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# AEROMEDICAL REVIEW

## RETINAL CHANGES INDUCED BY HEAVY PARTICLES: A NEW THERAPY MODALITY?

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USAF SCHOOL OF AEROSPACE MEDICINE  
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NOTICES

This interim report was submitted by personnel of the Weapons Effects Branch, Radiobiology Division, USAF School of Aerospace Medicine, Aerospace Medical Division, AFSC, Brooks Air Force Base, Texas, under job order 1921E18A. The research reported in this paper was conducted by personnel of the Ophthalmology Service, Wilford Hall USAF Medical Center, Lackland AFB, Texas, and the Radiobiology Division, USAF School of Aerospace Medicine, Brooks AFB, Texas. This investigation was supported in part by funds from the National Aeronautics and Space Administration (NASA). Exposures were made in cooperation with Dr. C. A. Tobias and the Bevatron staff, University of California at Berkeley.

When U.S. Government drawings, specifications, or other data are used for any purpose other than a definitely related Government procurement operation, the Government thereby incurs no responsibility nor any obligation whatsoever; and the fact that the Government may have formulated, furnished, or in any way supplied the said drawings, specifications, or other data is not to be regarded by implication or otherwise, as in any manner licensing the holder or any other person or corporation, or conveying any rights or permission to manufacture, use, or sell any patented invention that may in any way be related thereto.

The animals involved in this study were procured, maintained, and used in accordance with the Animal Welfare Act of 1970 and the "Guide for the Care and Use of Laboratory Animals" prepared by the Institute of Laboratory Animal Resources - National Research Council.

This report has been reviewed by the Information Office (OI) and is releasable to the National Technical Information Service (NTIS). At NTIS, it will be available to the general public, including foreign nations.

This aeromedical review has been reviewed and is approved for publication.

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20. ABSTRACT (Continue on reverse side if necessary and identify by block number) <b>The effects of accelerated oxygen nuclei upon the retina of a nonhuman primate have been investigated. This simulated deep space radiation affords the possibility of delivering great quantities of energy (at a predetermined depth) within the eye, while but minimally irradiating interposing tissues. When compared with the clinical results following the use of cobalt plaques the oxygen ion has demonstrated a significant compression of both time and dose in achieving the same degree of tissue effect, i.e., RBE &gt;&gt; than 1. Therefore, the possibility obtains for a greater local irradiation of intraocular neoplasms with a sharp reduction of radiation damage to surrounding non-neoplastic ocular tissues.</b>		

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## PREFACE

The Retina Society at its annual meeting (October 1973) invited a verbal summary of heavy ion retinal irradiation and a discussion of possible clinical applications to ophthalmology. In the absence of published proceedings, the oral remarks of Dr. Hunter have been reproduced as verbatim as possible in this Aeromedical Review. Dr. Hunter was with the Ophthalmology Service, Wilford Hall USAF Medical Center, Lackland AFB, Texas at the time of this study. At the present time, he is with Ophthalmology Associates, 1005 Nix Professional Building, San Antonio, Texas 78205.

Since the audience was composed of practicing ophthalmologists, the review, though clinically relevant, was simplistic in the treatment of cyclotron source description, delivery technique, general nature of the oxygen ion generation, and physical dosimetry.

Work published after this discussion by other groups has shown that the application of particle irradiation as a possible means of treating eye tumors is a viable one. The specific case of heavy ion utilization for ocular neoplasia is, however, suggested here for the first time.

The assistance of Dr. C. A. Tobias, University of California at Berkeley, has been generously given throughout the planning and conduct of the radiation exposures. Dr. L. C. Kiplin, Wilford Hall USAF Medical Center, has kindly provided necessary staff, instrumentation, and moral support. The technical assistance of Sergeant Albert E. Cummings, Sergeant William Rankin, and Sergeant Guy Conley, of the Radiobiology Division, USAF School of Aerospace Medicine, was most essential.

## RETINAL CHANGES INDUCED BY HEAVY PARTICLES: A NEW THERAPY MODALITY?

## INTRODUCTION

Several aspects of space-oriented radiation research could lead toward the realm of the clinical ophthalmologist. An early prediction that man in space might be able to "see" cosmic rays (1) was given substance when the crew of Apollo 11 and subsequent Apollo crews reported having seen "flashes of light" (2-5). Since that report, the "phenomenon of the light flash" in humans has been reproduced at the Lawrence Radiation Laboratory, Berkeley, California (6).

With support from the National Aeronautics and Space Administration, and, in conjunction with the Radiobiology Division, USAF School of Aerospace Medicine, a research effort to provide an assessment of the quality and degree of biologic hazard associated with this type radiation was undertaken. The tissue exposed and evaluated was the retina of the Macaca mulatta, rhesus monkey. A second series of animals was exposed to x-rays so that a comparison of heavy particle effects with x-ray effects could be made.

The radiation to which the astronauts, as well as the experimental animals, were exposed was highly energetic accelerated particles, the nuclei of atoms stripped of their orbital electrons. In this particular series of experiments the particles were nuclei of oxygen atoms. [NOTE: An atom of oxygen is introduced into the system and stripped of its outer electrons, accelerated in a linear accelerator, further accelerated\* by a series of intense magnetic fields, and then beamed to the exposure area (exit port). As it is accelerated it, of course, gains energy and, as it penetrates matter, through the processes of ionization and excitation, energy is transferred to surrounding matter. It is this rate of energy loss, with its associated ionizations occurring at a controlled depth in tissue, that offers interesting possibilities for clinical ophthalmology.]

## RETINAL EXPOSURES

Rhesus monkeys were transported to the Lawrence Radiation Laboratory for retinal exposure to the oxygen nuclei. Evaluation of the interaction of oxygen nuclei with the retina was conducted by the use of fundus photographs and fluorescein angiograms. These procedures were instituted immediately before and after exposure and repeated at postexposure intervals of 24 hours, 1, 2, and 5 weeks. At each of these postexposure intervals a series of animals were euthanized and perfused. Their eyes were removed and prepared for light and electron microscopy.

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\*Acceleration of an atomic nucleus in a laboratory requires a physically large facility and represents in itself a recent technical breakthrough (7).

At the time of exposure, the primates were sedated with phenylcyclidine HCl, so that a catheter could be placed in a saphenous vein to administer both sodium phenobarbital for anesthesia and later fluorescein for the angiogram. A suture was placed into but not through the upper lid of the eye to be exposed, the left eye. Thus, the lid could be positioned over the cornea to prevent drying during the exposures. The axial distance of the primate eye and lid was determined by an A-scan ultrasonography unit and the measurement was used to position a water column located at the exit port of the exposure device. Both the water column and the fluid content of the eye served as a braking mechanism or absorber to slow the particles (extract energy) in such a manner as to deposit the remaining energy exactly in the retina.

The anesthetized animals were placed in a visual stereotaxic instrument, modified by mounting on a stand with three degrees of freedom. Three scales were incorporated into the stand so that the position of the animal in the stereotaxic instrument could be accurately determined. A Zeiss fundus camera was mounted in front of the stand. Following the pre-exposure photographs the stereotaxic instrument with the animal in place was lifted off the stand and placed on a second stand in the radiation exposure area. By using the data from the scales on the first stand a like position was set on the second stand so that the axis of the radiation beam coincided with the axis of the fundus camera. Thus the area photographed would indeed be the area exposed to radiation. Following exposure, the animal, still in the stereotaxic instrument, was returned to the first stand and realigned so that the area of the fundus first photographed and then irradiated could be viewed accurately for the immediate postexposure series of photographs.

To assess the difference (the Relative Biological Effectiveness) of particle irradiation and x-rays, a second series of animals were similarly prepared and exposed so as to deliver 4000 rads of 200 KVP x-irradiation to the retina.

Animals were perfused with gluteraldehyde utilizing the technique of Coogan and Morris (8) at 24 hours, 2 weeks, and 5 weeks; eyes were then removed and placed in buffer. The tissue was imbedded in Epon, cut, and stained with toluidine blue.

Fifty-seven animals were exposed over a range of  $1.3 \times 10^7$  to  $5.9 \times 10^8$  particles/cm<sup>2</sup> (p/cm<sup>2</sup>), or approximately 170-7600 rads (Table 1).

#### CLINICAL OBSERVATIONS

The fundus photograph and fluorescein angiogram in the rhesus monkey appear virtually identical to those seen in man (Fig. 1 A-D).

TABLE 1. EXPOSURE OF MACACA MULATTA  
TO ACCELERATED OXYGEN NUCLEI

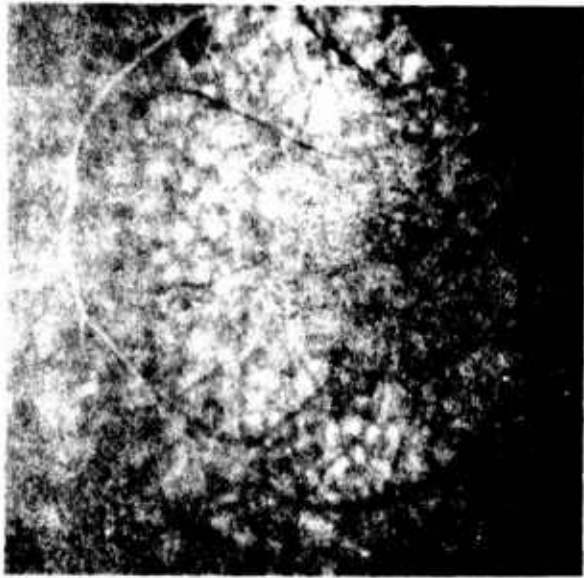
Number of animals	Number of particles/cm <sup>2</sup>	Retinal dose (rads)
14	$1.3 \times 10^7$	170
9	$3.9 \times 10^7$	500
3	$5.5 \times 10^7$	700
9	$7.7 \times 10^7$	1000
6	$1.5 \times 10^8$	2000
9	$2.3 \times 10^8$	3000
5	$3.1 \times 10^8$	4100
2	$5.9 \times 10^8$	7600

The earliest fundoscopic observation in the oxygen nuclei exposures was of small discrete retinal hemorrhages (Fig. 2). These were first seen 24 hours postexposure, at the lowest radiation dose of ~170 rads ( $\geq 1.3 \times 10^7$  p/cm<sup>2</sup>), as transient lesions with no definitive time relationship to the exposure. As the exposure level (dose) increased, the hemorrhages were seen with increasing frequency during the postexposure examinations.

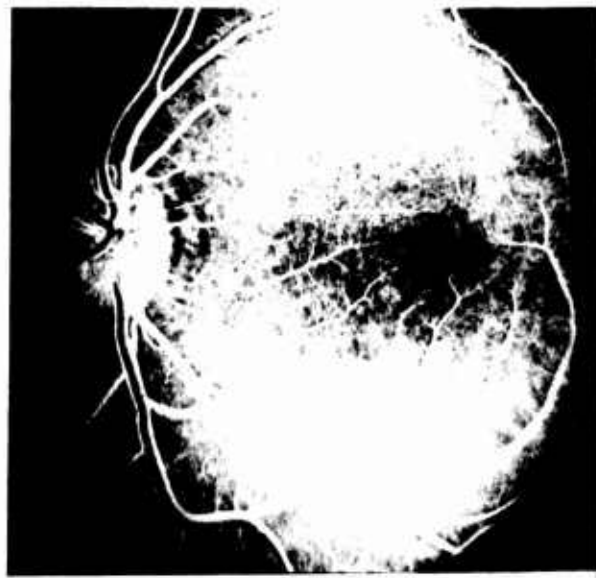
The earliest change occurring within a definite temporal relationship was the leakage of fluorescein, seen at the 24-hour postexposure levels at 1000 rads or more ( $\geq 7.7 \times 10^7$  p/cm<sup>2</sup>). The fundus photograph did not provide as much information about the degree of the retinal vascular change as did the fluorescein angiogram (Fig. 3 A-B). The leaks involve both the arterial and venous side of the circulation equally. Changes progressed over the next 7 days to a frank ischemic necrosis of the retinal tissue with development of multiple areas of hemorrhage, retinal edema, and a clinical appearance compatible with a cottonwool patch (Fig. 4). As the retinal edema subsided, the angiogram demonstrated marked destruction of the retinal capillary bed.

At the 2000-rad exposure level ( $1.5 \times 10^8$  p/cm<sup>2</sup>) the degree of fluorescein leakage seen at the 24-hour postexposure interval was increased. One animal showed a fundus lesion of ischemic necrosis at 24 hours rather than an initial phase of dye leakage. As the

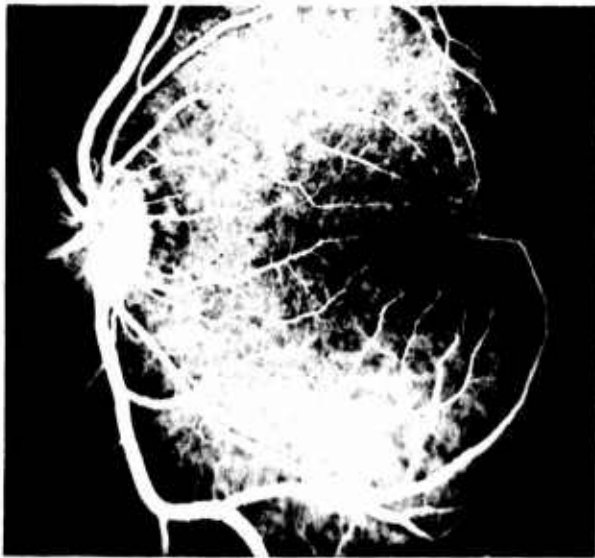
radiation dose increased ( $>1.5 \times 10^8$  p/cm<sup>2</sup>), the ischemic lesion appeared more frequently at 24 hours postexposure but was essentially the same lesion seen predominantly at the 1-week postexposure examination for the 1000- and 2000-rad exposures ( $7.7 \times 10^7$  p/cm<sup>2</sup> and  $1.5 \times 10^8$  p/cm<sup>2</sup>).



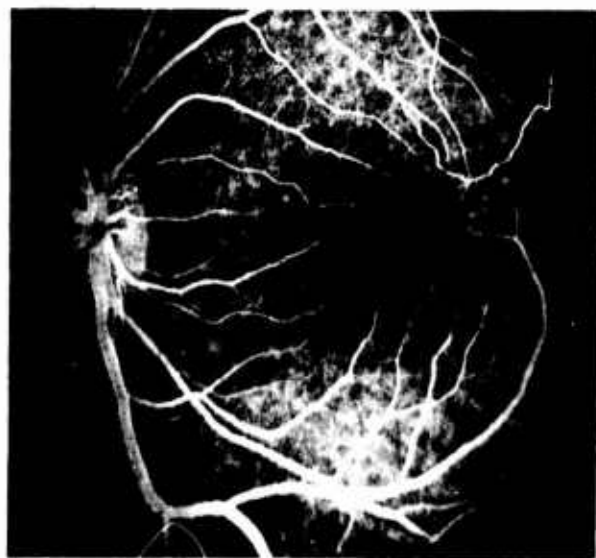
A. Choroid blush



B. Early arterial phase



C. Arteriovenous phase



D. Venous phase

Figure 1 A-D: Animal 214A; normal fundus angiogram of the Macaca mulatta.



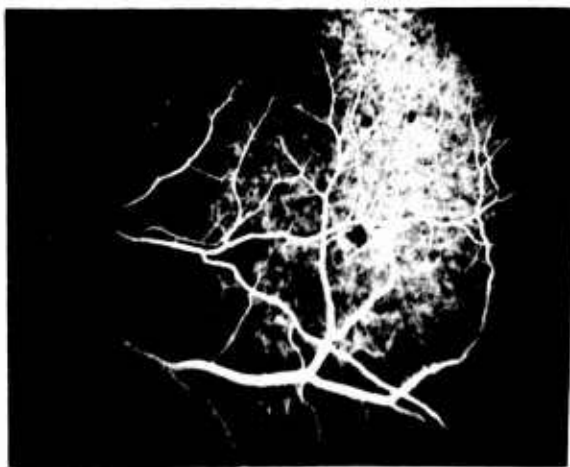
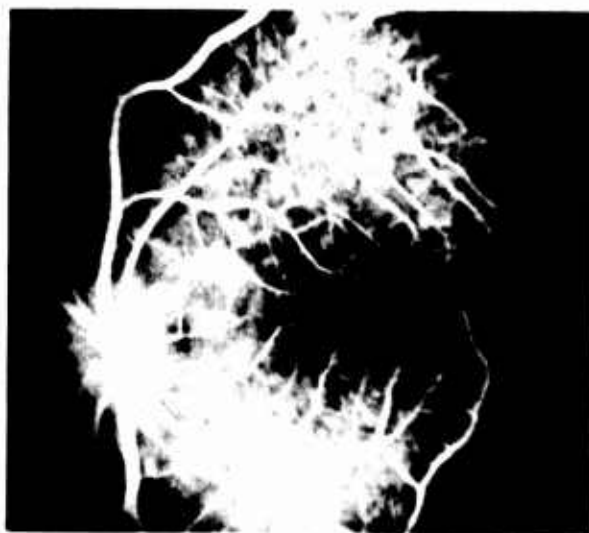


Figure 2: Animal 157A. Retinal hemorrhages present 24 hours following exposure to oxygen nuclei.



A. The fundus as it appeared 24 hours following exposure to  $7.7 \times 10^7$  particles/cm<sup>2</sup> ( $\sim 1000$  rads).



B. Angiographic study of the same fundus showing discrete leakage of dye.

Figure 3 A-B: Animal 111A. Comparison of a 24-hour postexposure fundus with the angiographic study.



Figure 4: Animal 374A. The fundus 1 week following an exposure to  $7.7 \times 10^7$  particles/cm<sup>2</sup> ( $\sim 1000$  rads). Development of a cotton-wool patch is evident.

Exposures of 3000 rads or greater ( $\geq 2.3 \times 10^8$  p/cm<sup>2</sup>) produced an ischemic lesion with hemorrhages visible at 24 hours. There was more damage to the underlying retinal pigment epithelium, choriocapillaris, and choroid at these higher radiation levels. Angiographically, the vasculature showed more diffuse leakage of fluorescein. The larger vessels, both arteries and veins, showed signs of permeability to fluorescein.

In the series of four animals with retinal exposures of 4000 rads of x-ray, there was marked damage to the anterior segment with no demonstrable retinal lesions developing within a 5-week postexposure time. The changes in this x-ray series were erythema and edema of the lids, conjunctivitis, and an iritis. A chronic purulent lacrimation was observed after the first week of exposure. Cloudiness of the vitreous developed at the 1-week postexposure interval. Damage was obviously much less than that produced by heavy ions.

## DISCUSSION

In these experiments, the slowing down and subsequent stopping of an oxygen nuclei takes place by the nuclei traveling through a water column placed at the exit port of the beam and then through the fluids of the eye. Thus the water column and the axial length of the eye serve as a braking mechanism. Variations in axial dimensions from one animal to another are compensated by making changes in the volume of the water column. The precise stopping of the particle with its subsequent energy release is the significant aspect of this radiation application.

A plot of energy vs. distance as a particle is stopped gives a quantitative relationship; such curves can be constructed for particles traversing different media and are known as Bragg curves (Fig. 5).

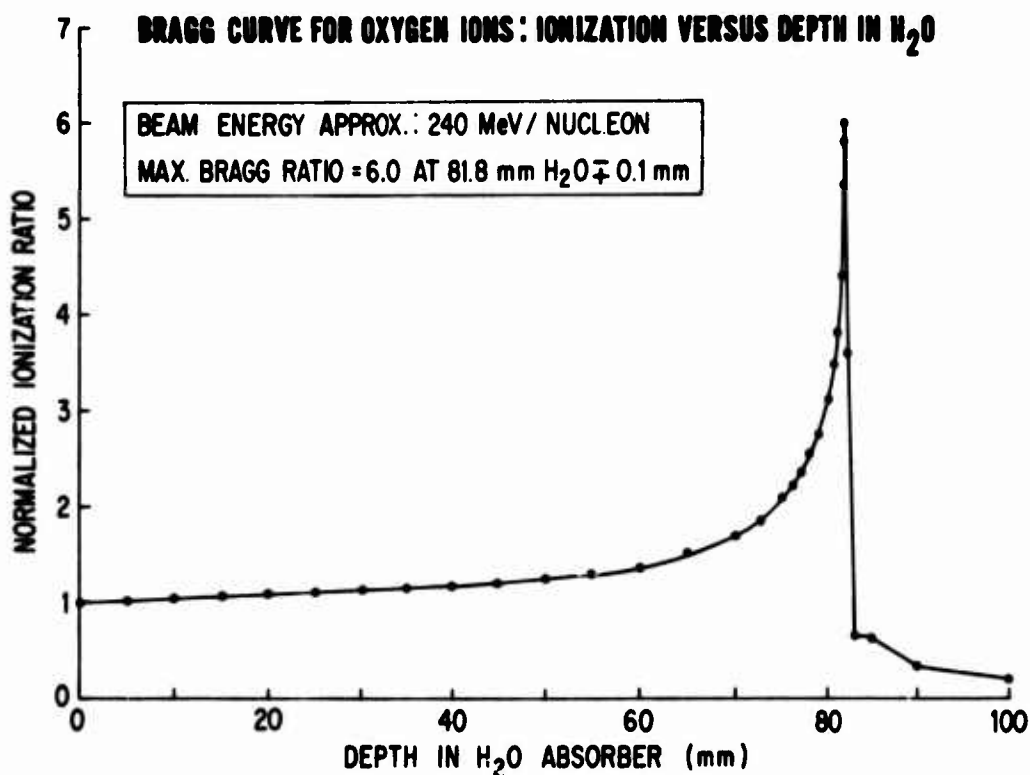


Figure 5: Bragg curve. The plateau of the curve represents the energy state of the particle as it is accelerated. The development of the peak and its sudden dropoff represents the slowing and stopping of the particle.

The energy peak is referred to as the Bragg peak. In this series of experiments the anterior segment of the eye was exposed to energies on the plateau of the Bragg curve while the retina was exposed to levels at the Bragg peak. The intraocular irradiation was thus greater than the radiation incident upon the eye. In Figure 6 the incident vs. retinal dose of x-irradiation is compared only in a qualitative manner with the irradiation profile from an accelerated particle.

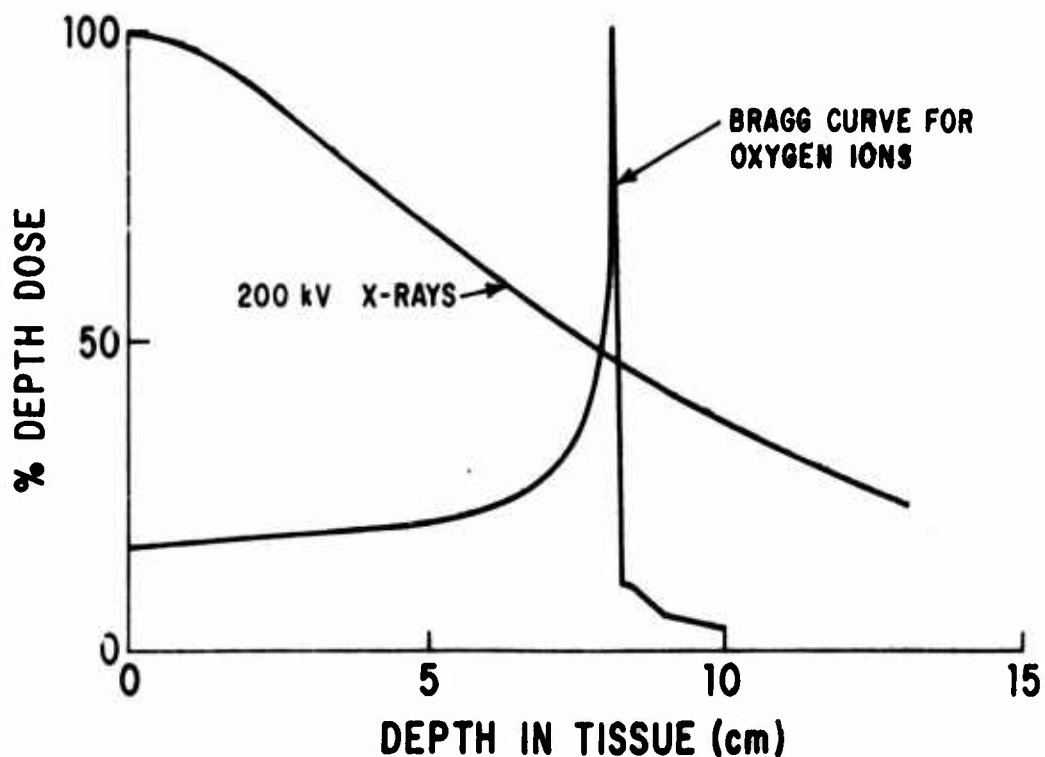


Figure 6: Comparison of x-ray and oxygen particle irradiation of a hypothetical neoplasia. The entrance or impinging dose of a gamma source will be higher than that desired at the site of the lesion under treatment. The accelerated particle, however, has a lower impinging energy than that delivered to the site of treatment.

As can be seen in this qualitative example, relative energy loss or the total ionization differs for the two sources. With the x-irradiation, ionization occurs uniformly through the eye, while the accelerated particle, as it is slowed down in the absorber media, has an increase in total ionization at the lesion site. The actual difference, as a result of ionization, is dramatically illustrated when a comparison is made

between animals actually exposed to the same retinal dosage in rads, i.e., 4100 rads. In the animal exposed to accelerated oxygen nuclei, there was no anterior segment change although a retinal lesion like that shown in Figure 4 was produced. The x-radiation produced edema, iritis, and clouding of the vitreous within 24 hours without a retinal lesion.

The nature of the lesions produced by the oxygen particles appears similar to the experimental and clinical radiation retinopathies which have been reported previously (9-15). These reports, as well as our own findings, indicate that the lesion is primarily a circulatory one, with other retinal changes being secondary. Retinal changes of the magnitude produced with the oxygen ions have been reported with the use of cobalt plaques sewn to the sclera in the treatment of intraocular tumors (9). Doses that led to such clinical changes, however, were 8 times that required with the accelerated particles and required months to develop rather than 1 day or 1 week. Thus, retinal lesions produced with accelerated oxygen particles exhibit a significant compression of time and dose over those reported in the clinical literature.

This study has demonstrated that the tissue effectiveness of the accelerated particle is far greater than that of any previously utilized irradiation source. The oxygen atom is only the beginning; with the introduction of the Bevalac at the Lawrence Radiation Laboratory, multiple ion sources of various atomic weights will be available in future years (6,7).

The radiation levels reported in this paper represent an "overkill" in the amount of radiation required for destruction of ocular tissue. With the development of a suitable particle source, and a collimated beam, these particles could become a clinically important therapeutic modality. By using B-scan ultrasonography and taking advantage of the relative energy absorption in tissue following heavy ion irradiation, one may have an effective radiation tool for treatment of choroidal melanomas and retinal blastomas.

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