


Unilateral optic nerve transection without damage to the intraocular circulation was performed on thirteen cats. Fluorescein angiograms, trypsin digestion, and histologic preparation of the retinas were carried out. No changes in the retinal circulation and angiarchitecture were observed. These findings were compared to those reported in humans with comparable optic nerve lesions. We conclude that optic nerve transection does not cause retinal vascular alteration, and this fact may be of pertinence to posterior ocular damage in glaucoma.

A significant, unanswered question concerning the pathogenesis of glaucoma is the relationship between increased intraocular pressure and field loss. Is there primary neuronal damage, or is the vascular bed initially compromised? Circumstantial evidence exists in support of the latter possibility: (1) Kornzweig, Eliasoph, and Feldstein demonstrated selective ipsilateral atrophy of the radial peripapillary capillaries in retinal digest preparations from humans with unilateral glaucoma, and (2) retinal digest preparations from longstanding glaucomatous eyes often reveal profound alterations in the vascular bed with prominent capillary dropout and arteriovenous collateral vessel formation. Neither observation, however, proves which comes first, neuronal degeneration or vascular involvement. It is well known that vascular occlusive disease, i.e., branch or central retinal artery occlusion leads to atrophy of the inner retinal layers. It has not been demonstrated what effect neuronal degeneration has on the retinal vascular bed.

Our experiment was designed to examine what effect destruction of the inner retinal layers, by posterior (retrograde) degeneration consequent to an optic nerve transection, would have on the retinal vessels.

Materials and methods. Twenty domestic cats were anesthetized with intramuscular ketamine HCl, 30 mg. per kilogram. After anesthesia occurred, pentobarbital, 15 mg. per kilogram, was administered intravenously to deepen and to prolong the anesthesia. The cats were placed in dorsal recumbency and the jaws widely separated. A 3 cm. incision was made into the soft tissue behind the last upper molar parallel to the midline. Because there is no bony floor of the cat orbit, blunt dissection allows visualization of the optic nerve as it emerges from the optic foramen. In 13 cats, the nerve was carefully dissected free from the ophthalmic artery and transected posterior to the point where it is penetrated by the ciliary arteries. In six animals, both the optic nerve and its blood supply were cut. Sham operations involving opening the orbit and isolating the optic nerve without transection were conducted in four animals. Seventeen cats were subjected only to a unilateral procedure; in three cats, a procedure was performed on both eyes (i.e., experimental plus sham).

Ophthalmoscopic examinations were conducted in all cats before and after optic nerve transection, and pre- and postoperative fluorescein angiography was performed in five cats.

Fig. 1. A, fluorescein angiogram of right fundus. B, fluorescein angiogram of same fundus 13 days after transection of optic nerve.
Fig. 2. A, retinal digest preparation left eye. B, Retinal digest preparation of right eye, 37 days after transection of optic nerve. Same animal as Fig. 2, A.

At the termination of the experiment, two days to ten weeks after operation, both eyes were enucleated and fixed in formalin. After fixation the globes were opened and a portion of the retina removed for trypsin digestion with flat mounts made of the retinal vessel preparations. Routine histologic sections were prepared from the remaining material and they were stained with hematoxylin and eosin, periodic acid-Schiff reagent, Masson's trichrome, axon, and myelin stains.
Results. Upon recovering from anesthesia, all cats having optic nerve transection were observed to be totally blind on their operated side; they had ipsilaterally fixed and dilated pupils. Within two or three weeks most of the animals regained a consensual reflex in the involved eye and their pupils returned to almost normal size.

Fundus examination revealed no abnormality of the retinal vascular bed in those animals only having optic nerve transection. In those with combined nerve and vascular supply transection there was ophthalmoscopic evidence of markedly diminished blood supply. There was no observable difference in retinal blood flow comparing the pre- and postoperative fluorescein angiograms in animals with optic nerve transection (Fig. 1). The longest postoperative study by angiography was 37 days.

Examination of routine histologic sections revealed alterations only in the eyes with optic nerve transection. There was loss of the ganglion cell-nerve fiber layer in eyes removed four or more weeks after nerve transection. In one eye removed ten weeks after surgery, there was marked cupping of the disc. In those cases where both the nerve and its blood supply were interrupted there was much more profound inner retinal atrophy, and deep cupping was obvious at four and eight weeks. The contralateral control eyes and the sham-operated eyes were normal.

Analysis of the retinal digest preparations revealed normal angioarchitecture and normal endothelial cell and intranuclear pericyte populations in both the normal and transected eyes (Fig. 2). In all instances where both the nerve and the vascular supply had been transected, the digests revealed markedly abnormal angioarchitecture, the vessels appearing as narrow acellular tubes (Fig. 3).

Discussion. From our results, we conclude that destruction of the inner retinal layers in the cat, caused by severing the optic nerve with consequent retrograde neuronal degeneration, does not significantly alter the retinal vasculature either anatomically or physiologically. The experiments were relatively short-term, lasting no more than ten weeks, and it could be argued that vascular alterations might take longer to appear. Evidence from man, however, confirms the general principle that inner retinal degeneration following upon distant optic nerve damage, without obvious interruption of the retinal blood supply, does not cause alterations in the retinal vasculature. For example, Henkind, Charles, and Pearson4 found a normal appearing retinal digest in an eye which had been blind for four months following an episode of acute ischemic optic neuropathy presumably secondary to giant cell arteritis. In this eye the entire retinal ganglion cell-nerve fiber layer was absent; the contralateral eye was uninvolved. Kurz, Ogata,
and Gross reported a case wherein the optic chiasm had been damaged 13 years previously by a bullet; there was loss of inner retinal layers, but the retinal digestion preparation demonstrated no vascular abnormalities.

While this experiment did not address itself to the pathogenesis of cupping of the disc, several points are noteworthy. In cats with both optic and blood vessel transection there was obvious cupping evident on histologic cross-sectioning, and this could be seen by four to eight weeks. In our longest surviving case, ten weeks, marked cupping was present even though the optic nerve and retinal circulation remained intact. Miller suggests that neuronal destruction itself does not induce cupping, and he presented a case with a flat optic disc after surgical removal of an optic nerve glioma. Hayreh has noted a number of entities associated with cupped optic discs, not all of which have obvious disruption of the disc or retinal circulation. Whether optic disc cupping can be caused consistently by neuronal damage alone deserves further investigation.

It seems likely from available experimental and relevant clinical data that two statements can be made: (1) destruction of the vascular supply to the inner retina leads to degeneration of the ganglion cell-nerve fiber layer; (2) retrograde degeneration of the neuronal elements of the inner retina does not cause degeneration of the neighboring retinal blood vessels. Thus, if one can demonstrate retinal vascular degeneration in glaucomatous individuals, it is likely that such degeneration was primary and not a consequence of the neuronal damage.

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REFERENCES

Vitreous structure. IV. Chemical composition of the insoluble residual protein fraction from the rabbit vitreous.*

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Analysis of the structural proteins in the rabbit vitreous showed that the hydroxyproline content was 3.1 per cent w/w compared to a value of 1.9 per cent w/w for equivalent samples obtained from cattle. In contrast to the discreet fibers in bovine vitreous, the rabbit constituents occur as an aggregate of fibrils with a diameter of 15 to 20 A. The amino acid and carbohydrate composition was similar to vascular basement membrane and isolated fractions contained significant amounts of palmitic and stearic acids. The data indicate that the variability of vitreous structure in different species is not only quantitative, but also qualitative. It is suggested that in the rabbit the structural proteins may be derived primarily from the atrophied hyaloid system and that little, if any, secondary vitreous formation occurs in this animal.

Early studies showed that the principal component of the bovine vitreous fibers was a collagen-like moiety and in a later electron microscope study, Olsen was able to prepare segment-long-spacing (SLS) aggregates from trypsin-digested vitreous fibers which showed the same banding pattern as SLS aggregates prepared from rat tail tendon collagen. More recently, it was shown that after extraction with saline and 5M guanidine hydrochloride, 85 per cent of the "residual protein" fraction from the bovine vitreous was recovered as an insoluble collagenous residue. It is known that both the form of the vitreous (gel or fluid) and the hydroxyproline concentration vary markedly in different species. These differences may be caused by variations in both the type and amount of collagen present and the extent to which the collagen occurs together with the other structural constituents. A preliminary study on the chemical composition of the rabbit vitreous...