HISTOPATHOLOGIC OBSERVATIONS ON HUMAN EYES FOLLOWING NEODYMIUM:YAG LASER CYCLOPHOTOCOAGULATION FOR GLAUCOMA*

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ABSTRACT

Purpose: Although Nd:YAG laser cyclophotocoagulation has been extensively used for nearly a decade in treatment of severe glaucoma, there have been remarkably few reports (each of them extremely brief) of histopathological examination of glaucomatous human eyes that had been so treated. We undertook this study to provide further details regarding the nature of the lesions produced in this type of ciliary ablation.

Methods: We chose three representative cases in which a glaucomatous human eye had been subjected to Nd: YAG cyclophotocoagulation, and was subsequently enucleated. To better understand the temporal evolution of the lesions, we selected eyes that were enucleated 1 day, 20 days, and 3 months, respectively, after they had been treated with noncontact Nd: YAG laser cyclophotocoagulation.

Results and Conclusions: (1) energy levels ranging from 4.4 Joules to 5.6 Joules were effective in producing appropriate lesions; (2) direction of the laser beam 1 to 1.5 mm behind the limbus caused severe destructive lesions of the pars plicata; (3) toward the periphery of the individual treatment sites, the stroma and ciliary muscle continued to exhibit severe degeneration, as did the epithelium lining the valleys between the crests of the ciliary processes; but in those peripheral zones of individual treatment sites, the epithelium lining the crests of the ciliary processes survived and appears normal; (4) bleb-like separations of the ciliary epithelium from the adjacent stroma, particularly along the posterior aspect of the ciliary body lesions, are a prominent early feature of Nd:YAG cyclophotocoagulation; (5) the pigmented epithelium is more vulnerable to laser energy than is the nonpigmented epithelium of the ciliary body; (6) the destruction of the ciliary epithelium is permanent; (7) deeply pigmented persons have more melanocytes in the ciliary body muscle and stroma than do more lightly pig-

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mented individuals, a circumstance that renders the tissues more vulnerable to laser energy; (8) the ciliary muscle was always severely damaged; (9) no scleral injury was observed other than evanescent, focal areas of edema of the deep sclera; and (10) except in the episclera, inflammatory cells were strikingly few in number, a circumstance providing support for the clinical observation that eyes treated with laser cyclophotocoagulation exhibit less of an inflammatory response than do those treated with cyclocryotherapy.

INTRODUCTION

In their quest to reduce intraocular pressure in severely glaucomatous eyes, ophthalmologists have used a variety of ciliary ablation techniques for almost 60 years. The purpose of ciliary ablation is to reduce the amount of aqueous humor being elaborated by the ciliary epithelium. Energy sources that have been used to effect destruction of the ciliary epithelium include coagulation with chemicals, diathermy, freezing, xenon light, laser light delivered directly to the ciliary processes or across the sclera, and ultrasound.[1]

In 1972, Beckman and colleagues[2] reported their initial results with use of a ruby laser to perform transscleral cyclophotocoagulation. In the early 1980s, Fankhauser and associates[3] reported a series of studies summarizing their use of a neodymium:YAG laser in performing transscleral laser cyclophotocoagulation.

These techniques were not widely used until commercial laser systems became available later in the 1980s. Despite the relative popularity that transscleral neodymium:YAG cyclophotocoagulation has enjoyed for nearly a decade, there have been remarkably few histopathologic studies of the effects of this procedure on living human glaucomatous eyes. We have been able to find only five reports, each describing a single case, in which glaucomatous human eyes of living patients were treated with this technique and were subsequently subjected to histopathologic examination.[4-8]

Each of these reports is remarkably brief. Two of them are in the form of Letters to the Editor.[4,5] Two of the others were published because sympathetic uveitis had developed. The reports were chiefly concerned with that phenomenon, and only passing reference was made to ciliary body abnormalities induced by laser cyclophotocoagulation.[6,8]

We describe in this presentation the results of histopathologic examination of three human glaucomatous eyes that had been treated with noncontact neodymium:YAG cyclophotocoagulation 1 day, 20 days, and 3 months, prior to enucleation.

REPORT OF CASES

CASE ONE

A 67-year-old fair-complexioned white woman of Scandinavian descent developed ischemic oculopathy following rupture of an aortic aneurysm 2 years

previously. At the time of aneurysmal rupture, her blood pressure had fallen to zero, where it remained for a prolonged period. Over the course of the subsequent 2 years, she developed bilateral neovascular glaucoma and progressive visual loss. Although the patient was now unable to perceive light with either eye, the right eye underwent extracapsular extraction of an intumescent cataract and trabeculectomy for angle-closure glaucoma. The eye became phthisical postoperatively.

During the subsequent year, her left eye followed a similar course marked by development of a dense cataract and angle-closure glaucoma. The intraocular pressure was equivalent to 68 mm Hg and did not respond to medical therapy, including administration of mannitol intravenously. The patient refused enucleation and was referred to our institution for neodymium:YAG laser cyclophotocoagulation of her left eye.

Using the noncontact Lasag laser (Microruptor II) at a setting of 5.4, Mj 33 spots were placed 1.5 to 2 mm posterior to the limbus. These burns were placed between 3:30 and 8:30 o'clock, and between 9:30 and 1:00 o'clock, encompassing 270° of the circumference of the ciliary body.

Postoperatively, the intraocular pressure was reduced to 50 mm Hg, but the patient continued to have severe pain for which she required oral analgesics. Enucleation was again advised, but the patient declined. Seventeen days after the initial cyclophotocoagulation, the procedure was repeated. Using a power setting of 5.4, Mj 34 spots were placed 1 to 1.5 mm behind the limbus, between 8:30 and 3:30 o'clock, and between 9:30 and 2:30 o'clock, avoiding the 3- and 9-o'clock positions. The eye was enucleated 1 day after the second cyclophotocoagulation.

On gross examination of the enucleated eye, "no external abnormalities" were seen. On microscopic examination, the lumen of the central retinal artery was patent. There was neovascularization of the cup of the optic nerve head and of the iris. The anterior chamber angle was occluded by peripheral anterior synechia formation. The lens was cataractous and intumescent. The ciliary body exhibited severe abnormalities attributable to laser therapy. The lesions were generally well placed, being confined in most regions to the pars plicata and to the anterior portion of the pars plana. But in some sections, marked disruption of the iris pigment epithelium was also present (Fig 1). There was marked coagulation necrosis of all layers of the ciliary body (Fig 2). The epithelium surmounting the most anterior portion of the ciliary processes escaped destruction, even at the center of each laser burn (Fig 3). Moving away from the center of the lesion, the laser-induced necrosis tended to spare the outermost strands of the longitudinal bundles of the ciliary muscle, as well as the crests of the ciliary processes (Fig 3). But the bulk of the ciliary muscle, stroma, and the epithelium lining the valleys between the crests of the ciliary processes exhibited severe coagulation and hemorrhagic necrosis. Extravasations of blood extended from the ciliary body into the anterior chamber.

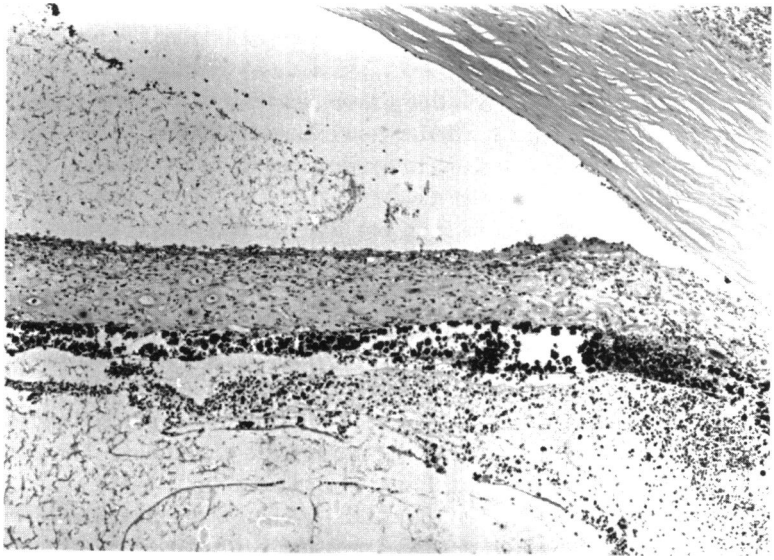


FIGURE 1

Case 1. Severe disruption of iris pigment epithelium. Iris is neovascularized, and extravasations of blood are present in anterior and posterior chambers (hematoxylin-eosin, X 48).

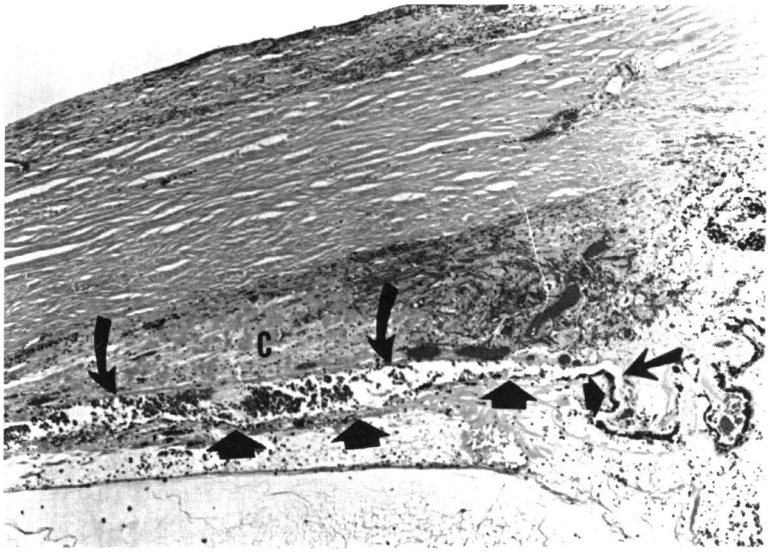
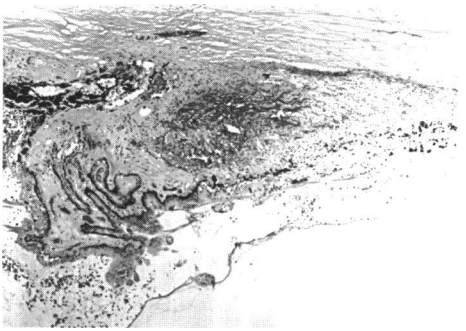


FIGURE 2

Case 1. Severe hemorrhagic and coagulation (C) necrosis involves entire ciliary body except crests of ciliary processes. A bleblike space separates epithelial layers (arrowheads) from adjacent stroma (arrows). Extravasated blood is present in this cleft (hematoxylin-eosin, X 48).

A



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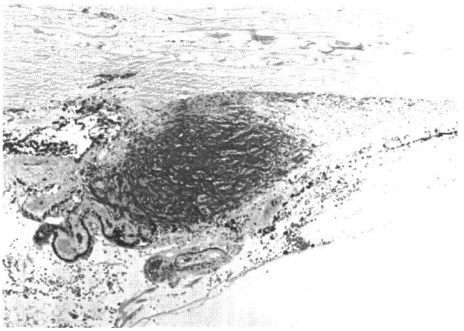

C

FIGURE 3

Case 1. A, In periphery of laser burn, a cleft between epithelium and adjacent stroma is present. Epithelium of posterior slope of pars plicata is necrotic. Epithelium lining valleys between ciliary processes exhibits patchy necrosis, but epithelium at crests of processes appears normal (hematoxylin-eosin, X 48). B, Further centrally in laser burn, epithelium lining posterior slope of pars plicata is severely necrotic and barely recognizable. Hemorrhagic and coagulation necrosis has destroyed all of ciliary muscle except for outermost layers of longitudinal muscle. Focal areas of necrosis are now apparent in epithelium surmounting crests of ciliary processes (hematoxylin-eosin, X 48). C, Even at center of laser burn, some of epithelium lining crests of ciliary processes has escaped injury in this lightly pigmented patient of Scandinavian descent (hematoxylin-eosin, X 48).

FIGURE 4
Case 1. In this region, cleft occurs between nonpigmented epithelium (arrowheads) and pigmented epithelial layer (arrows). Extravasated blood is present in cleft's lumen (hematoxylin-eosin, X 120).

Prominent bleblike separations of the structures in the ciliary body were present. In some areas the separation occurred between the pigmented and nonpigmented layers of the ciliary epithelium (Fig 4). In other areas, the pigmented and nonpigmented epithelial layers remained together but were separated from the overlying stroma (Fig 2). The sclera exhibited only minimal edema and was virtually free of inflammatory cell infiltration. The number of scleral cells present was not reduced. In sections that included the center of a laser burn, tinctorial changes were present in the deepest layers of the sclera, suggesting laser-induced injury.

CASE TWO

A 50-year-old black man was struck in his right eye by the pull cord of a lawn mower when he was about age 40. Secondary glaucoma developed. Over the subsequent 5 years, vision was progressively lost until he was no longer able to perceive light with his right eye. During the year preceding his referral to our institution, severe bullous keratopathy and increasing pain had developed. On slit-lamp biomicroscopic examination, a trace of conjunctival injection and moderate haze of the corneal stroma were present. There were scattered epithelial bullae centrally and inferiorly. There was

no evidence of iris neovascularization. Intraocular pressure was equivalent to 64 mm Hg. The fundus could not be seen. Vision in the left eye was correctable to 20/20, and intraocular pressure was equivalent to 18 mm Hg. The anterior chamber angle was open on gonioscopic examination.

The patient underwent noncontact slit-lamp neodymium: YAG laser cyclophotocoagulation (right eye). Using the Lasag Microruptor II instrument, 30 laser spots at 5.6 in a continuous-wave mode, and a retrofocused setting of 9, were placed 1 mm posterior to the limbus. The treatment sites were situated at about equal distances between 3:30 to 8:30 o'clock, and between 9:30 and 2:30 o'clock, avoiding the 3- and 9-o'clock meridians. At the end of the procedure, 0.5 mL of Decadron was administered subconjunctivally.

Following cyclophotocoagulation, the patient's intraocular pressure remained elevated and he continued to have severe pain. Retrobulbar injection of ethanol failed to relieve the pain. The eye was enucleated 20 days after cyclophotocoagulation had been performed.

On gross examination, there was "no visible area of injury." The eye was opened vertically. On microscopic examination, the anterior chamber angle was open and exhibited a mild degree of recession. Corneal endothelium had proliferated onto the inner surface of the trabecular meshwork, the face of the ciliary body, and for a short distance onto the peripheral iris, laying down a new Descemet's membrane–like substance along its course. The trabecular meshwork was compressed and disorganized. The retina and optic nerve exhibited changes characteristic of advanced glaucoma.

Prominent laser-induced lesions were present in the ciliary body. They were generally well placed, the main area of destruction being in the pars plicata and the most anterior portion of the pars plana. But in some sections there was prominent disruption of the iris pigment epithelium, and in some planes of section there were iridodialyses, interpreted as the result of inadvertent laser iridotomies (Fig 5). Bleblike separations of the ciliary epithelium of the type observed immediately after laser cyclophotocoagulation (case 1) were not present. The edema and extravasation of blood that were also such prominent features of the acute injury (case 1) were only present to a minimal degree in this eye that was enucleated 20 days after cyclophotocoagulation had been performed. Near the center of the individual treatment sites, the destruction of the ciliary body was full-thickness, including the ciliary muscle, stroma, and epithelium. In these areas, the laser had succeeded in destroying even the epithelium surmounting the crests of the ciliary processes (Fig 6). Moving away from the center of each laser-induced lesion, the ciliary muscle and stroma continued to exhibit severe degeneration, as did the epithelium lining the valleys between the crests of the ciliary processes. But in these areas, the ciliary epithelium lining the crests of the ciliary processes had survived and appeared normal (Fig 7). In the periphery of the individual laser-induced lesions, approaching normal

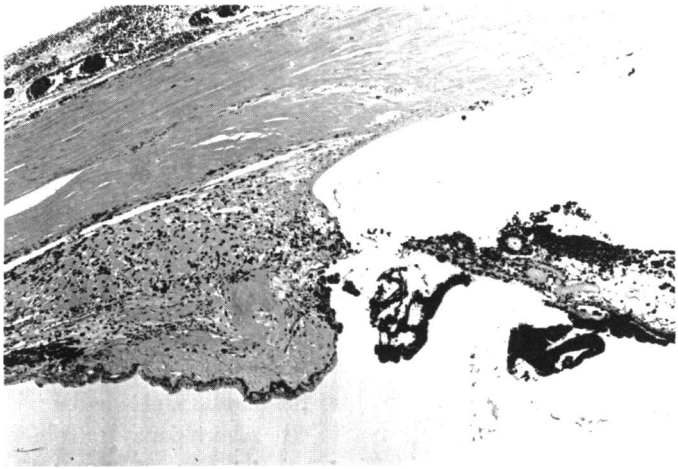

FIGURE 5

Case 2. Laser-induced peripheral iridotomy is present. There is severe coagulation necrosis of ciliary muscle. Epithelium surmounting the crest of ciliary body is intact. Just visible at this magnification is endothelialization of anterior chamber angle, with laying down of a new Descemet's membrane-like material over trabecular meshwork, scleral spur, and the face of the ciliary body (hematoxylin-eosin, X 48).

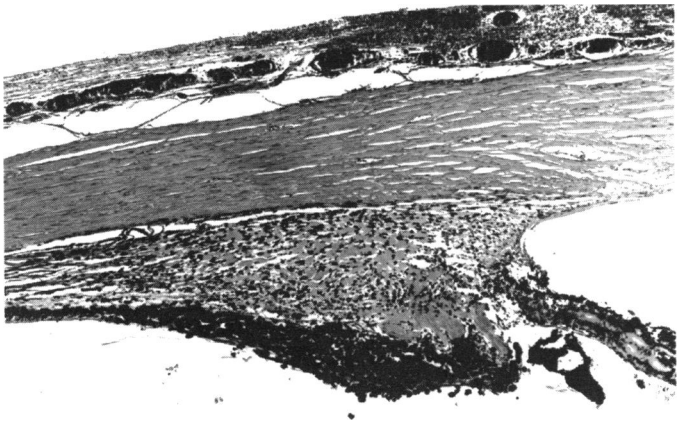

FIGURE 6

Case 2. Near center of laser burn, necrosis of full thickness of ciliary body, including epithelium lining crests of ciliary processes, has been effected. Note numerous necrotic melanocytes present in necrotic ciliary muscle and stroma of this black patient. Epithelium of pars plana (extreme left side of field) is intact. There is prominent edema and hyperemia of the episclera (hematoxylin-eosin, X 48).

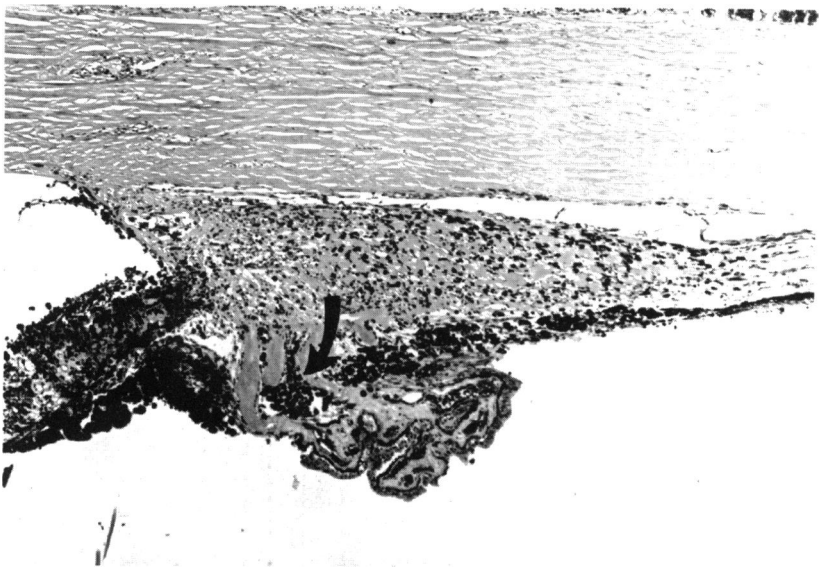

FIGURE 7

Case 2. Toward periphery of laser burn, ciliary muscle and stroma continue to exhibit severe coagulation necrosis. Epithelium lining valleys between ciliary processes (arrow) is severely necrotic, as is epithelium lining posterior slope of pars plicata. Epithelium surmounting crests of ciliary processes has escaped laser-induced injury. Epithelium of pars plana (extreme right side of field) is intact. Slight separation of ciliary body from sclera near junction of pars plicata and pars plana is an artifact (hematoxylin-eosin X 48).

ciliary epithelium, the changes induced in the pigmented layer were much more profound than were those in the nonpigmented layer (Fig 8).

Although the ciliary muscle was broadly destroyed in its full thickness near the center of each lesion, closer to the periphery of the lesion, the outermost fibers of the longitudinal muscle were spared. The overlying sclera was unremarkable. A normal complement of scleral cells was present, and there was no inflammatory cell infiltrate. The overlying episclera was severely edematous, hyperemic, and contained a prominent infiltrate of inflammatory cells.

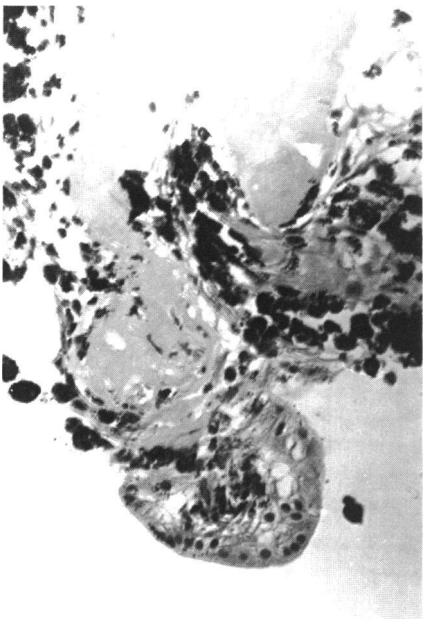

FIGURE 8
Case 2. Approaching summit of one of the ciliary processes, there is severe degeneration along sides of crest. At summit (bottom of field), where laser-induced energy was lower, just enough heat was generated to destroy pigmented layer of epithelium, but nonpigmented layer has survived (hematoxylin-eosin, X 300).

CASE THREE

A 75-year-old white man had had recurrent anterior uveitis in his left eye since the age of 55 years. He had a mature cataract in that eye, and had recently developed an increase in the activity of his iritis. This was associated with elevation of intraocular pressure which remained in the upper 20s despite medical therapy. Because of the risk of phacolytic glaucoma, he underwent uneventful intracapsular cataract extraction, with resultant corrected vision of 20/25. One month later he developed pupillary block glaucoma, and he underwent vitrectomy for control of his intraocular pressure. Two days postoperatively he developed a total hyphema and subsequent corneal blood staining. Over the course of the following year, the blood staining cleared but neovascular glaucoma developed.

The patient was referred to our institution because of his chronically elevated intraocular pressure and complaints of severe pain. Vision in his right eye was correctable to 20/25, and no abnormalities other than fine macular drusen were observed. Intraocular pressure was equivalent to 13

mm Hg in the right eye. Visual acuity of the left eye was limited to light perception. There was a marked afferent pupillary defect. Slit-lamp biomicroscopic examination disclosed corneal haze, old keratic precipitates, no cells or flare in the anterior chamber, and a pupillary membrane with corectopia. There was prominent iris neovascularization, and the lens was absent. On gonioscopic examination the anterior chamber angle was closed for 360°. Ophthalmoscopic examination disclosed a pale optic nerve head with prominent cupping. Intraocular pressure varied from 31 to 48 mm Hg.

The patient was treated with neodymium:YAG cyclophotocoagulation for uncontrolled secondary glaucoma of his left eye. Using the noncontact Lasag Microruptor II instrument, 30 laser spots at a setting of 4.4 in a continuous-wave mode, and a retrofocus setting of 9, were placed 1 mm posterior to the limbus. The treatment consisted of 20 spots between 3:30 and 8:30 o'clock, 5 spots between 9:30 and 10:30 o'clock, and 5 spots between 1:30 and 2:30 o'clock, avoiding the 3- and 9-o'clock meridians. Following the procedure, 0.5 mL of Decadron was administered subconjunctivally.

Following cyclophotocoagulation, the patient's intraocular pressure remained elevated, and he continued to have pain. Injection of retrobulbar ethanol failed to relieve it, and 3 months after cyclophotocoagulation had been done, the left eye was enucleated. Episodic pain continued after enucleation and was attribued to migraine.

On gross examination, the eye was opened vertically. A pupillary membrane was observed. The lens was absent. On microscopic examination, a healed perforating corneal wound was present superiorly, at a considerable distance central to the limbus. This marked the site of cataract surgery. The cornea was thinned and vascularized in the region of the scar. There was a prominent fibrous ingrowth extending from the inner aspect of the incision toward the pupillary region, where the fibrous membrane merged with the atrophic inferior leaf of the iris. Corneal endothelium had proliferated along the anterior surface of this fibrous membrane superiorly, and inferiorly it had also proliferated onto the anterior surface of the iris. The endothelium had laid down a Descemet's membrane–like material along the course of its proliferation. The anterior chamber angle was occluded inferiorly by broad peripheral anterior synechia formation. Remnants of severely degenerated uveal tissue obliterated the trabecular meshwork superiorly. The retina and optic nerve head exhibited changes characteristic of those seen in far advanced glaucoma.

The laser-induced lesions in the ciliary body were well-placed, involving the pars plicata and the most anterior portion of the pars plana (Fig 9). There was marked atrophy and scarring of the stroma of the ciliary body. Most of the ciliary muscle was replaced by scar tissue, although a prominent band of the longitudinal muscle persisted just inside the sclera. The pars

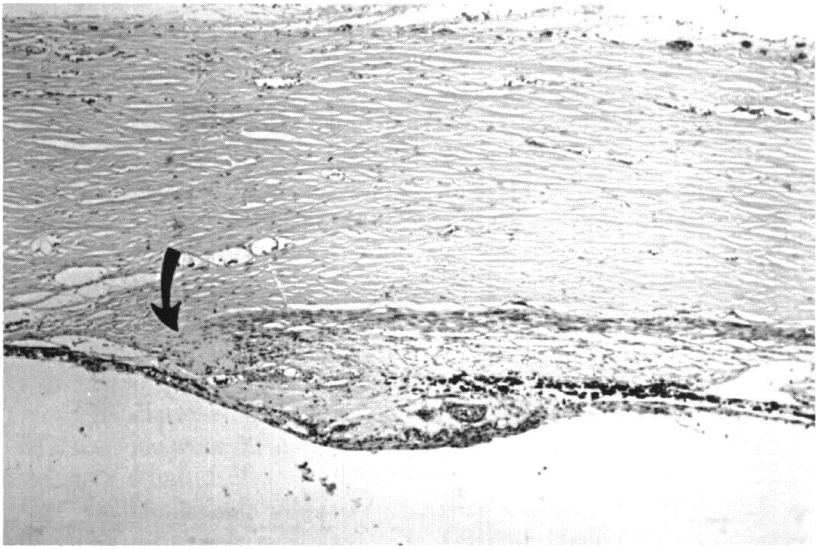

FIGURE 9
Case 3. Three months after laser cyclophotocoagulation, there is marked atrophy and scarring of ciliary body. A prominent residual band of longitudinal component of ciliary muscle inserts upon scleral spur (arrow) (hematoxylin-eosin, X 48).

plicata had assumed the shape of a flattened mound. Buried in the stromal scar were clusters of degenerated pigmented epithelial cells. The inner surface of the scarred mass that had replaced the pars plicata was lined by abnormal, nonpigmented ciliary epithelial cells. The pigmented epithelial layer was absent in this region. Along the posterior slope of the pars plicata, both layers of the ciliary epithelium were severely degenerated. The sclera was unremarkable.

DISCUSSION

During the course of a panel discussion on cyclocryotherapy in 1975, a prominent glaucoma specialist asked me about the basis of some statements I (A.P.F.) had just made regarding the histopathologic features of lesions caused in glaucomatous human eyes by cryosurgery of the ciliary body. I replied that these were well known and that I was sure I had seen this information published in the literature on a number of occasions. He said he did not recall ever having seen any such report.

It turned out that he was correct and I was wrong. Although I had studied a number of such eyes in my laboratory, as of then there had been

only one published report[9] of histopathologic examination of a glaucomatous human eye that had been treated with cyclocryotherapy and subsequently subjected to histopathologic examination. This report was an extremely brief, and the effect of cryosurgery on the ciliary body was not the reason for the authors' decision to publish their case. What had attracted their interest was the development of a scleral staphyloma. They were unaware that they were also publishing the first report of pathologic examination of a glaucomatous human eye that had been subjected to cyclocryotherapy.

The following year I presented a study of 12 such eyes at the annual meeting of the American Academy of Ophthalmology and Otolaryngology.[10] I was struck by the fact that although cyclocryotherapy for glaucoma had been introduced more than a quarter of a century earlier and had been widely used for the past decade, only one report of pathologic examination of a treated human glaucomatous eye had ever appeared. On the other hand, the literature was studded with reports of pathologic examination of the eyes of laboratory animals that had been subjected to cyclocryotherapy. The interpretation of the cryosurgically induced lesions in the ciliary body was, in a number of instances, unauthoritative and inaccurate.

This extreme paucity of reports of pathologic examination of human glaucomatous eyes that had been subjected to cyclocryotherapy was even more remarkable when one considers that the very eyes subjected to cryosurgery are typically in an end-stage of glaucoma and have a variety of associated abnormalities that tend to cause severe pain, –a combination of circumstances increasing the likelihood that enucleation may eventually come to pass, thereby rendering these eyes available for histopathologic examination.

One experiences a sensation of déjà vu when considering the paucity of reports of pathologic examination of human glaucomatous eyes that have been treated with neodymium:YAG laser cyclophotocoagulation. The technique has enjoyed considerable popularity for nearly a decade, and the eyes most likely to be treated with neodymium:YAG laser cyclophotocoagulation tend to be approaching an end-stage of glaucoma. They are likely to have associated abnormalities that render a sizable proportion of them candidates for eventual enucleation.

And yet, only a handful of reports of histopathologic examination of living human glaucomatous eyes that had been treated with this technique have appeared.[4-8] In addition to these reports, there have been several describing the results of pathologic examination of eyes that were destined for surgical enucleation for other reasons, the patients having consented to undergo neodymium:YAG laser cyclophotocoagulation so their physicians might study the effect of the procedure on their eyes (Blasini and colleagues, one case[7]; Brancato and colleagues, two cases[11]).

A number of studies of the effects of neodymium:YAG laser on human autopsy eyes have been reported.[12-19] These have been of considerable value

in determining optimal location of probe placement and in demonstrating (1) bleblike separations of the ciliary epithelium from the adjacent stroma, (2) the presence of coagulation necrosis in the ciliary body, and (3) that heavily pigmented eyes require less energy for development of an appropriate lesion than do lightly pigmented ones. None of these reports noted that any of the treated autopsy eyes were known to be glaucomatous.[12-19]

Use of autopsy eyes for this purpose has a number of major drawbacks. First, the lack of blood circulation in the nonliving eye affects the nature of the induced lesion. The ciliary body is richly vascular and may be regarded as a thermal sink. That is, heat resulting from a burst of laser energy will be immediately decreased as blood flow through the region carries away some of the generated heat, thereby lessening the amount of laser-induced injury at the locus. Put another way, more energy is required for laser cyclophotocoagulation in living eyes because of heat convection by blood flow. A second key point when considering the difficulty in defining clinical parameters (eg, power settings) based on studies of nonliving eyes is that in addition to the well-known propensity of neodymium:YAG laser energy to be absorbed by melanin, it is also absorbed by oxygenated hemoglobin, but not by reduced hemoglobin.[17]

There are still other limitations to the use of nonliving eyes in assessing the effects of laser energy on the ocular structures. Because of the absence of blood flow in autopsy eyes, the presence of severe, laser-induced hemorrhagic necrosis of the type demonstrated in case 1 will not be seen. A second major consideration has to do with the attempt of the eye to repair the injury it has sustained. The nonliving eye is unable to mount any attempt at repair. The living eye can do so, as exemplified by cases 2 and 3.

Five brief reports have each described a single case of histopathologic examination of a glaucomatous human eye that had been treated in vivo with neodymium:YAG laser cyclophotocoagulation.[4-8] The first appeared in the *American Journal of Ophthalmology* in 1988, as a letter.[4] The patient's eye was enucleated 70 days after neodymium:YAG cyclophotocoagulation. A discrete destructive lesion involving the full thickness of the ciliary body was present in the region of the posterior slope of the pars plicata.

The second report appeared in the following year and was also in the form of a letter.[5] A previous letter writer had suggested that the mechanism by which neodymium:YAG laser cyclophotocoagulation exerts its intraocular pressure–lowering effect may involve a process other than destruction of ciliary epithelium. This suggestion prompted March and Shaver to publish a photomicrograph of a glaucomatous human eye that had been treated with the neodymium:YAG laser 1 week before enucleation. Again, their illustration depicts a full-thickness destructive lesion of the ciliary body in the region of the pars plicata, behind which is a prominent, bleblike cleft separating the ciliary epithelium of the pars plana from the adjacent stroma.

In two of the remaining three reports, a patient who had been treated

with neodymium:YAG laser cyclophotocoagulation subsequently developed a clinical picture regarded as sympathetic uveitis.[6,8] In both cases, the authors were more interested in discussing the bilateral ocular inflammation than they were in detailing the effects of laser therapy on the structure of the ciliary body. As part of the inflammatory process, both eyes exhibited a severe panuveitis. The inflammatory reaction in the ciliary body also hampered evaluation of the laser-induced changes in the region. Nevertheless, the single photomicrograph of the ciliary body published in the first report shows a full-thickness destructive lesion involving the pars plicata.[6] In the more recent report, a single photomicrograph of the ciliary body region was offered. The description of architectural changes caused by laser therapy was limited to the following statement: "There was extensive damage to the ciliary body, especially at the interface between pars plana and pars plicata, with pigment dispersion in the area of laser treatment."[8]

It is more difficult to unravel the facts pertaining to the last of the five reports.[7] The authors set out to study the effects of laser cyclophotocoagulation on five eyes, each of which had been enucleated from 1 to 3 days postoperatively. But only two of them were deemed adequate for histopathologic study. One of the eyes had been glaucomatous. The other had not been glaucomatous, but was scheduled for enucleation because of complications resulting from failed retinal detachment operations. The authors did not indicate which of their photomicrographs pertained to which case. Nor did they indicate the interval from treatment to enucleation or the power settings used in treating the sites that are the subject of their illustrations. The authors regarded the most significant finding to be disruption of the ciliary epithelium with separation of the epithelial layers from the adjacent stroma. Compared with the full-thickness destructive lesions observed in the cases we are presenting, and as depicted in the four other brief reports in the literature, the ciliary muscle exhibited only minimal damage in the illustrations published by Blasini and colleagues.[7]

Most authorities regard direct damage of the ciliary epithelium as the mechanism by which transscleral cyclophotocoagulation lowers intraocular pressure.[7,20] Other mechanisms have been suggested, particularly the possible role of inflammation in contributing to the reduction of intraocular pressure.[21] Preliminary studies have shown that those patients who have attained satisfactory lowering of intraocular pressure after undergoing ciliary ablation typically have ciliary body detachments demonstrable on ultrasonographic examination (personal communication, D. Jackson Coleman, MD, May 8, 1995). This suggests another mechanism by which neodymium:YAG cyclophotocagulation may exert its pressure-lowering effect.

All of the human glaucomatous eyes that have been studied histopathologically following neodymium:YAG laser cyclophotocoagulation have been treatment failures. The therapy failed to lower the intraocular

pressure to a suitable level, or complications supervened, leading to enucleation. Nevertheless, the structural changes induced in the ciliary body by laser therapy are remarkably comparable in these reports.

One wishes for the opportunity to study pathologically the eyes of patients who have undergone cyclophotocoagulation and who have achieved a satisfactory lowering of intraocular pressure. But glaucomatous eyes that have been successfully treated by any of the standard techniques rarely have become available for pathologic examination, and information on this subject is astonishingly absent from textbooks of ophthalmology, glaucoma, and ophthalmic pathology.[22]

Key conclusions of our study are as follows:

1. Energy levels ranging from 4.4 to 5.6 were effective in producing appropriate lesions.

2. Direction of the laser beam 1 to 1.5 mm behind the limbus caused severe destructive lesions of the pars plicata.

3. Toward the periphery of the individual treatment sites, the stroma and ciliary muscle continued to exhibit severe degeneration, as did the epithelium lining the valleys between the crests of the ciliary processes; but in those peripheral zones of individual treatment sites, the epithelium lining the crests of the ciliary processes survived and appears normal.

4. Bleblike separations of the ciliary epithelium from the adjacent stroma, particularly along the posterior aspect of the ciliary body lesions, are a prominent early feature of neodymium:YAG cyclophotocoagulation.

5. The pigmented epithelium is more vulnerable to laser energy than is the nonpigmented epithelium of the ciliary body.

6. The destruction of the ciliary epithelium is permanent.

7. Deeply pigmented persons have more melanocytes in the ciliary body muscle and stroma than do more lightly pigmented individuals, a circumstance that renders the tissues more vulnerable to laser energy.

8. The ciliary muscle was always severely damaged.

9. No scleral injury was observed other than evanescent, focal areas of edema of the deep sclera.

10. Except in the episclera, inflammatory cells were strikingly few in number, a circumstance providing support for the clinical observation that eyes treated with laser cyclophotocoagulation exhibit less of an inflammatory response than do those treated with cyclocryotherapy.

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ADDENDUM

Since this paper was presented, our attention has been called to a report we overlooked in our review of the literature. The authors of that publication summarized the results of histopathological examination of three glaucomatous human eyes that had been treated with neodymium: YAG laser cyclophotocoagulation.

Marsh P, Wilson DJ, Samples JR, et al: A clinicopathologic Correlative Study of Noncontact Transscleral Nd:YAG Cyclophotocoagulation. *Amer J Ophthalmol* 1993; 115:597-602.

DISCUSSION

DR. RALPH C. EAGLE. I would like to thank Dr Ferry for allowing me to review histologic sections from his cases. I am in total agreement with his histopathologic observations.

Although the eyes examined by Dr Ferry were, as he emphasized, glaucomatous human eyes, laser cyclophotocoagulation failed to successfully control the intraocular pressure. In 1977 Dr Ferry published a paper on the histopathology of cyclocryotherapy in the *Transactions of the American Academy of Ophthalmology and Otolaryngology*.[1] The section of that paper includes the following statement, which is equally germane to the present study. Referring to the eyes he studied, Dr Ferry stated: "All of the eyes had been removed surgically...usually because of persistence of pain and elevated intraocular pressure... It would be most interesting to examine postmortem eyes from a group of patients who had been treated with cyclocryotherapy and whose intraocular pressure had been controlled thereby."

A fairly large number of histopathologic studies have examined the effects of Nd:YAG cyclophotocoagulation on the eyes of living and dead humans and several species of animals. To my knowledge, however, only a single eye has been examined histopathologically after successful Nd:YAG cyclophotocoagulation for glaucoma.[2] That case was briefly reported by March and Shaver as a letter in the March 1989 issue of *Ophthalmology*. Their patient had a posterior malignant melanoma and neovascular glaucoma. The eye was enucleated 9 days after Nd:YAG cyclophotocoagulation, which had reduced the intraocular pressure from 48 to 24 mm Hg. Histopathologic examination showed destruction of the ciliary processes. The laser had been applied 2 mm posterior to the limbus.

Most of the experimental studies that have dealt with the actions of Nd:YAG cyclophotocoagulation assume that the procedure lowers intraocular pressure by destroying the pars plicata and decreasing aqueous production. This basic paradigm is implicit in the term "cyclodestructive" applied to the procedure.

As Blasini and associates[3] have emphasized, however, the precise mechanism by which transscleral cyclophotocoagulation lowers intraocular pressure is uncertain. Although it is possible or even probable that Nd:YAG cyclophotocoagulation works by decreasing the production of aqueous by the ciliary body, other mechanisms may be operative. Schubert[4] has proposed that the procedure might lower intraocular pressure by increasing aqueous outflow, either by transscleral filtration or by increasing posterior uveoscleral outflow. Evidence for this latter somewhat controversial hypothesis are several clinical studies that employed posteriorly placed laser burns.[5,6] Schwartz and Moster[5] reported successful control of intraocular pressure in 69% of their patients using laser applications 3 mm posterior to the limbus.

The pars plicata is only about 2 mm in length. A burn applied 3 mm posterior tho the limbus is located well within the pars plana and totally spares the ciliary processes. Additional circumstantial evidence for increased aqueous outflow after cyclodestructive surgery is provided by a tonographic study published in the *Klinische Monatsblätter für Augenheilkunde,* which documented increased facility of aqueous outflow after cyclocryotherapy.[7]

Controversy also surrounds the association of Nd:YAG cyclophotocoagulation with sympathetic uveitis. At least six cases of sympathetic uveitis have been reported in patients who had undergone Nd:YAG cyclodestructive procedures, including a cluster of cases at the University of Illinois, where the incidence of sympathetic ophthalmia after Nd:YAG cyclodestruction was reported to be 5.8%.[8-11] There was a tendency to discount the role of laser cyclodestruction in earlier reports, because most patients had also undergone multiple invasive surgical procedures, including glaucoma or cataract surgery. Last year, however, Bechrakis and associates[11] reported a case of sympathetic uveitis that occurred after laser cyclophotocoagulation in a patient with Coats' disease and neovascular glaucoma who had no history of surgery or perforating injury. That case certainly raises the level of concern about a possible association between Nd:YAG cyclophotocoagulation and sympathetic uveitis. When I was a resident I was taught that the only operation that should be performed on a blind eye is enucleation. Perhaps we should reexamine this old clinical dictum with Bechrakis' case in mind. In this regard, it must be noted that two of the eyes in Dr Ferry's series were no light perception when Nd:YAG cyclophotocoagulation was performed. Fortunately, the association between Nd:YAG cyclophotocoagulation and sympathetic uveitis appears to be quite rare. I have not seen a case of sympathetic uveitis that has occurred after Nd:YAG cyclophotocoagulation in Philadelphia, and would like to ask the members if they are aware of other cases.

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DR ROBERT STAMPER. I truly enjoyed this paper. I think transscleral Nd:YAG treatment is a modality of increasing importance in the management of end-stage glaucoma. I congratulate Dr. Ferry on addressing a significant issue. I would like to ask one question. We do know that there are two different approaches used in this therapy - the contact and the non-contact. I have no idea if there is any practical, histological or any other difference between the two approaches. However, I do think it important to identify which madality was used here.

DR PAUL KAUFMAN. I found both the paper, and Dr Eagle's discussion about the mechanism by which the modality works, fascinating. They show the number of stimulating questions that can be raised by a very small case series. It was pointed out that the epithelium at the crest of the ciliary processes near the periphery of the lesion was still intact. Aqueous humor is made in the ciliary epithelium at the crest of the processes, not in the valleys, based on ultrastructural characteristics of the epithelium. For this reason it might be interesting to get some idea as to the percentage of crest epithelium around the circumference that you feel might still be intact. The second point relates to other possible mechanisms of action besides secretory suppression. It was pointed out that the ciliary body was detached or possibly detached, particularly in cases in which the pressure seemed to be especially low. This raises the possibility of enhanced uveoscleral outflow via a cyclodialysis-like mechanism, rather than merely secretory suppression, as was shown experimentally by John Pederson. Furthermore, destruction of the ciliary muscle might also promote prostaglandin synthesis. Even though inflammation was not seen, there might have been a chronically enhanced level of eicosanoid synthesis as a consequence of tissue destruction. This would also tend to increase uveoscleral outflow; that is how we think these compounds work in lowering intraocular pressure. I would be interested in your comments on these points.

DR DOUGLAS GAASTERLAND. When looking at the histopathologic response of ciliary tissue to transscleral cyclophotocoagulation, we must consider the wavelength, direction, energy, and duration of exposure. The wavelength affects absorption by tissue pigments. The direction affects where the light intercepts the tissue and the thickness of the target zone. The energy and duration determine the power at the target. For example 5.4 Joules in 20 milliseconds will be likely to explode target tissue while the same energy in

2 1/2 seconds will coagulate the tissue. These considerations are also important when we consider the clinical response of the eye to this laser treatment.

DR ANDREW FERRY. I thank Dr Eagle for his authoritative review of the paper. He commented on reports of association of sympathetic uveitis with previous neodymium:YAG laser cyclophotocoagulation. Some of the patients described in those reports also had a history of a previous penetrating wound, either accidental or surgical (eg, full-thickness glaucoma surgery), which is a well-known risk factor for developing sympathetic uveitis. In patients treated with laser cyclophotocoagulation, scleral perforation has been recognized and reported in a few instances. Unrecognized scleral perforations have been postulated as being a possible pathogenetic factor in those cases in which a patient without a history of previous accidental or surgical penetration of the eye developed sympathetic uveitis.

The two men we are reporting as cases 2 and 3 each had a unilateral glaucoma that had reduced vision profoundly. In case 2, there was no light perception. In case 3, vision was limited to perception of light. The fellow eye was normal in both patients. In view of sympathetic uveitis being a possible risk factor in patients undergoing neodymium:YAG laser cyclophotocoagulation, the wisdom of having subjected these blind, painful eyes to laser therapy is open to question.

In response to Dr Stamper's question, the instrument used for cyclophotocoagulation in each of the patients we are reporting was the Lasag Microruptor II.

In adding to the discussion of mechanisms other than ablation of ciliary epithelium by which laser cyclophotocoagulation may induce lowering of intraocular pressure, Dr Kaufman touched upon one that has received relatively scant attention. Stimulation of the ciliary muscle, resulting in a pull on the scleral spur or trabecular meshwork, has been postulated for decades as one of the mechanisms by which use of miotics may improve outflow facility. When the ciliary muscle undergoes extensive destruction, as it does in response to laser cyclophotocoagulation, one could argue that the muscle's ability to exert its influence upon aqueous outflow facility has been severely impaired.

Dr Gaasterland emphasized the importance of paying close attention to the fine points involved, including precise determination of the various settings, in use of these powerful instruments. Even aiming the noncontact laser is not easy to do and is an activity not to be undertaken lightly. The remarkable accuracy in direction of the laser beam, as evidenced by destruction of the ciliary processes (but with sparing of the pars plana), seen in the cases we are describing and in the several reported in the literature is a tribute to the skill of the surgeons involved.

In closing, I wish to relate an experience I had in 1981. My wife and I

had occasion to spend 3 weeks in East Germany, when that geopolitical region was still firmly under the Soviet yoke. One day, Mercedes and I came upon this most attractive monument dedicated to the memory of Albrecht von Graefe. It is situated along a public street, just outside the Charité Hospital in East Berlin.

This splendid memorial was completed in 1882, 12 years after von Graefe's death. In his right hand, he holds the ophthalmoscope of von Helmholtz; his left hand rests upon the arm of an antique chair.

The multicolored majolica panels bear quotations from Friedrich Schiller's play, Wilhelm Tell.

On the left: "Oh, the light of the eye is a noble gift of Heaven - All creatures live from the light."

On the right:"Every fortunate creature, even the plant, joyfully turns toward the light."

Albrecht von Graefe is widely regarded as the greatest ophthalmologist who ever existed. When discussing the newer surgical methods of treating glaucoma, such as use of the laser, we recall that one of von Graefe's outstanding achievements was the introduction of iridectomy for glaucoma, a procedure that afforded the first effective surgical treatment for this disease.

Monument dedicated to the memory of Albrecht von Graefe; located outside the Charité Hospital in East Berlin.