Experimental ocular irradiation with accelerated protons*

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High-energy proton beams of 7 mm. diameter or less were used to irradiate monkey eyes. When the Bragg peak was positioned immediately in front of the retina, it was possible to apply an acute radiation burn to a discrete area of the retina and choroid while delivering much smaller doses to other ocular and orbital tissues. The minimal scatter, finite penetration, and advantageous dose-distribution curve for soft tissues make this mode of radiotherapy very attractive for the treatment of ocular and orbital tumors.

Key words: irradiation, retina, protons, Bragg peak, dosimetry, stereotaxis, cyclotron.

External beam irradiation utilizing photons has been successfully employed in the treatment of retinoblastoma, since many of these tumors respond well to relatively small doses of radiation. Even at these doses, however, a variety of ocular and orbital complications have been reported. Because the dosage delivered falls off only exponentially with penetration, external photon beams deliver excessive doses to normal tissues beyond the ocular target. Photon beams from modern supervoltage x-ray machines produce less scattered radiation than orthovoltage equipment, but still do not allow very large doses to be delivered to small intraocular targets. In order to avoid the problem of affecting tissues beyond the target, electron beams have been used, but excessive scatter limits their usefulness for targets as small as the eye. Another limitation inherent in both photon and electron ocular radiotherapy at present is the lack of precise aiming techniques for small targets.

The development of cyclotrons, which can produce beams of high-energy, heavy, charged particles, has provided another possible approach to localized irradiation. Such beams consist of high-energy protons, deuterons, or alpha particles and are not subject to significant scatter. Thus, they can be collimated into narrow beams which retain their shape while penetrating to a target. They have a well-defined range in tissues, and no radiation is delivered beyond their stopping point. Furthermore, the density of ionization along the particle's path through tissue is almost inversely
proportional to the energy of the particle, resulting in a characteristic maximum dose near the end of the path, called the Bragg peak. Tissue effects are thus much more pronounced in the last few millimeters of the path of the beam. Finally, the concentration of energy transfer to tissues located at the Bragg peak may result in greater relative biologic effectiveness than X- or gamma-rays of comparable dose. These characteristics make heavy particle irradiation especially suitable for focusing large doses on small targets.

During the past decade, the Bragg peak effect has been utilized to apply necrotizing doses to the pituitary gland. This method has proved to be an acceptable form of therapy in acromegaly and Cushing's disease.

This paper describes the technique we are developing for irradiating discrete areas of the posterior segment of the eye, utilizing high-energy protons generated by the 160 MeV Harvard cyclotron.

Materials and methods

Proton beam generation and collimation. Hydrogen atoms are bombarded in the cyclotron with electrons, converting them to hydrogen ions (protons). The protons are then accelerated by electric fields while being guided in stable orbits by a magnetic field. The high-energy particles are channeled off at a tangent, using subsidiary magnetic forces.

The proton beam is directed along an evacuated pipe by magnetic lenses, and out of the cyclotron chamber into a treatment area. Here the beam passes through a large cylindrical collimator (Fig. 1). Within the collimator, the protons pass through polystyrene slabs (P), which reduce their capacity to penetrate and scatter them so that a uniform beam passes through aperture A. The beam then passes through an ionization chamber (I), which monitors the dose during treatment. The diameter and angular divergence of the final beam emitted is determined by the aperture (D) in the extension column.

Preliminary beam alignment and dosimetry. Prior to irradiation of an animal, the axial alignment of the beam is checked by irradiating photographic film which is placed in the position of the ocular target. A small silicone diode is then placed on the end of the extension column to map the dose distribution of the beam in a water-filled phantom.

This diode is calibrated against the ionization chamber (I) used to monitor dosage during treatment. Absolute calibration of the diode is made against a Faraday cup which measures the proton beam in a standardized geometry.

Once the dose-distribution of the beam in water has been located in space, the collimator is adjusted so that the plane of the Bragg peak will coincide with the vertical axis of rotation of the stereotactic apparatus.

Preparation of animals. Young owl monkeys (350 to 600 grams) have been selected for these experiments. The animals are anesthetized with pentobarbital sodium (30 mg. per kilogram). The pupils are dilated with phenylephrine 10 per cent and scopolamine 0.3 per cent.

Alignment of the ocular target. The monkey's head is fixed in a metal frame (Fig. 2, H) which is suspended from an overhead circular metal plate around which the frame can be accurately rotated to a tenth of a degree. The design of the head-holder incorporates screw-motion slide assemblies and Vernier scales to allow accurate adjustment of the head in the horizontal, vertical, and antero-posterior directions. After approximate visual align-
Fig. 3. Posteroanterior radiograph with markers (M) on head-holder aligned with right orbit of monkey.

Fig. 4. Lateral radiograph with circular test beam superimposed on orbits. The center of the beam spot measured 5.5 mm. anterior to the posterior orbital wall, and 5.5 mm. superior to the junction of the posterior wall with the orbital floor and base of the skull.

Fig. 5. Anesthetized monkey in position ready for treatment. A latex diaphragm on the end of the water-filled extension column (X) is in direct contact with the eye.

ment of the target, accurate alignment is achieved by stereotactic radiography. The radiographic equipment is precisely aligned with the path of the beam from the collimator, being mounted behind the animal to the same overhead apparatus (Fig. 2, X). An x-ray picture is first taken from the posteroanterior direction to verify symmetry of the head position, and to check the alignment of two markers mounted on the head-holder (Fig. 3). The head-holder is then adjusted horizontally until the markers are the desired distance from the midline. This distance is varied depending on what area of the retina is to be treated. The head-holder and animal are then rotated exactly 90°. A lateral x-ray is taken, and a test-beam spot of protons is superimposed on the film to confirm the alignment (Fig. 4).

The animal may now be moved forward or backward so that the center of the test spot (and hence the Bragg peak) will fall an arbitrary distance in front of the posterior orbital wall (Fig. 4). This distance is selected on the basis of previous combined A and B scan ultrasonography. In converting x-ray measurements to actual distances in space, a magnification factor of 1.23 must be taken into account. Vertical positioning of the target is measured from the center of the test spot on the lateral x-ray to the junction of the posterior wall of the orbit with the base of the skull (Fig. 4). Once the ocular target is positioned on the center of rotation of the head-holder, it is possible to treat from any direction, and the Bragg peak will always fall on this same target.

Treatment procedure. The telescoping extension is placed on the end of the collimator and the animal is rotated into position for the treatment (Fig. 5). The beam is either directed through the center of the lens, or around the lens, in which case the eye is held in a position of duction by a traction suture at the limbus. Using this technique, it is possible to treat peripheral areas of the retina without passing the beam through bone. The thin rubber diaphragm on the end of the water-filled extension tube is brought into direct contact with the eye. Care is taken to avoid excessive pressure on the eye, while maintaining even contact. The operators then retire from the treatment area to monitor the dose, which under these conditions is delivered at the rate of about 300 to 400 rads per minute. A closed-circuit television screen is used to watch the animal.

Forty-six monkey eyes have been irradiated with single doses ranging from 800 to 20,000 rads. Most beams have been 7 mm. in diameter, directed either around the lens or through its center. The
Bragg peak has been focused at various positions ranging from the center of the lens to 5 mm. behind the posterior orbital wall in the frontal lobe of the brain.

Results

Dose distribution to tissues. The dose distribution of the 7 mm. collimated beam measured with the water phantom prior to treatment of an eye is depicted in the graphs in Fig. 6. The curves have been plotted after calculation for peak doses of 7,500, 5,000, and 3,500 rads, respectively. Below the curves is a diagrammatic section of the eye and orbit drawn to the same scale as the graphs. It can be seen that if the Bragg peak is focused 1 or 2 mm. in front of the retina, very small doses are delivered to the orbit and brain surface. Table I shows the approximate dosage to each tissue from the cornea to the brain surface when the eye is treated from the direct anteroposterior portal, and a peak dose of 5,000 rads is located 4.5 mm. and 5.5 mm. anterior to the posterior orbital wall, respectively. If the Bragg peak is placed 4.5 mm. in front of this point, the
cornea receives about 50 per cent of the peak dose. The brain surface receives about 27 per cent, assuming it is located 1 mm. posterior to the orbital wall. If the Bragg peak is placed 5.5 mm. anterior to the x-ray landmark, then the cornea receives 52 per cent and the brain surface about 14 per cent of the peak dose.

Effect of varying single dose. No early changes were seen in any eyes given less than 3,500 rads at the retina. Clinical observations over the first eight months have shown no delayed changes in the lens, retina, or optic disc in this dose range, whether treating through the center of the lens or around it.

With retinal doses of 3,600 to 4,000 rads, three out of five eyes treated with a 7 mm. beam developed a localized patch of acute retinal edema within one to two days. The patch was smaller in diameter than the beam. It settled gradually over two weeks, leaving a barely discernible stippling of the retinal pigment epithelium.

Retinal doses of 4,500 to 12,000 rads caused a sharply demarcated circular lesion in the fundus, which appeared one day after treatment and corresponded in diameter to that of the beam (Fig. 7). The retina was locally detached with underlying serous fluid. Multiple folds were present in the deep retinal layers. Several small
intraretinal hemorrhages were sometimes found with larger doses. Beyond the sharp edges of the lesion, the retina and choroid appeared normal. Over the first two weeks, each lesion flattened, losing all signs of edema. A slight flare in the aqueous and vitreous also resolved within two weeks. In this intermediate dose range, the lesion evolved into a discrete circular area of thinned retina with mottled pigmentation (Fig. 8). By six to eight months, the surrounding retina, the vitreous, and lens all appeared normal. There were no signs of extraocular side effects within this period of observation.

When retinal doses of 15,000 to 20,000...
Table II. Effect of moving plane of Bragg peak relative to posterior orbital wall

<table>
<thead>
<tr>
<th>Bragg peak position</th>
<th>Retinal dose in rads</th>
<th>Acute retinal lesion</th>
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<tr>
<td>+10 mm.</td>
<td>2,000</td>
<td>No</td>
</tr>
<tr>
<td>+7 mm.</td>
<td>5,100</td>
<td>Yes</td>
</tr>
<tr>
<td>+4 mm.</td>
<td>7,400</td>
<td>Yes</td>
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<tr>
<td>+1 mm.</td>
<td>6,750</td>
<td>Yes</td>
</tr>
<tr>
<td>-2 mm.</td>
<td>5,400</td>
<td>Yes</td>
</tr>
<tr>
<td>-5 mm.</td>
<td>4,750</td>
<td>Yes</td>
</tr>
</tbody>
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+ Anterior, - posterior to posterior orbital wall. Peak dose of 7,500 rads. Retina is assumed to be 3.5 mm. anterior to the posterior orbital wall.

Rads were applied, the same localized disciform exudative retinal detachment occurred within one day, but large numbers of intraretinal hemorrhages also developed within the irradiated area. The retinal detachment settled, but the retina itself developed a ragged appearance over the first month. All small retinal and choroidal vessels within the treated area became obliterated, and the retinal pigment epithelium did not proliferate. After six weeks, a sharply demarcated necrotic white lesion remained with little clinical evidence of reparative processes in the retina or choroid. The large retinal vessels were irregular in caliber and showed sheathing. As in the intermediate dose range, no corneal, lenticular, or extracocular side effects developed within six months. If the optic disc was included in the treated area, it became atrophic, and all the major vessels were partially obliterated. Six to eight weeks later, secondary edema and hard exudates appeared in the entire peripheral retina outside the treated area.

Effect of varying the position of the Bragg peak. In a group of six eyes, a 7,500 rad peak was delivered to each eye through the center of the lens. When the Bragg peak was placed 10 mm. anterior to the retina, the retina received 2,000 rads. No retinal, lenticular, or corneal lesion developed. As expected from the estimated retinal doses in Table II, a discrete, acute retinal lesion developed when the Bragg peak was placed 7 mm., 4 mm., and 1 mm. in front of the posterior wall of the orbit. A visible retinal lesion also developed when the Bragg peak was placed at 2 mm. and 5 mm. behind the posterior orbital wall.

Discussion

The dose-distribution curves (Fig. 6) illustrate the theoretical advantages of heavy particle irradiation for a small target within the orbit. If the Bragg peak is focused in front of the retina, the steep fall-off in penetration insures that acceptably small doses will be delivered to tissues beyond the eye. At the same time, the plateau on the curve before the Bragg peak falls on the cornea and lens (or the sclera, if treating around the lens). The result is that doses of only 40 to 60 per cent of the peak dose are delivered to these tissues. The negligible scatter of the protons allows a sharply circumscribed lesion to be placed on the retina. It is hoped that this lack of scatter will also avoid complications in the lens or optic nerve.

Electrons of appropriate energy (about 5 million volts) also have a sufficient range of penetration in tissue and give a steep fall-off in dose beyond the lesion. However, being small particles, they scatter more than protons. In addition, it is not possible to deliver a smaller dose to the cornea and lens or to the sclera, there being essentially no plateau and Bragg peak effect.

It will require long-term observations to prove whether it is possible to treat through the center of the lens with proton beams. Even with orthovoltage x-rays, however, there is good evidence that the axial portion of the lens is less sensitive than the equatorial region, where the epithelial cells undergo mitosis throughout life.

Our present indirect stereotactic aiming method allows precise positioning of the Bragg peak in the eye. However, the aiming procedure is only accurate to 2 or 3 mm. in the vertical and horizontal meridians, particularly if the target is located in the peripheral fundus, and if the posi-
tion of gaze varies. We are, therefore, developing an ophthalmoscopic aiming system to supplement stereotactic radiography. It seems likely that the improved dose distribution of proton irradiation as compared to that of photons or electrons will be better tolerated by the eye. It should then be possible to apply larger doses of therapeutic irradiation to ocular tumors with this method and obtain decreased side-effects.

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REFERENCES