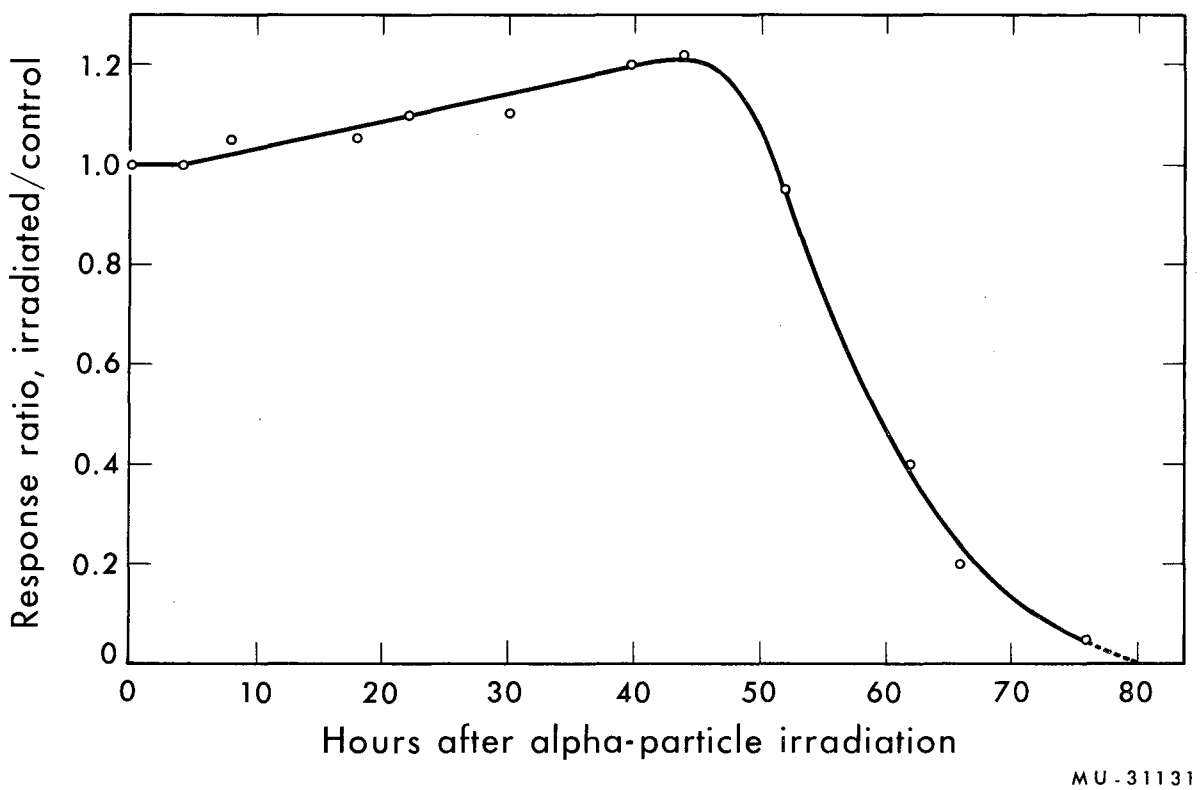


Fig. 13. The time course for the inhibition of the photically evoked response of the irradiated optic tract. The irradiated optic tract received 35,000 rad of 910 MeV α-particles. The ratio of the irradiated/control response to a light stimulus is plotted against postirradiation time.

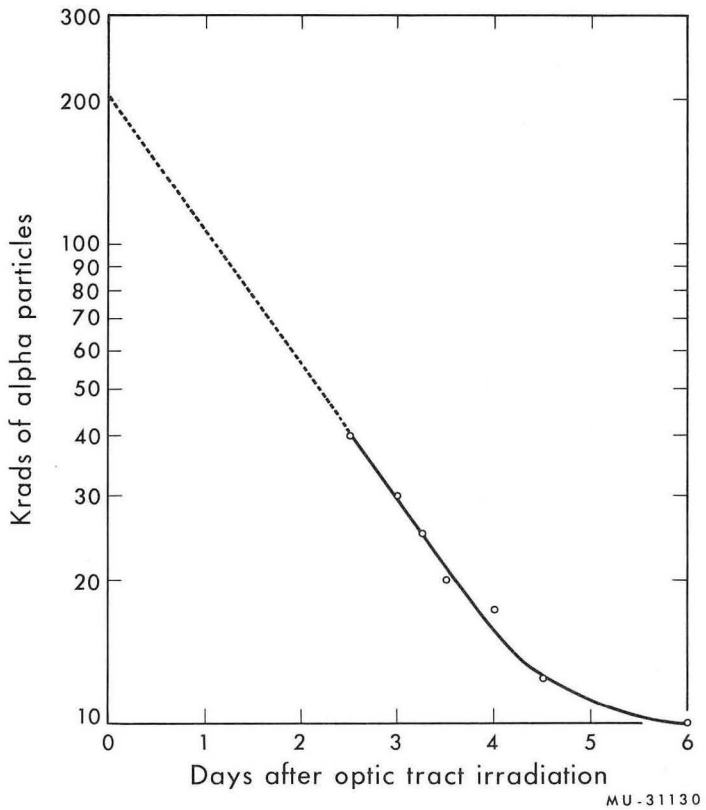


Fig. 14. The logarithm of the dose of irradiation (910 MeV α-particles) is plotted against survival time for the photically evoked response of the optic tract. A dose of 40,000 rads of high-energy α-particles inhibits the optic tract activity in 2-1/2 days.

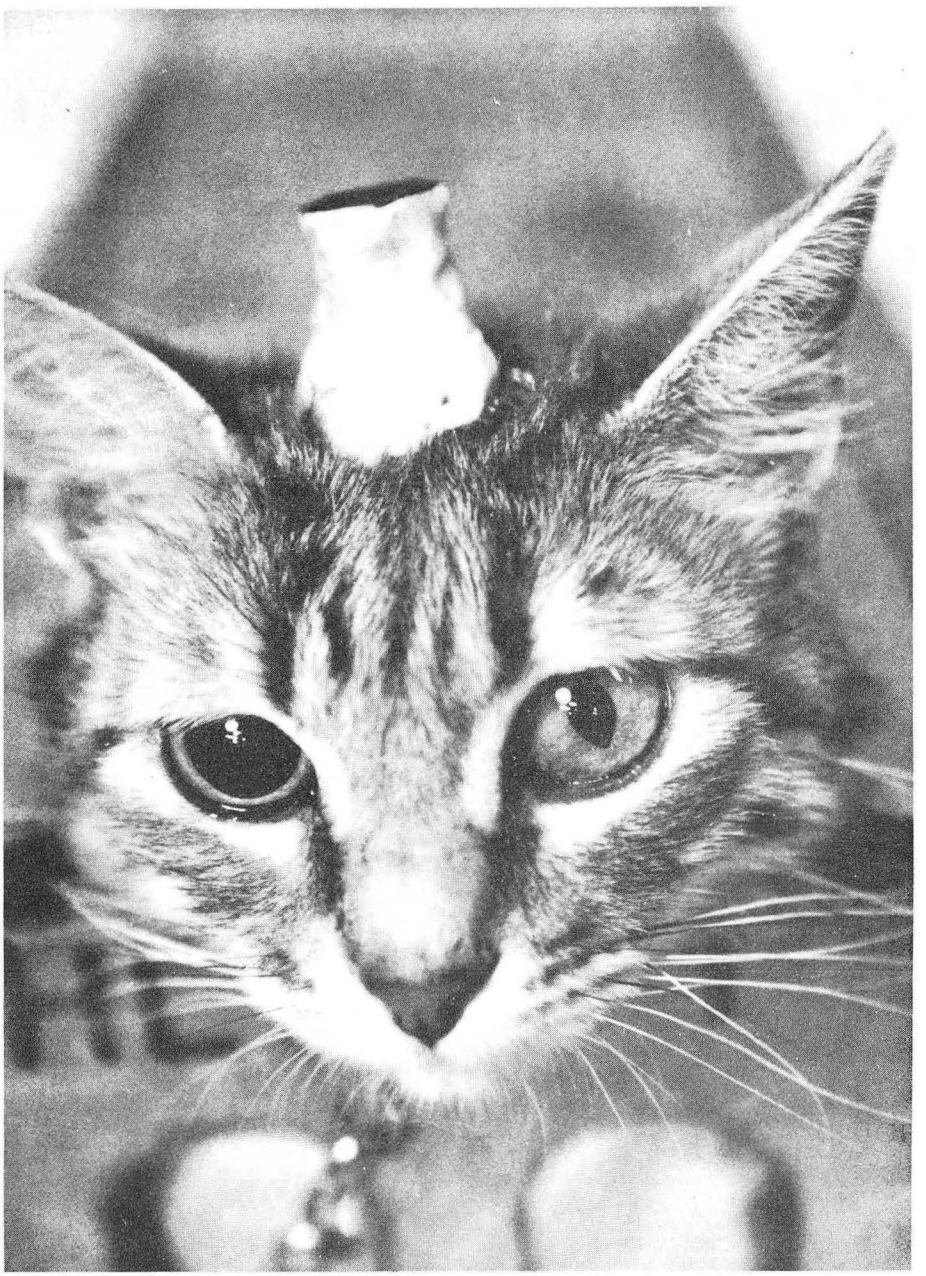


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Fig. 15. Photograph of a cat after receiving 15,000 rad of 910 MeV α-particles in an optic tract irradiation. Pupillodilation results from irradiation of the right optic tract.

A 1% isoptoatropine was effective in equalizing pupil diameters by dilating the pupil on the nonirradiated side to the size of the pupil on the irradiated side.

The minimum α-particle dose that produces pupillodilation is not known at this writing. Thus far a dose of 15 000 rad provides immediate pupillary dilation.

Experiments to Stimulate Directly the CNS, Peripheral Nerve, and Nitella Cells by Radiation

Optic irradiations suggest that α-particle ionizing radiation is capable of directly stimulating pupillodilation. One can hypothesize that the metal of the OT bipolar electrodes caused stray radiation by scattering the high-energy α-particle beam and that this stray radiation had an excitation effect in the pupillodilation center of the brain. This seemed unlikely because this center was 2.7 beam radii from the site of irradiation. Nevertheless, we tested the possibility of direct stimulation of the pupillodilation center with ionizing radiation.

Chronically implanted bipolar electrodes were stereotaxically placed in the pupillodilation center of the brain, i.e., in the region of the nucleus perifornicalis of the hypothalamus (Hess, 1957). The tips of the bipolar electrodes served as markers at which to aim the 910-MeV α particles. By a multiple-plane rotation procedure, irradiation was focused directly at the brain's pupillodilation center. Doses as high as 100 000 rad of high-energy α particles failed to evoke pupillodilation during or after irradiation.

Precautions were taken to place the bipolar electrodes most effectively. During implantation a Grass stimulator (Model S-4) delivered a biphasic pulse 1 msec in duration at 40 pps, and pupillodilation was immediately evoked. The electrode was placed at the location where the minimal current was required for dilation of the pupil. Although irradiation was not effective in directly stimulating the nervous system's pupillodilation center, it was effective in blocking the electrical current that would elicit pupillodilation. Immediate inhibition of electrical pupillodilation required 125 000 rad of α particles. Lesser doses also caused such inhibition, but the onset of this effect occurred at longer times after irradiation (Gaffey and Kelley, unpublished data).

A reexamination of factors that could be causing immediate pupillodilation during OT irradiation is needed. From anatomical considerations it would seem most probable that the oculomotor nerve (third cranial nerve) has been intercepted by the same spheroid volume that contains the OT bipolar electrodes. It is known that destruction of the oculomotor-inhibiting portion of the pupillodilation pathway causes immediate and permanent enlargement of the pupil (Langworthy, 1943). These are the characteristics of pupillodilation caused by high-energy α particles. However, this interpretation remains to be proven. It is safe to conclude that in the cat, irradiation of the nucleus perifornicalis does not stimulate the pupillodilation center in the central nervous system.

Experiments were done to determine if high-energy α particles could directly stimulate an action potential from the isolated frog sciatic nerve or an internodal Nitella cell. The procedure for recording action potentials of sciatic nerve can be found in Gaffey's (1962) report, and that for recording action potentials from giant plant cells in the report by Gaffey and Mullins (1958).

The 910-MeV α particles from the Lawrence Radiation Laboratory's 184-inch cyclotron and the 40-MeV α particles from the Berkeley heavy-ion linear accelerator (Hilac) have failed to trigger excitability in the frog's sciatic nerve and internodal Nitella cells. The characteristics of the Hilac have been presented in Tobias's paper (1962). The Hilac might be considered suitable for providing excitation because it can deliver single or multiple pulses of α particles, vary the duration of the pulse, and vary the dose per pulse up to 10^7 rad/pulse. Hilac parameters were varied as follows in tests to determine if radiation is analogous to electric current in exciting sciatic nerve: (a) the duration of the radiation pulse was lengthened as much as to 2.0 msec; (b) the dose was increased as high as 300 000 rad/pulse; (c) the range of the α particles in the nerve was adjusted for complete passage, 75 % passage, 50% passage, and 25% passage; (d) the length of the nerve exposed to irradiation was varied from 4 to 8 mm. None of these radiation characteristics or combinations of characteristics permitted stimulation of the sciatic nerve.

About 300 000 rad of 40-MeV α particles from the Hilac causes a conduction block. This is evidenced from the product of the number of pulses multiplied by the dose per pulse. For example, the following combinations of 40-MeV α particles induced a conduction block in the frog's sciatic nerve:

2 Hilac pulses (150 000 rad/pulse)
3 Hilac pulses (100 000 rad/pulse)
6 or 7 Hilac pulses (50 000 rad/pulse)

A dose of 300 000 rad would be expected to cause a rise in temperature of 0.72 ° C.

One-msec pulses of 40-MeV α particles consisting of 50 000 rad/pulse were sufficient to induce instant wilting in the plant cell Nitella. The only electrophysiological effect recordable was the irreversible mechanical collapse of the internodal cell. Thermal stress produced effects indistiguishable from high-energy α-particle irradiation.

Optic Chiasma Irradiation

Photically induced responses from the bipolar electrodes chronically implanted in the optic tract were recorded before and after optic chiasma (OC) irradiation with 910-MeV α particles. First one eye was masked, then the other, during photic stimulation. Seven cats received doses as high as 50 000 rad of α particles from the cyclotron's beam restricted to a 0.5 × 25.4-mm slit. In no instance was there a blockage at the chiasma of contralateral retinal light stimulation. The homolateral OT continued to show bioelectric responses to photic stimulation of the contralateral eye, and this indicates that functional transfer across the OC has not been interrupted.

Additional attempts were made on Four Cats to functionally bisect the OC with the cyclotron's beam limited to 2 × 10 mm. These dimensions proved sufficient to block interocular transfer across the OC. A dose of 20 000 rad of high-enerby α particles blocked crossed retinal fibers 36 h after irradiation (Fig. 16). The data from four experiments are scanty, and it would be dangerous to sugfest that the dose-response curve is a logarithmic function of the delivered dose. The dotted dose-response line in Fig. 16 is what one would expect to find if this were the case.

DISCUSSION

ERG Comments

The electronic current recorded as the ERG from the eye is a mass surface response that is often taken as an indication of retinal activity and retinal sensitivity. Evidence for the reliability of the ERG as an index of a functional retina has been given by Noell and Baily (1956) in their finding that the amplitudes of the a and b-waves of the rabbit's ERG are related to the number of visual cells affected by injurious agents. Noell, Eichel, and Cibis (1954), and Noell (1962) state that a quantitative evaluation of x-ray damage to the rabbit's retinal cells can be made by the electrophysiological technique of recording the ERG. In our study, focal eye exposure to x rays and high-energy α irradiation has been carried out, and the cat's ERG was used as an indicator of radiosensitivity. After x-ray doses ranging from 600 to 1 500 r, the b-wave amplitude of the ERG passed through a transient enhancement phase before being attenuated. Baily and Noell (1958) reported that the rabbit's ERG remained constant until a damaging dose was administered, and that then the b wave declined steadily. A dose of 4 428 rad of 250-kV x rays caused retinal cell death (ibid.). Noell, Eichel, and Cibis (1954) applied x rays to the orbital areas and whole heads of rabbits and noted the complete disappearance of the ERG 10 minutes after 29 040 r. Death of the entire visual cell population in the irradiated rabbit eye was evident histologically within 10 hours (ibid.). Our studies showed that a dose of 2 000 r of x rays eliminated the cat's ERG within 15 minutes after exposure. Cibis, Noell, and Eichel (1955) reported that the specific reaction within the retina after exposure to 2 000 r was irreversible damage to the rod-cell population. Primary damage to cone cells was observed at 30 000 r (ibid.). It was proposed that disappearance of the b-wave potential of the ERG was due to the selective neutral death of the rod cells at 2 000 r (ibid.).

The view that rods and cones of the retina are the source of the ERG (exluding the c wave) is quite untenable now (Brindley, 1960). It is reasonable to expect that ERG attenuation caused by irradiation should be related to the functional state of the cellular elements, the bipolar cells (Tomita, 1950; Ottoson and Svaelichin, 1953), generating the ERG. Histological evidence correlating the decline of the ERG b wave and radiation damage of bipolar cells is wanted. Noell, Eichel, and Cibis (1954) stated that damage to bipolar cells in one mammalian eye was caused by 35 000 r of 260 kV x rays.

Winter, Reinhardt, and Madden (1958) found no change in the retinas of cats exposed to 10 000 r of α irradiation, but after 20 000 r necrosis of rod

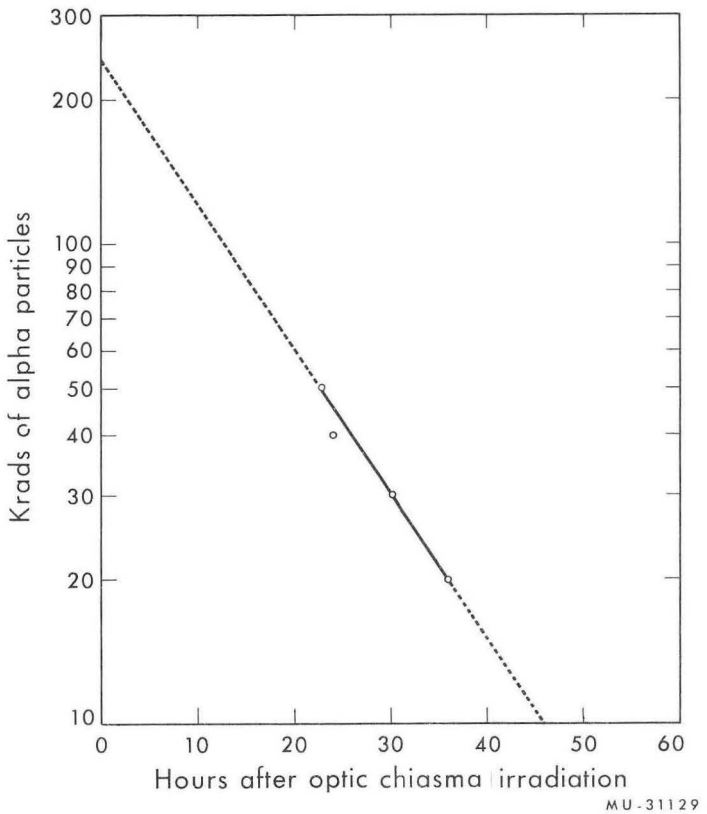

Fig. 16. The logarithm of the dose of irradiation (910 MeV α-particles) is plotted against survival time of the photically evoked response of the optic chiasma. A dose of 40,000 rads of high-energy particles inhibits optic chiasma activity in 24 hours.

and cone cells occurred. At this dose there was no difference in the susceptibility of rods to irradiation (ibid.). Cibis, Noell, and Eichel (1955) stated that the x ray threshold for rod degeneration in the rabbit was one-tenth that of the threshold in the cat. Winter, Reinhardt, and Madden (1958) fractioned the dose, and this procedure may account for some of the difference.

Ophthalmoscopic Comments

An ophthalmoscopic examination of the cat's eye showed constriction of the arterioles followed by venous constriction 6 to 10 h after administration of 2 000 r. Since the latency period for ERG inhibition was at the most 15 min in the eye exposed to 2 000 r, irradiation-induced vascular changes cannot account for the observed bioelectric changes. Detailed ophthalmoscopic changes in the irradiated eyes of the guinea pig, rabbit, rhesus monkey, and dog are described in the elegant paper of Cibis, Noell, and Eichel (1955). Ham (1953) has presented an extensive review of the radiation cataract, and Lucas (1962) has summarized the histological effects of irradiation on the immature mammalian retina.

Optic Tract Comments

After high-energy α-particle irradiation of the optic tract, the survival period of the photically evoked response was logarithmically related to doses greater than 12 500 rad. The dose-response curve of Fig. 14 shows that 200 000 rad of α particles would be required to promptly inhibit the optic tract's bioelectric response to light stimuli. Since the cat loses its ERG after 2 000 rad of α particles (Fig. 10), we concluded that the retina is 100 times as sensitive to irradiation as the optic tract. The optic tract and the optic chiasma (Fig. 16) are of similar sensitivity to irradiation; each requires about 200 000 rad of α particles for an immediate loss of activity. A study of the bioelectric effects of high-energy α particles on frog sciatic nerve (Gaffey, 1962) showed that the action potential was promptly inhibited after a dose of 300 000 rad. Hence, the radiation resistance of axonal fibers--such as those of the optic tract, the optic chiasma, and the sciatic nerve--appears to be extremely high. A membrane model, interpreting the molecular events occurring in axonal material after irradiation, has been offered (ibid.). The retina/optic-tract radiosensitivity ratio suggests a dendrite/axone radiosensitivity ratio of 100/1.

Optic Chiasma Comments

The axones of the ganglion cells of the retina are the fibers of the optic nerve. In the cat one-third of the fibers decussate at the optic chiasma (Glees, 1961). When the cat's crossed fibers are sectioned at the chiasma, the animal retains most of its visual field. However, stereoscopic overlap is eliminated, and each eye feeds impulses to its homolateral hemisphere (Sperry, 1962). Our experiments have demonstrated that midline radiosurgery of the optic chiasma can be performed by using a 2-mm-wide beam of high-energy α particles. The great advantage of radiosurgery in the central nervous system is that the risk of infection is eliminated. However, because the rate of lesion formation is a function of dose, there is an interval during which the nervous system adjusts to the development of the lesion. Lesions can be produced by heat, freezing, ultrasound, and chemicals, but immediate

stress to the central nervous system limits the usefulness of such procedure.

The relation between beamwidth and the threshold dose radiogenic brain lesions caused by cyclotron-accelerated particles has been reported by Zeman, Curtis, Gebhard, and Haymaker (1959); Zeman, Curtis, and Baker (1961); and Ordy, Barnes, Samorajski, Curtis, Wolin, and Zeman (1963). Although lesions can be induced readily with high-energy particles, attempts to functionally block crossed-fiber transmission at the optic chiasma (with a 0.5×25.4-mm slit of high-energy α particles were unsuccessful. Doses as high as 50 000 rad were employed, and even after 6 months there was no blockage of crossed-fiber impulse transmission. The observation that brain transection does not always block neural transmission is not new (Libet and Gerard, 1939). It is most likely that a 0.5-mm beam of α particles fails to interrupt communications because of the cable properties of the fibers. The distribution of current along the length of the fiber permits the passage of a signal through a damaged region, if the damage has been less than the fiber's length constant. As a 2×10-mm beam of 910-MeV α particles does induce a functional blockage, we can provisionally accept that the length constant of the optic chiasma fibers is between 0.5 and 2.0 mm. The length constant for the crab's nerve is 0.5 mm; that for a frog's sartorius muscle is 1 mm; and that for a frog's medullated nerve is 2 mm (Davson, 1954).

Pupillodilation Comments

Experiments presented in this paper have dealt with an immediate pupillodilation response to high-energy α-particle irradiation of the optic tract. Although it is most tempting to interpret this phenomenon as the result of direct stimulation of the sympathetic nerve supplying the dilator pupillae, our investigations have indicated that this hypothesis is not useful. The most probable explanation is that the parasympathetic fibers (oculomotor nerve) sending constrictor impulses to the pupil are blocked. Functional blockage of the oculomotor nerve is characterized by loss of the constrictor mechanism of the pupil, loss of all the voluntary movement of the eye innervated by this nerve, and paralysis of accommodation. These are the symptoms induced by irradiations with 910-MeV α particles in the region of the optic tract. It could be expected that the sphere of irradiations (1/4-in. diameter) containing the optic tract would also intercept the oculomotor nerve. What was not expected was the prompt effect on the oculomotor nerve.

Our opinion is that the oculomotor nerve is probably as resistant to irradiation as is the optic tract. What makes the oculomotor nerve so readily susceptible to ionizing radiation is its vascular relation. Aneurysmal dilation of the superior cerebellar, posterior cerebral, or posterior communicating artery could compress the oculomotor nerve (Peele, 1954), and this compression would produce pupillodilation, fixed far vision, and ophthalmoplegia.

Direct observation in animals has revealed that irradiation exposures on the order of 10 000 r are required to cause functional changes in vessel diameter and blood flow (Downing, Bishop, and Warren, 1940; Smith, Svihla, and Patt, 1951). Winter, Reinhardt, and Madden (1958) have shown that 100 to 800 r of γ rays dilate the uveal vessels. Thus far in our study we have observed that 15 000 rad of high-energy α particles causes pupillodilation.

It is the opinion of some scientists (Hug, 1960; Hug and Schleip, 1961; Garcia, Buchwald, Feder, and Koelling, 1962; Tobias, 1962, Hunt and Kimeldorf, 1962; Hunt and Kimeldorf, 1963; Smith, Kimeldorf, and Hunt, 1963) that the effect of ionizing radiation on the functional state of the nervous system is analogous to the effect of electrical stimulation. Hug (1960) has stated that if a minimum dose rate is achieved, radiation-induced reflect responses in lower animals and mammalian organs can be obtained. In contradiction to this we have found that it is not possible to stimulate directly with high-energy α particles an action potential in a frog's sciatic nerve or an internodel Nitella cell.

SUMMARY

(a) Using a procedure that restricted 250-kV x rays to a 25.4-mm circular beam, we irradiated one eye of the cat. Doses of 2 000 r promptly abolished the electroretinogram. There was attenuation of the b wave of the electroretinogram at doses less than 2 000 r. X ray dosages from 600 to about 1 500 r produced for a period an electroretinogram with a b wave larger than the preirradiated value. Enhancement of the b wave response with 910-MeV α particles was not a prominent feature. In other respects 910-MeV α-particle irradiation was similar to 250-kV x ray irradiation.

(b) An ophthalmoscopic examination revealed constriction of arterioles followed by a reduction in diameter of the retinal veins to 1/3 their normal size, after x ray doses of 2 000 r. This vasoconstriction was not associated with the loss of evoked retinal activity because this change in the caliber of the retinal vessels occurred 6 to 10 h after electroretinographic criteria indicated blindness.

(c) The radiosensitivity of the optic tract to 910-MeV α particles was studied. Light-evoked bioelectric responses that were recorded from chronically implanted bipolar electrodes provided a means for the evaluation of ionizing radiation effects. The survival time for the evoked response to light stimulation of the optic tract was within limits, a logarithmic function of the delivered dose.

(d) To promptly block the optic tract's responses to a light stimulus would require 200 000 rad of 910 MeV α particles. As this is 100 times the dose that blocks the electroretinogram, it appears that the sensitivity of the retina relative to the optic tract is 100:1.

(e) Midline radiosurgery of the optic chiasma has been performed with a 2 × 10-mm beam of 910 MeV α particles. When the cyclotron's high-energy beam was restricted to a 0.5×25.4-mm slit, the optic chiasma was not functionally bisected. We can accept provisionally that the length constant of the optic chiasma fibers is between 0.5 and 2.0 mm. The data suggest that the radiosensitivity of the optic chiasma fibers is a logarithmic function of the delivered dose.

(f) In testing the radiosensitivity of the optic tract to 910 MeV α particles, we noted that the homolateral pupil was dilated maximally after irradiation whereas the contralateral pupil (control side) was normal size. A multiple-plane rotation technique had been employed in irradiating the optic tract, and the expected volume of the irradiated tissue was a spheroid 1/4 in. in diameter. Pupillodilation occurred during irradiation and was evidenced at the termination of the delivered dose. Fixed far vision and ophthalmoplegia accompanied permanent pupillodilation.

(g) The pupillodilation center of the brain, the region of the nucleus periformicalis of the hypothalamus, was irradiated with a 1/4-in. circular beam of 910-MeV α particles. Although not effective in directly stimulating the nervous system's pupillodilation center, irradiation was effective in blocking electrically induced pupillodilation.

(h) It is the view of some scientists that the effects of ionizing radiation on the functional state of the nervous system is analogous to the effects of electrical stimulation. In contradiction to this opinion we have found that it is not possible to stimulate directly with 40-MeV and 910-MeV α particles an action potential in the frog's sciatic nerve or an internodal Nitella cell.

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