

# HISTOPATHOLOGIC STUDIES OF ISCHEMIC OPTIC NEUROPATHY\*

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## ABSTRACT

*Purpose:* To define the histopathologic features of eyes in which a pathologic diagnosis of ischemic optic neuropathy had been made in the years 1951 through 1998.

*Methods:* The following data were documented: age of patient, race, sex, source of tissue, cause of death, clinical history, interval from loss of vision to death, enucleation, exenteration, and biopsy. The histopathologic criteria for diagnosis of ischemic optic neuropathy were the presence of localized ischemic edema, cavernous degeneration, or an area of atrophy located superior or inferior in the optic nerve. Cases with history of abrupt loss of vision were combined with reports from the literature to construct a time table of histopathologic features and associated conditions.

*Results:* Ischemic optic neuropathy was present in 193 eyes. There were 88 females and 65 males. The average age was 71.6 years. Ischemic edema without (early) and with (later) gitter macrophages was present in 26 (13.5%). Cavernous degeneration was present in 69 nerves (36%). Mucopolysaccharide (MPS) was present in 37 cavernous lesions 1 month or longer after loss of vision. Cavernous lesions were seen in 3 eyes in which peripapillary retinal nerve fiber layer hemorrhage had been observed prior to death. Atrophic lesions, the most common pattern, were observed in 133 optic nerves (66.8%). More than 1 ischemic lesion was seen in 38 optic nerves (19.7%). Bilateral ischemic lesions were seen in 50 (35.2%) of 142 paired eyes.

*Conclusions:* Ischemic optic nerve lesions are initially acellular and later show macrophage infiltration. Cavernous lesions with MPS are present 4 weeks or longer after vision loss. The location of MPS posteriorly and along the internal margin suggests that MPS is produced at the edges of lesions. Progressive vision loss in ischemic optic neuropathy may be secondary to compression of intact nerve from ischemic edema and cavernous swelling, or a second ischemic lesion.

*Tr Am Ophth Soc 2000;98:203-222*

## INTRODUCTION

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Interest in the histopathology of ischemic optic neuropathy can be placed in 2 periods. The first period was initiated by I. Schnabel<sup>1-3</sup> at the end of the 19th century in a series of articles in which he presented descriptions of optic nerve lesions that he attributed to glaucoma. One variant has become known as Schnabel cavernous optic atrophy.

Between 1901 and 1914, German colleagues reported over 30 articles that noted changes similar to those described by Schnabel in nerves associated with glaucoma and myopia.<sup>4-7</sup> In 1914, Ichikawa<sup>8</sup> summarized the literature to that time, presented his own cases, and contended that Schnabel cavernous lesions were the result of glaucoma causing a progression from small to large retrolaminar

cystic lesions, which eventually coalesced to form large caverns. Few articles were published between 1915 and 1945.

The second phase began with articles by Loewenstein<sup>9,10</sup> in 1945 and Wolfe<sup>11</sup> in 1947. These investigators described their material and redirected attention to material presented by Schnabel<sup>1,3</sup> in 1892 and 1905. Loewenstein and Wolff disagreed with Schnabel's emphasis that glaucoma was responsible for large areas of atrophy that had become known as Schnabel cavernous optic atrophy. Other investigators<sup>12-14</sup> challenged Schnabel's ideas, arguing that interference with blood supply was responsible.

The histopathologic features of acute ischemic optic neuropathy were further defined in a series of papers between 1950 and 1983. These included several studies of ischemic optic neuropathy in the setting of giant cell arteritis.<sup>15-23</sup>

In 1971, Knox and Duke<sup>24</sup> reported the changes in an eye that had experienced an initial sudden and then progressive loss of vision from internal carotid artery occlusion. Autopsy studies reported by Giarelli and associates<sup>25</sup> in 1977 and by Isayama and Takahashi<sup>26,27</sup> in 1983

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further defined the nature of ischemic lesions.

The purpose of this report is to describe the histopathologic features of ischemic optic neuropathy in 193 eyes accessioned from 1951 through 1998.

## MATERIALS AND METHODS

The pathologic material studied for this report was obtained from the collection of the Wm. R. Green Laboratory of Eye Pathology of the Wilmer Ophthalmological Institute. This collection is based on eyes from eye banks, autopsies, enucleations, exenterations, interlaboratory exchanges, and biopsies. Ischemic optic neuropathy was designated as anterior when the process occurred within 10 mm of the lamina cribrosa and was designated as posterior when the process was greater than 10 mm posterior to the lamina cribrosa.

Sections of the eyes through the plane of the pupil, optic nerve head, and macula and cross sections of the optic nerve had been prepared and stained with hematoxylin-eosin and Verhoeff-van Gieson. Findings on microscopy led to additional staining as indicated with periodic acid-Schiff, Mallory trichrome, colloidal iron and/or alcian blue, and the Bodian silver stain.

In 1994, a list of cases indexed as ischemic optic neuropathy was prepared. The criteria for a diagnosis of ischemic optic neuropathy were based on histopathologic observations of focal ischemic edema, cavernous lesions, and atrophic areas. Atrophic lesions were designated as ischemic optic neuropathy when located superiorly or inferiorly in the absence of evidence of glaucoma.

Data recorded included age, sex, race, source of specimen, cause of death, and time from loss of vision to death. Morphologic details included location, size, type and pattern of lesions, unilaterality or bilaterality, staining characteristics, and presence of cells, as seen in longitudinal and cross sections of optic nerves. Sketches of areas of involvement of each nerve were recorded. Data were entered into a computerized data base for analysis and collation.

The types of lesions identified were: acute ischemic edema (acellular and cellular), cavernous atrophy, and atrophic lesions. The number of nerves with more than 1 lesion and the number of cases with bilateral ischemic lesions were determined.

A time table of histopathologic features was constructed by combining details from cases with a clear history of abrupt loss of vision and reports from the literature.

## RESULTS

One hundred ninety-three optic nerves were diagnosed as

having ischemic optic neuropathy: 142 postmortem, 6 enucleations, 2 exenterations, 2 biopsies of optic nerves, and 4 interlaboratory exchanges. The average patient age was 71.6 years. Age distribution of all cases is depicted in Fig 1. There were 88 females and 65 males. The number and types of ischemic lesions are recorded in Table I. Bilateral ischemic lesions were found in 50 (35.2%) of the 142 paired eyes. More than 1 ischemic lesion was found in 38 (19.7%) of the 193 ischemic nerves. The first eye in this study was accessioned in 1951 and the last in December 1998. In that period, approximately 61,000 postmortem cases were accessioned. We identified 27 cases in which clinical details were well known and documented by ophthalmologists (Table II). There were 12 cases from the Wilmer Institute, 5 of which have been published.<sup>24,30,32,39,43</sup> Tissues obtained by interlaboratory exchange of 3 cases, which had been published from other institutions, were studied and included.<sup>31,35,44</sup> Twelve cases published from other institutions but not studied personally included 9 with giant cell arteritis<sup>15-23</sup> and 1 each of blood loss,<sup>12</sup> polymyalgia rheumatica,<sup>45</sup> and arteriosclerosis.<sup>46</sup> Three morphologic forms were defined.

## MORPHOLOGIC TYPES OF ANTERIOR ISCHEMIC OPTIC NEUROPATHY

### *Recent Ischemic Edema (Acellular Type)*

"Ischemic edema," a term coined by C. Miller Fisher,<sup>26,29</sup> was present in 26 eyes (13.4%) and is characterized by edema, loss of cellularity, distention of nerve fiber bundles in the retrolaminar area, and distention of the collagen lamellae of the lamina cribrosa plate. Fibrovascular septae are separated but intact, and the spaces formerly occupied by axons and myelin have no cells. The ischemic process may extend into the optic nerve head.

Multiple calcific emboli from cardiac catheterization, 24 hours before death, was the apparent cause of acute acellular ischemic edema in 1 case (Fig 2). Thrombotic emboli caused a similar lesion in a second case. A similar, previously reported case was associated with platelet-fibrin<sup>30</sup> (Fig 3). Chondrosarcoma tumor emboli were observed in 1 case.<sup>31</sup> Subarachnoid hemorrhage

TABLE I: NUMBER AND TYPES OF ISCHEMIC LESIONS

Eyes studied	279
Optic nerves with ischemic lesions	193
Total number of lesions	228
Ischemic edema	26
Cavernous degeneration	69
Atrophic	133
Bilateral lesions	50 (35.2%)
Two lesions, same nerve	38 (19.7%)

*Histopathologic Studies of Ischemic Optic Neuropathy*

**TABLE II: CHRONOLOGY, ASSOCIATED CONDITIONS, AND HISTOPATHOLOGIC FINDINGS IN ISCHEMIC OPTIC NEUROPATHY**

INTERVAL	EP NO./REFERENCE	ASSOCIATED CONDITION	FINDINGS
<1 Day	74706 (Fig 2)	Cardiac catheterization, calcific emboli	Acellular infarct, anterior and posterior to lamina
1 Day	88384 (Fig 4)	Ruptured intracranial aneurysm subarachnoid hemorrhage	Subarachnoid, subretinal, and intraretinal hemorrhage; anterior acellular ischemic edema
9 Days	56947, Burde et al <sup>31</sup>	Chondrosarcoma emboli	Acellular infarction, temporal half
9 Days	74655, Johnson et al <sup>28</sup>	Gastrointestinal bleed, hypotension	Bilateral ischemic edema, centrally acellular, gitter cells at margins of lesions
10 Days	49234 (Fig 8)	ASCVD, rupture cardiac papillary muscle, septic shock	Bilateral ischemic edema, anterior and posterior to lamina, hypocellular, no MPS
14 Days	Spencer & Hoyt <sup>18</sup>	Giant cell arteritis	Retrolaminar cellular ischemic necrosis with gitter macrophages
14 Days	7945439 (Fig 15)	Bilateral jugular vein ligation for cancer of throat	Central hemorrhagic infarction with gitter cells at margin, no MPS
15 Days	Kreibig <sup>16</sup>	Giant cell arteritis	Retrolaminar infarction, upper portion of nerve, acellular center, gitter cells at periphery
18 Days	27007 <sup>24</sup> (Fig 13)	Internal carotid occlusion, suicide 18 days after loss of vision, which had progressed	Ischemic edema, small retrolaminar temporal lesion, gitter cells, prelaminar edema nasally
18 Days	Hinzpeter & Naumann <sup>22</sup>	Giant cell arteritis	Optic nerve head edema, postlaminar hypocellular cavernous spaces, minimal gitter cells, MPS anterior and posterior to lamina
19 Days	Rootman & Butler <sup>23</sup>	Giant Cell Arteritis, gastrointestinal blood loss, diabetic ketoacidosis	Bilateral retrolaminar infarctions
? Days	40441 (Fig 16)	Diabetes, mucormycosis, orbital cellulitis, exenteration	Two infarctions with gitter cells, vasculitis and fungal occlusions of blood vessels
20 Days	Goerlitz <sup>12</sup>	Blood loss	Mild prelaminar cellular edema, small retrolaminar infarction, MPS not reported
27 Days	75869 <sup>32</sup> (Fig 20)	Lymphoma, sepsis	Central ischemia with gitter cells, central retinal artery occlusion, gram-positive cocci in thrombus
3 Weeks	Rödenhauser <sup>19</sup>	Giant cell arteritis	Lymphocytic and histiocytic infiltrate of nerve bundles
3+ Weeks	Stefani et al <sup>45</sup>	Polymyalgia rheumatica, diabetes, heart failure	Bilateral retrolaminar caverns, chiasm and geniculate atrophy
4+ Weeks	78342	Lower field loss documented 1 month before death	Large acellular cavernous lesion in temporal half of nerve, MPS
4.5 Weeks	75496, Margo et al <sup>44</sup>	Penetrating keratoplasty, endophthalmitis, vitrectomy, enucleation	Cavernous distention, staining for MPS not reported
4.5 Weeks	Henkind et al <sup>21</sup>	Lymphocytic infiltrates around arteries	Infarction with gitter cells immediately behind cribriform plate
8 Weeks	46188 <sup>43</sup> (Fig 19)	Progressive loss of vision, III palsy, mass in apex of orbit, mild diabetes	Infarction with gitter cells
8 Weeks	Crompton <sup>17</sup>	Giant cell arteritis	Mild cellular edema, vasculitis of pial and central vessels
8 Weeks ?	42871 <sup>30</sup> (Fig 3)	Perinephric abscess, sepsis, auricular fibrillation	Multiple fibrin emboli, straight-walled hypocellular cavern, AB positive staining of "gitter cells"
9 Weeks	Greenfield <sup>15</sup>	Giant cell arteritis, coronary, carotids, cerebral, retinal, ciliary	Optic disks sunken, sparse ganglion cells, optic nerves sudanophilic degeneration of myelin, slight microglial reaction
16 Weeks	Manschot <sup>20</sup>	Giant cell arteritis	Clinical central retinal artery occlusion, diffuse optic atrophy
24 Weeks	71103	Splinters, hemorrhage noted left nerve head	Retrolaminar temporal cavern, secondary atrophy nerve in transverse and cross sections
3 Years	Kubota et al <sup>46</sup>	Generalized arteriosclerosis	Bilateral prelaminar and postlaminar cavernous degeneration with MPS
3 Years	48729	Exenteration left orbit, squamous cell carcinoma, left paranasal sinuses	Large and long area of cavernous degeneration with MPS

ASCVD, arteriosclerotic cardiovascular disease; MPS, mucopolysaccharide

from ruptured intracranial aneurysm caused hemorrhage along the optic nerve sheath, under, within, and anterior to the retina in the vitreous (Terson's syndrome). The anterior portion of the nerve shows early necrosis without any cellular infiltrate (Fig 4). Further examples of ischemic edema are presented in Figs 5 through 12.

#### *Ischemic Edema With Gitter Cells (Cellular)*

Nerve fiber bundles are edematous with swollen macrophages ("gitter cells") (Figs 13 through 23). This pattern was present in 7 cases. In 1 of these cases, the interval known between visual loss and death was documented at 18 days.<sup>24</sup> None of these ischemic edema areas with or without a cellular infiltrate stained positively for mucopolysaccharide (MPS).

Severe optic nerve head edema and crowding of peripapillary retina were associated with large retrolaminar infarctions in 5 cases (Figs 2, 4, 5, 8, and 9). The optic nerve head is swollen on the same side but may be swollen on the side opposite the area of infarction.

Etiologically associated conditions were internal carotid artery occlusion<sup>24</sup> (Fig 13), giant cell arteritis, vasculitis associated with rheumatoid arthritis (Fig 6), and lymphoma with sepsis<sup>32</sup> (Fig 20).

#### *Cavernous Lesions*

These lesions are characterized by swelling of nerve bundles, with separation and occasional rupture of septae, loss of axons and myelin, and formation of caverns (Figs 24 through 29). Caverns distend the area of infarction, stretch pial membranes on the surface, and compress adjacent, more normal, often central, nerve fibers (Figs 24 and 25). Sixty-nine cavernous lesions from 55 subjects were observed. Bilateral cavernous lesions were present in 14 subjects. Cavernous areas contained varying amounts of MPS in 37 nerves. Stains for MPS were negative in 7 and were not performed in 25.

Cavernous lesions varied in size from 120  $\mu$ m to involvement of the entire nerve in cross section (Figs 24 through 29). Large elongated lesions observed both anteriorly in longitudinal sections and posteriorly in cross sections were seen in 13 nerves. Cavernous lesions, involving less than 50% of the nerve diameter, were present in 18 nerves. There were 2 large lesions in which the cavernous process extended into the optic nerve head. Cavernous lesions appeared to compress adjacent optic nerve tissue in 17 specimens (Figs 24 and 25).

Small cavernous lesions were present just posterior to the lamina cribrosa (Fig 27) and were less frequently encountered more posteriorly (Figs 25, 26). Six eyes with clinically documented glaucoma had both glaucomatous optic atrophy and retrolaminar cavernous lesions. Three eyes had both large and small cavernous lesions. Three

eyes had severe glaucomatous atrophy from longstanding neovascular glaucoma and a large cavernous lesion (Figs 24 and 26). The fibrovascular pial septae were unusually thickened in these cases.

In 2 eyes, where there was no clinical history of glaucoma, the histopathologic findings of cupping and atrophy were compatible with glaucoma. One of these eyes had a large cavernous retrolaminar lesion that stained positively for MPS.

MPS deposition was observed in small (Figs 25B and C, and 27) and large (Figs 24A,B and D, and 25B) lesions. Subtle staining of cells and spaces was occasionally seen in the middle of the early lesions<sup>30</sup> or completely filling the cavernous spaces. In some eyes the greatest concentration of MPS staining was seen in cavernous spaces, centrally adjacent to more normal nerve, in the posterior aspect of retrolaminar nerve lesions (Fig 24A and B), and occasionally near the pia mater.

In 2 eyes, MPS was traced from vitreous through the optic nerve head to the area of staining posterior to the lamina cribrosa (Fig 24E and F). In 2 eyes there was MPS in the optic nerve head. In 4 cases, 2 cavernous lesions with different intensities of MPS staining were present in the same eye (Fig 25B and C).

MPS was not demonstrated in infarctions less than 18 days in duration that were associated with emboli, carotid occlusion, or giant cell arteritis or in lesions labelled cellular ischemic edema. The earliest appearance of MPS in this series was in a lesion that was at least 1 month in duration.

Optic disk drusen on 1 side and a small cavernous lesion on the opposite side were present in 3 eyes<sup>33,34</sup> (Fig 29).

A small cavernous lesion just posterior to compressed fibers of the lamina cribrosa (Fig 25D) was present in an eye with a large optic nerve head and amblyopia. The eye had been removed because of a malignant neoplasm in the apex of the orbit. This cavernous area was located at the anterior aspect of a large lesion that extended posteriorly to where MPS was mostly located in the central aspect of the nerve (Fig 25E). A peripapillary hemorrhage of the nerve fiber layer had been observed at the time of loss of a sector of visual field 3 years before autopsy. The small retrolaminar cavernous lesion illustrated in Fig 27A was seen in an eye that had sudden loss of vision and had been observed to have a juxtapapillary retinal nerve fiber layer hemorrhage. A third eye with a history of a peripapillary hemorrhage was subsequently found to have a retrolaminar cavernous degeneration.

#### *Atrophic Lesions*

These were characterized by loss of nerve fiber bundles, demyelination, collapse of the pial septae, and apparent glial hypercellularity (Figs 27, 30, and 31). Patterns included a spot (Fig 30B), sectoral wedge (Fig 30A), slab

(Fig 30C), and peripheral concentric (Fig 31). Figure 27 demonstrates a medium-sized, cavernous lesion anteriorly, an area of atrophy immediately posteriorly, and a wedge of atrophy in cross sections occurring in the same eye.

Of the 133 atrophic lesions, 65 (48.5%) were seen only in cross sections of the optic nerve of eyes in which no other lesions were present. The central retinal vessels were present in cross sections of 61 of those 65 nerves (Fig 30). This establishes that these atrophic areas were close to the globe in a zone defined as retrolaminar.<sup>35</sup> There were 4 atrophic lesions in which no central vessels were seen in cross section. These were located in areas definable as "posterior" because they were posterior to the optic nerve entry of the central retinal artery. The small cavernous lesions shown in Fig 28A and B were localized to the retrolaminar area of the nerve because of the presence of cross sections of artery and vein. These lesions stained intensely for MPS.

*Associated Condition*

Ischemic optic neuropathy was associated with systemic conditions that are likely important in the pathogenesis of ischemic optic neuropathy (Table III). Giant cell arteritis and rheumatoid arthritis (Fig 6) caused anterior cellular ischemic edema from vasculitis in 1 case each. Severe optic nerve ischemic necrosis (Figs 10 through 12) was found in the enucleated eye of a 60-year-old woman who was a heavy smoker, had retinal vasculitis, and was suspected of having Winiwarter-Buerger disease.<sup>36-38</sup> Mild vasculitis in mesenteric and coronary vessels was found at autopsy.

*Posterior Ischemic Optic Neuropathy*

Acute posterior ischemic edema with gitter cells was pres-

ent in 7 eyes that were obtained relatively early after onset vision loss. These were associated with jugular vein ligation<sup>39</sup> (Fig 17A and B), blood loss with hypotension,<sup>35</sup> Clostridia welchi orbital abscess, mucormycosis vasculitis, Degos disease,<sup>40-42</sup> diabetic optic neuropathy,<sup>43</sup> and lymphoma.<sup>32</sup>

Mucormycosis in a diabetic patient produced ethmoid sinus and orbital infection, which was eventually treated by exenteration. Examination disclosed an extensive area of ischemic infarction with gitter cells involving much of the optic nerve (Fig 16). Some short ciliary arteries were occluded by thrombus containing large, branching, nonseptated, hyphae (Fig 17).

Biopsy of an enlarged optic nerve disclosed thrombotic occlusion of some vessels, inflammatory cells in the adventitia of central blood vessels, and capillaries in optic nerve septae in a patient with Degos disease. Areas of gitter cells were present<sup>40</sup> (Fig 18).

A painful orbital apex mass of 2 months' duration was associated with loss of vision and oculomotor nerve palsy in a 57-year-old man with undiagnosed diabetes. Biopsy of the enlarged nerve revealed a large area of ischemic necrosis with gitter macrophages<sup>43</sup> (Fig 19).

Lymphoma diffusely infiltrated the fibrovascular septae, pia mater, and arachnoid, causing extensive infarctions of entire optic nerves of 1 patient who also had sepsis<sup>32</sup> (Figs 20 through 23).

**DISCUSSION**

The present study shows that ischemic optic nerve lesions are initially acellular and later demonstrate macrophage infiltration as observed in previous studies.

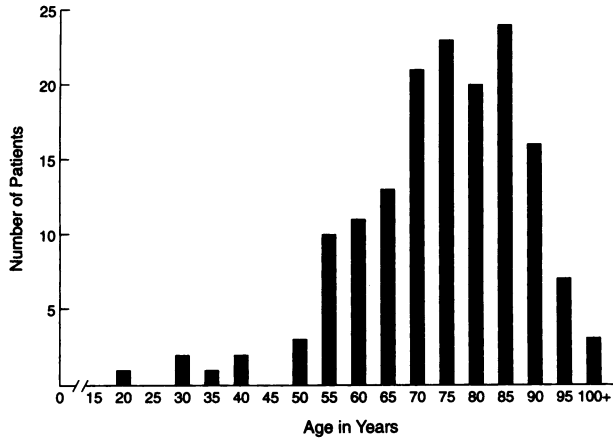
Duke-Elder and Scott<sup>54</sup> suggested that these macrophages have been transformed from existing glia. In contrast, Russell<sup>55</sup> and Konigsmark and Sidman<sup>56</sup> felt that macrophages enter ischemic lesions from blood circulating through damaged vessels.

Chuaqui and Tapia<sup>57</sup> describe histopathologic findings of recent brain infarctions in 30 autopsied cases. Few macrophages were seen before 8 days after onset, reaching the highest number from 15 to 27 days after onset. These investigators support Lindenberg's concept that intact and newly formed capillaries are "the main source of macrophages." Lindenberg, Walsh and Sacks<sup>58</sup> stated their belief that these macrophages originate from 3 sources: vascular pericytes, glia cells in the damaged tissue, and tissue macrophages.

Lindenberg and associates<sup>58</sup> observed phagocytosis by pericytes and microglia after approximately 48 hours of ischemia. Microglia migrated before becoming phagocytes and were most active in tissue loosened by edema. These macrophages may fill the dead tissue and then

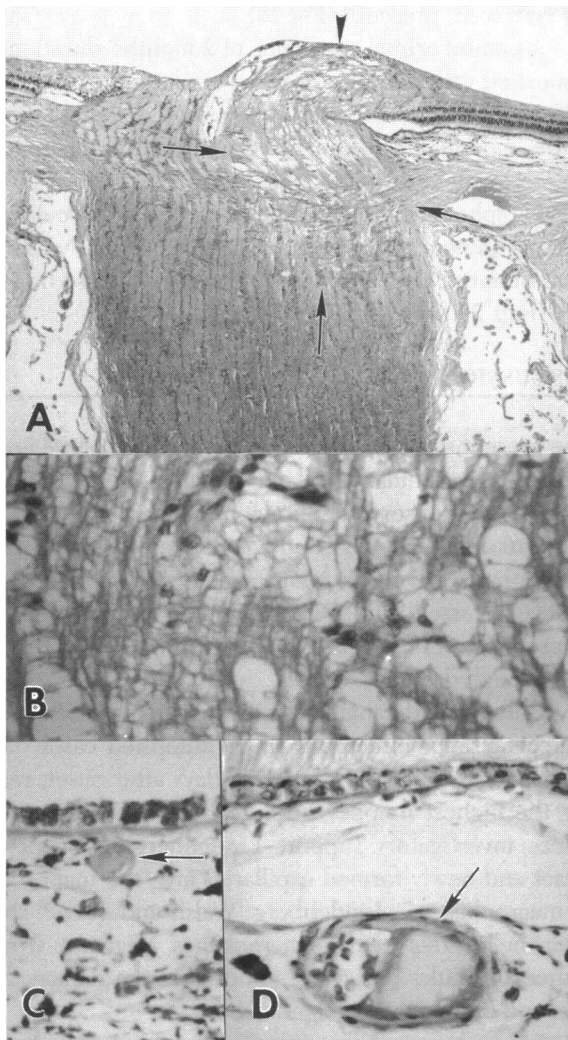
**TABLE III: CONDITIONS ASSOCIATED WITH ISCHEMIC OPTIC NEUROPATHY**

Giant cell arteritis <sup>15-23</sup>
Vasculitis: rheumatoid arthritis
Vasculitis: ?thromboangiitis obliterans
Mucormycosis: vasculitis and mycotic emboli
Gas gangrene
Degos syndrome <sup>40</sup>
Diabetes mellitus <sup>43</sup>
Lymphoma and sepsis <sup>32</sup>
Sepsis: after cerebro vascular accident
Alcoholism, gastrointestinal bleeding, Subdural hematoma <sup>35</sup>
Jugular vein ligation <sup>39</sup>
Subarachnoid hemorrhage, Terson's syndrome
Emboli
Chondrosarcoma <sup>31</sup>
Cardiac valve calcification
Platelet-fibrin <sup>39</sup>
Glaucoma



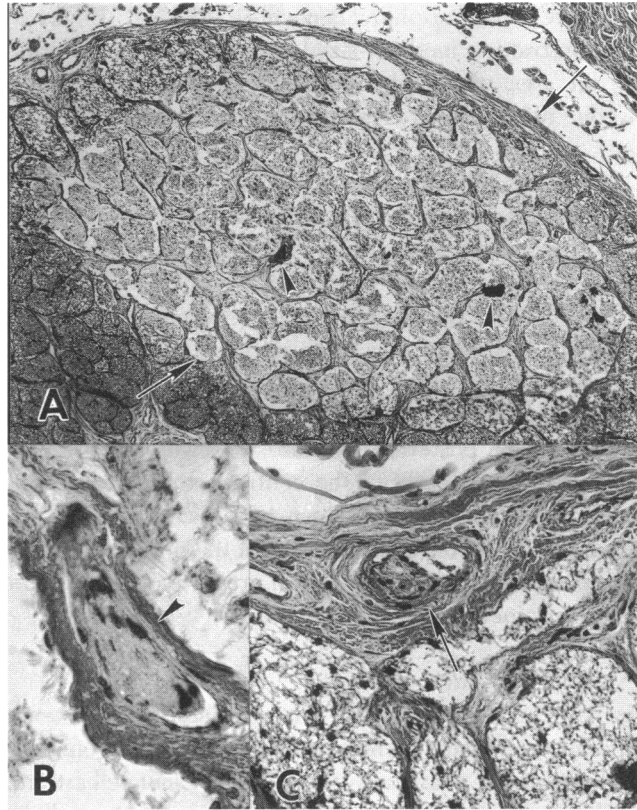
**FIGURE 1**

Age distribution of cases. Average age (71.6 years)



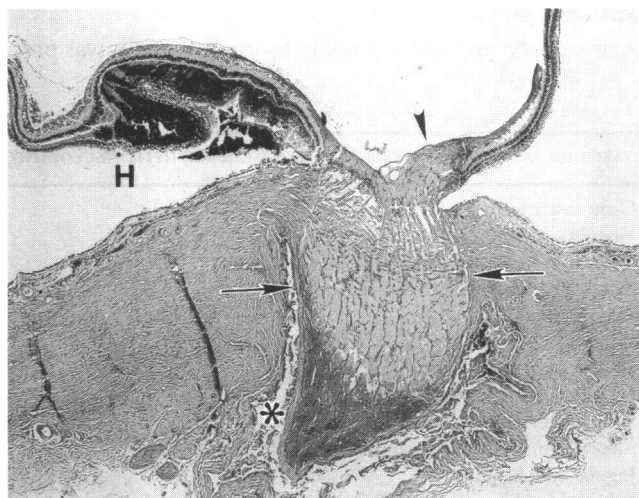
**FIGURE 2**

A, Acute bilateral prelaminar (arrowhead) and postlaminar (between arrows) acellular ischemic edema with dissolution of nerve fiber bundles (B) associated with calcific emboli (arrows) (C and D). Time, less than 24 hours (EP 74706) (hematoxylin-eosin, original magnification x35).



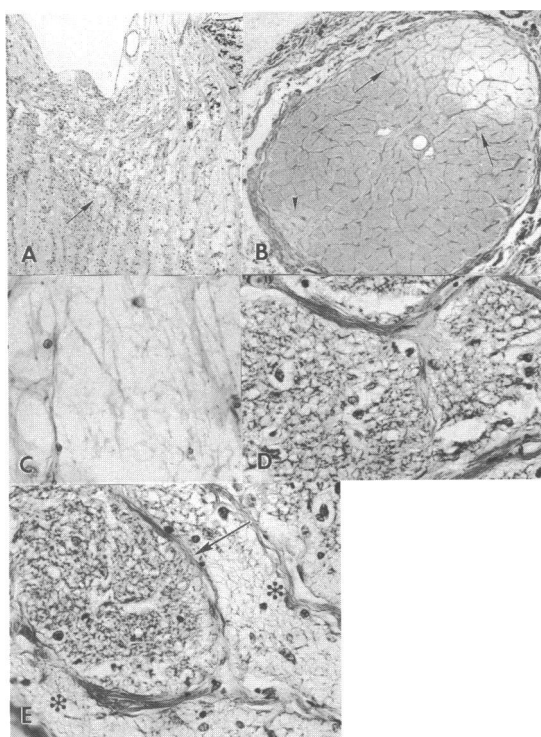
**FIGURE 3**

A, Large and superior sectorial infarction with hypocellular infarction (between arrows) in subject who had perinephric abscess, sepsis, atrial fibrillation, and multiple platelet-fibrin emboli. Interval from vision loss to autopsy was about 8 weeks.<sup>30</sup> Several vessels infibrovascular pial and pia mater (C, arrow) septae (arrowheads and B) were occluded by fibrin-containing emboli (EP 42871) (Verhoeff van Gieson: A, original magnification x50; phosphotungstic acid hematoxylin: B, x550; C, x220).



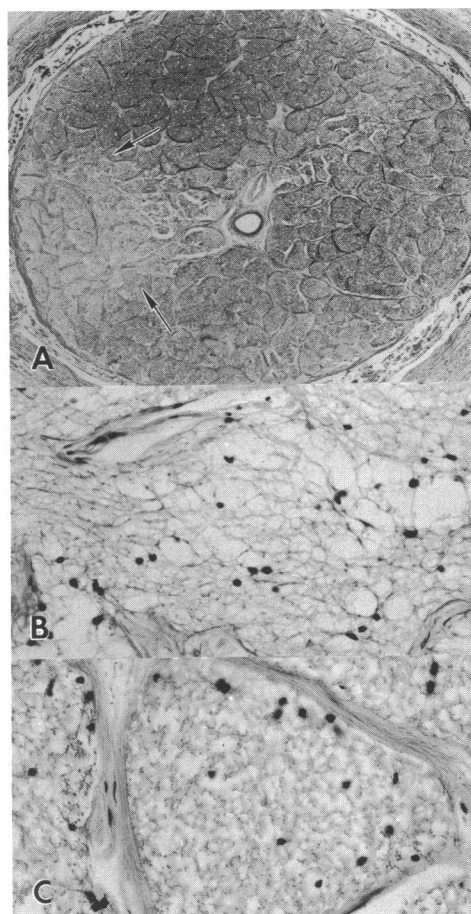
**FIGURE 4**

Anterior ischemic optic neuropathy (between arrows) with optic nerve head involvement (arrowhead) associated with Terson syndrome with subdural (asterisk) and subretinal (H) hemorrhage in a 69-year-old woman who died 1 day after intracranial hemorrhage (EP 88384) (periodic acid-Schiff, original magnification x20).



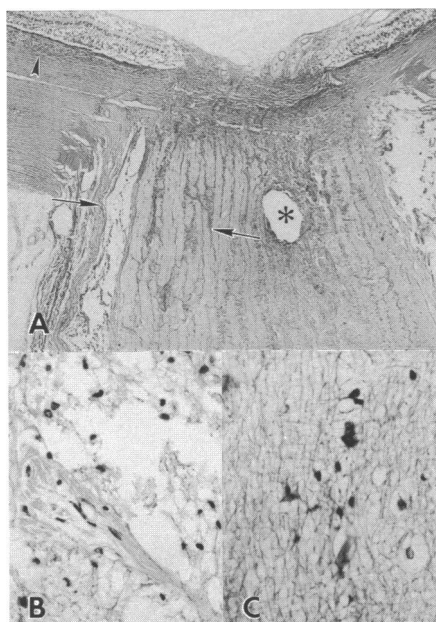
**FIGURE 5**

A and B, One large (arrows) and 1 small (B) (arrowhead) area of ischemic edema in 58-year-old woman with no ocular history. C, Area of ischemic edema with loss of myelin and nerve bundles. D, Area of normal nerve. E, Area of small infarct (asterisk) and relatively intact nerve fiber bundle (arrow) (Alcian blue: A, original magnification x50; C, x425) (EP 45857) (PTAH: B, x45; D and E, x400).



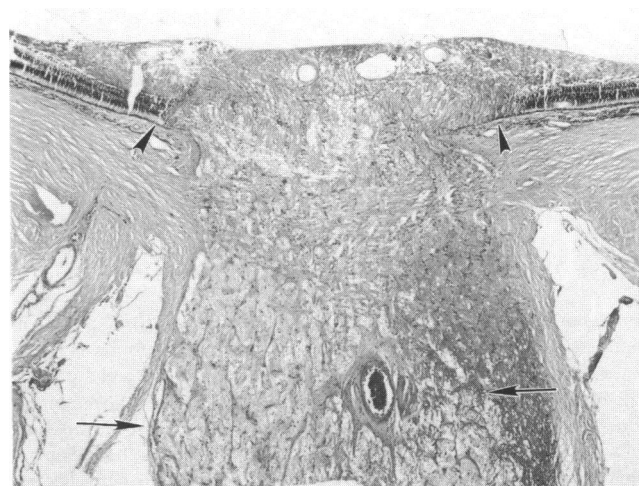
**FIGURE 7**

Cross sections of same case as in Fig 5. A, Wedge-shaped, acellular infarction (between arrows). Higher power contrasts infarcted area (B) and normal area (C) (hematoxylin-eosin: A, original magnification x30; B and C, x425).



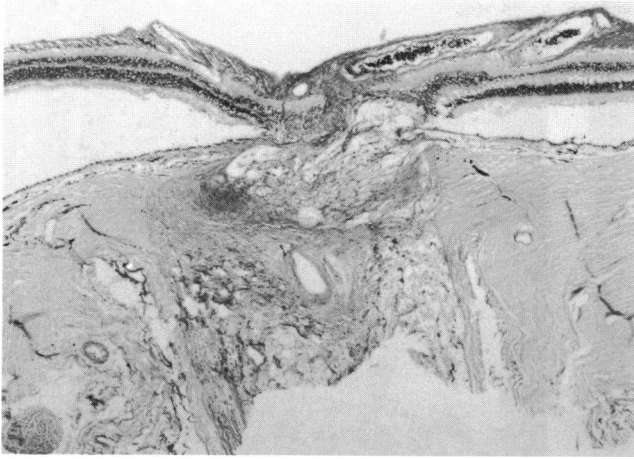
**FIGURE 6**

A, Retrolaminar, relatively acellular, ischemic edema (between arrows) in 81-year-old woman with history of rheumatoid arthritis. Central defect (asterisk) is an eye bank pin artifact. Higher-power view of infarcted area (B) and normal area (C) in longitudinal sections (EP 43097) (hematoxylin-eosin, original magnification: A, x20; B and C, x425).



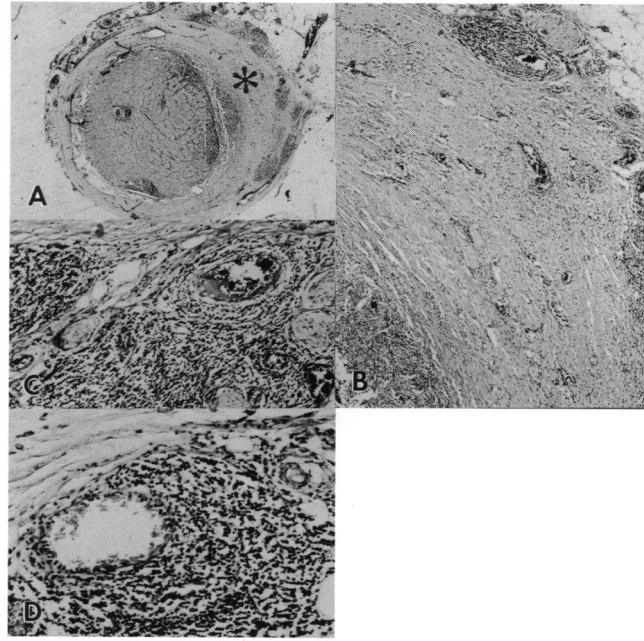
**FIGURE 8**

Recent infarction involving optic nerve head with swelling and peripapillary crowding of retina (arrowheads) and large retrolaminar area (between arrows) in patient with ruptured cardiac papillary muscle and hypotension who noted loss of vision 10 days prior to death (EP 49234) (hematoxylin-eosin: original magnification x35).



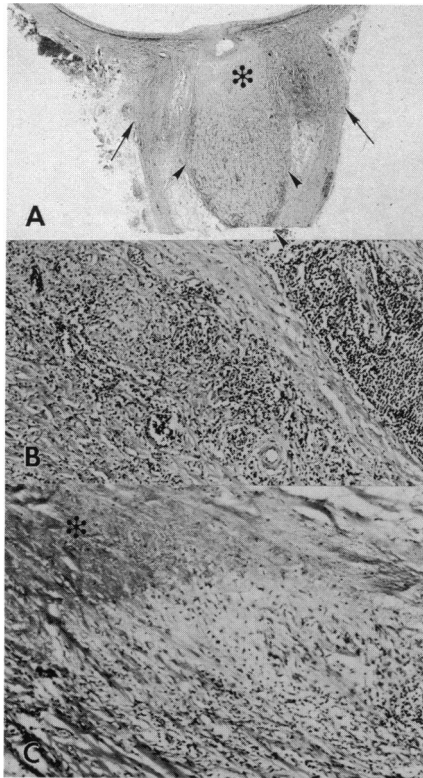
**FIGURE 9**

Extensive ischemic changes of distal optic nerve and optic nerve head in 81-year-old woman who died following cerebral vascular event (EP 67120) (hematoxylin-eosin: original magnification x35).



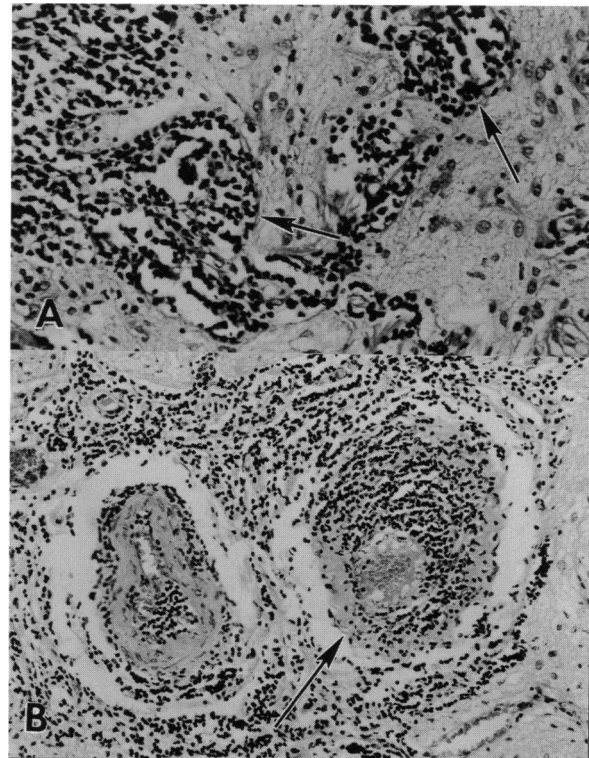
**FIGURE 11**

Same case as in Fig 9. A, Cross section shows infarction that involves much of nerve. Dura is markedly thickened (asterisk and B) and has prominent inflammatory cell infiltrate within dura (B and C) and epidural area (D) (hematoxylin-eosin: A, original magnification x10; B, x55; C, x100; D, x155).



**FIGURE 10**

Infarction involving optic nerve head and almost entire distal portion of optic nerve (A) in 58-year-old woman who had bilateral uveitis with retinal vasculitis and who was a heavy cigarette smoker and had a positive tuberculin skin test. She was considered to have von Winniwarther-Buerger disease. Right eye developed neovascular glaucoma and blindness and was enucleated. Autopsy 2 years later disclosed inflammation of mesenteric and cardiac muscle arteries. Retrolaminar area has loss of all cells (asterisk) and more proximal nerve has some remaining cells in fibrovascular pia septae (between arrowheads). Optic nerve head is markedly cupped. Leptomeninges, especially dura, are markedly thickened, have an intense lymphocytic infiltrate (B) and an area of necrobiosis (asterisk) and a zonal inflammatory cell infiltrate (C) (EP 31552) (hematoxylin-eosin: A, original magnification x7.5; B and C, x100).



**FIGURE 12**

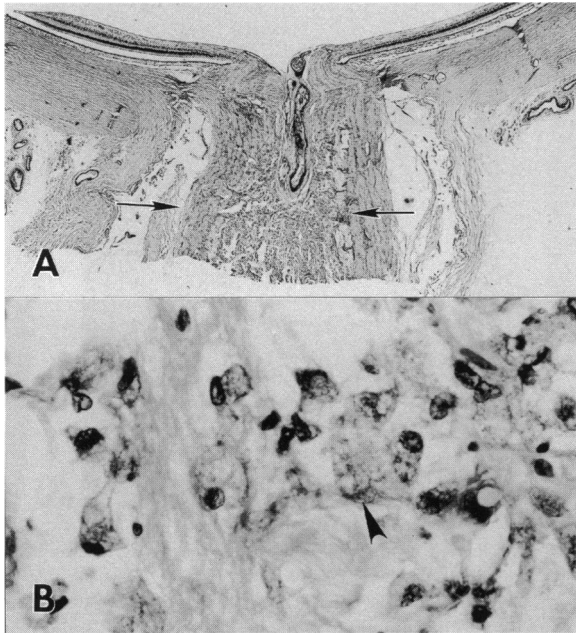
Same case as Fig 9. A, Area where fibrovascular pia septae are distended by intense lymphocytic infiltrate (arrows). B, Intense lymphocytic infiltrate is present around central retinal vessels and in wall of central retinal vein (arrow) (hematoxylin-eosin: A, original magnification x180; B, x260).





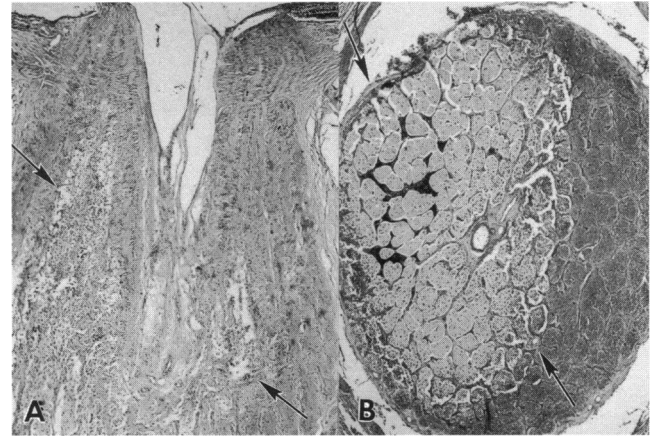
**FIGURE 13**

Anterior cellular ischemic lesion in 55-year-old man that was slowly progressive. Interval from start of vision loss to autopsy was 18 days.<sup>24</sup> There is dissolution of nerve fiber bundles with gitter cells in temporal portion of retrolaminar area (EP 27007) (hematoxylin-eosin: A, original magnification x50; B, x544).



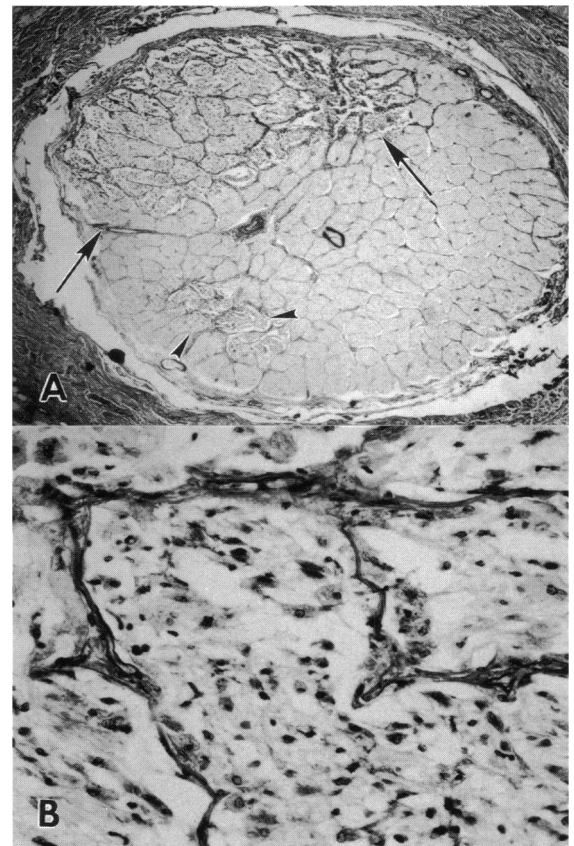
**FIGURE 14**

A, Recent infarction involving retrolaminar area of optic nerve with gitter cells (B) in 73-year-old woman who died of metastatic breast carcinoma (EP 65570) (periodic acid-Schiff: A, original magnification x30; B, x700).



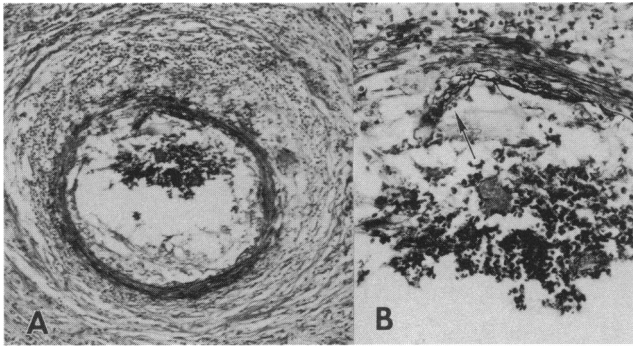
**FIGURE 15**

Extensive ischemic edema, examined 14 days after bilateral jugular vein ligation for lateral pharyngeal squamous carcinoma.<sup>39</sup> Longitudinal (A) and cross (B) sections illustrate large area of infarction (between arrows) that tapers toward lamina cribrosa. Many gitter cells are present. Infarction extended to orbital apex and is shown here at about 9 mm posterior to eye (EP 79454) (Verhoeff van Gieson: A and B, original magnification x30).



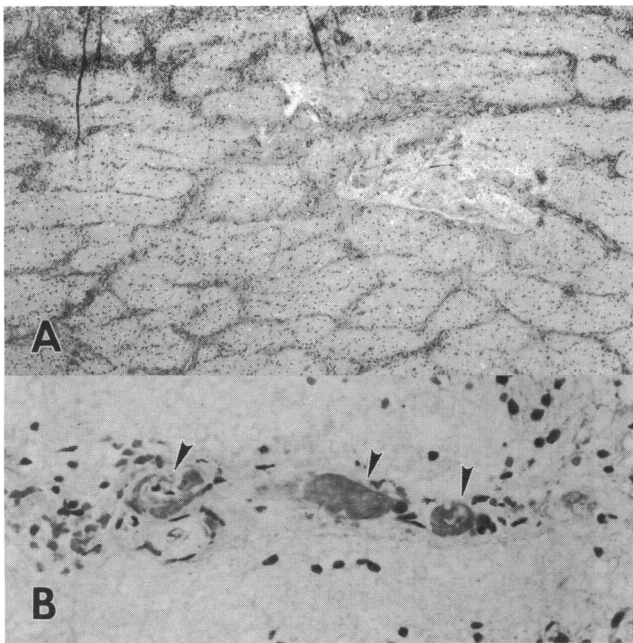
**FIGURE 16**

Extensive optic nerve infarction in 55-year-old diabetic man with mucormycosis who developed ophthalmoplegia and proptosis. Orbital exenteration was performed 4 weeks after onset of symptoms. A, Almost entire nerve in cross section has ischemic edema with 1 large (between arrows and B) and 1 small (between arrowheads) area with clusters of gitter cells (EP 40441) (hematoxylin-eosin: A, original magnification x30; B, x340).



**FIGURE 17**

Same case as in Fig 15. Short ciliary artery is occluded by thrombus with fungus (arrow). (periodic acid-Schiff: A, original magnification x100; B, x300).

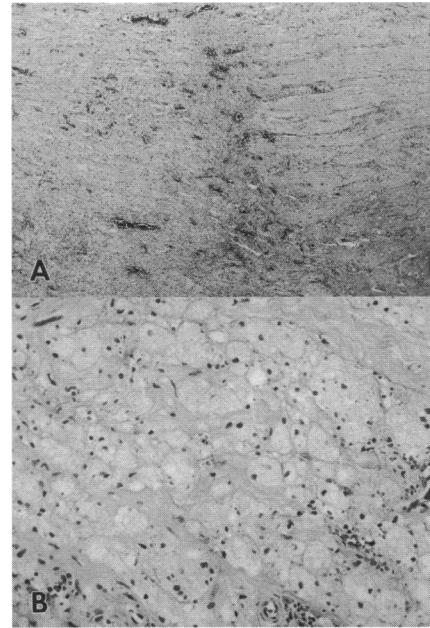


**FIGURE 18**

Posterior optic nerve infarction in 17-year-old girl who progressively lost vision to no light perception in left eye over 5 weeks. Computed tomography disclosed slight enlargement of orbital optic nerve. Kronlein orbital exploration revealed swollen optic nerve, which was excised. Ten months later, headache, right hemiparesis, language difficulties, and skin rash led to diagnosis of Degos disease.<sup>40</sup> A, Nerve fiber bundles are disintegrated and swollen and have gitter cells. B, Vessels in fibrovascular pial vessel are occluded by fibrin-containing thrombus (arrowheads) (EP 47217) (hematoxylin-eosin: A, original magnification x45; B, x544).

gradually die and dissolve by lysis, leaving a cystic space traversed by septae.<sup>58</sup>

Lindenberg and associates<sup>58</sup> also described a “circulatory status spongiosis” at “the margins of old cerebral infarcts, a transitional zone in which astrocytes survived the early phase of necrosis and give the tissue a spongy appearance.” A similar cellularity was seen in our cases at the junction of normal and totally empty tissue in both anterior and posterior optic nerve infarctions, with and



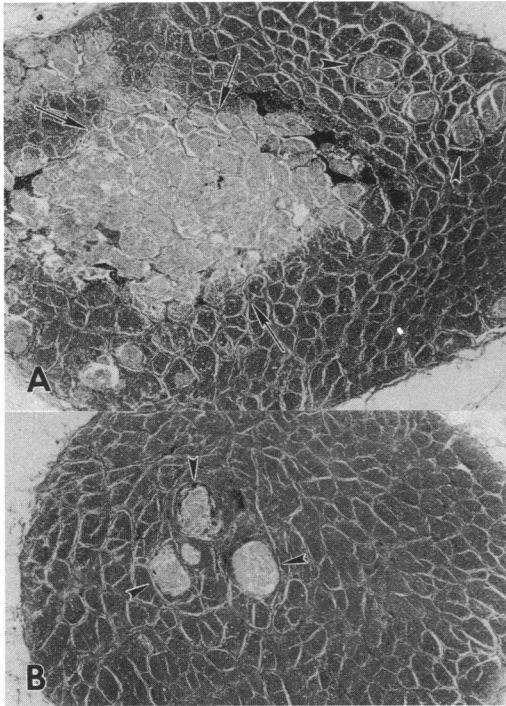
**FIGURE 19**

Painful orbital apex mass with loss of vision and oculomotor nerve palsy in man with undiagnosed diabetes mellitus. Nerve was biopsied 8 weeks after onset of visual complaints.<sup>43</sup> A, Transitional area between infarcted (to the left) and relatively intact (to the right) areas. B, Numerous gitter cells are present in infarcted area (EP 46188) (hematoxylin-eosin: A, original magnification x40; B, x280).



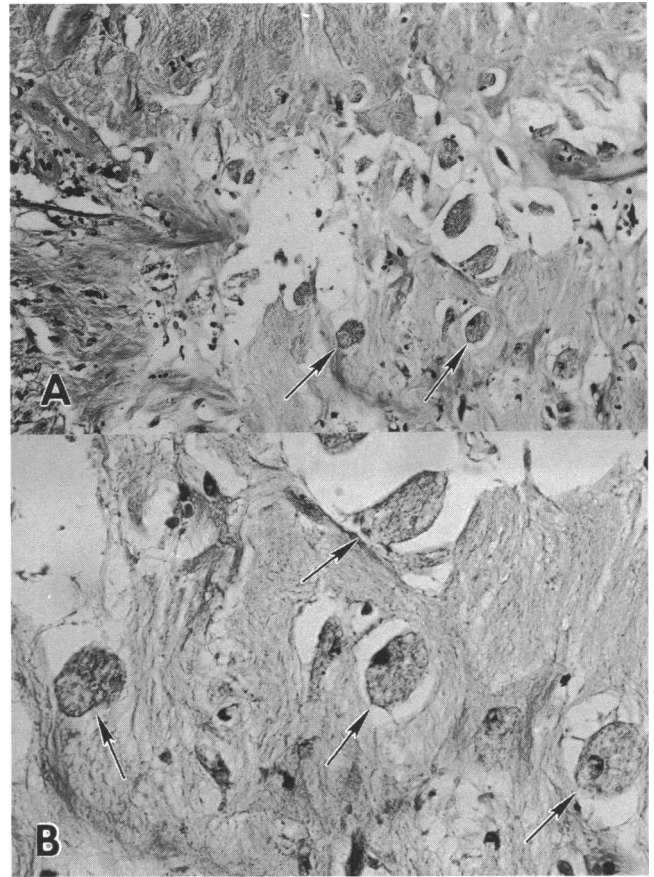
**FIGURE 20**

Left eye obtained postmortem, 27 days after visual loss, discloses extensive acellular infarction of much of optic nerve in 57-year-old woman with lymphoma and sepsis<sup>32</sup> (EP 75869). A, Optic nerve head (arrowhead) and entire distal optic nerve is infarcted, swollen, and acellular. Fibrovascular pial septae are infiltrated by lymphomatous process, except in 1.2 mm of retrolaminar nerve (arrows). B, Cross section of nerve about 10 mm proximal to eye is swollen and acellular except for lymphoma infiltration of fibrovascular pial septae (EP 75869) (hematoxylin-eosin: A, original magnification x11; B, x30).



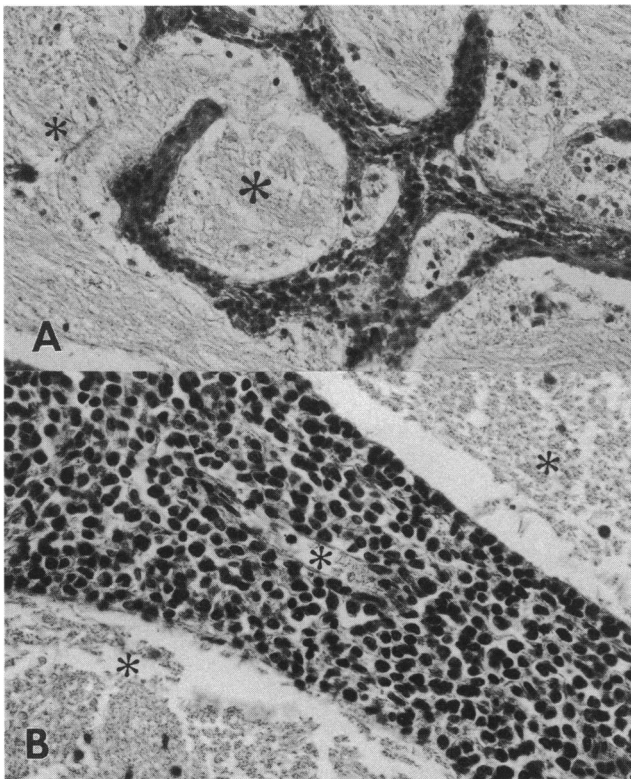
**FIGURE 21**

Same case as in Fig 19. Infarction becomes smaller (between arrows) and multifocal (arrowheads) at midorbit level (Verhoeff, van Gieson: A&B, original magnification x30).



**FIGURE 23**

Same case as in Fig 19. Area of infarction with small cluster of gitter cells (hematoxylin-eosin: A, original magnification x180; B, x425).



**FIGURE 22**

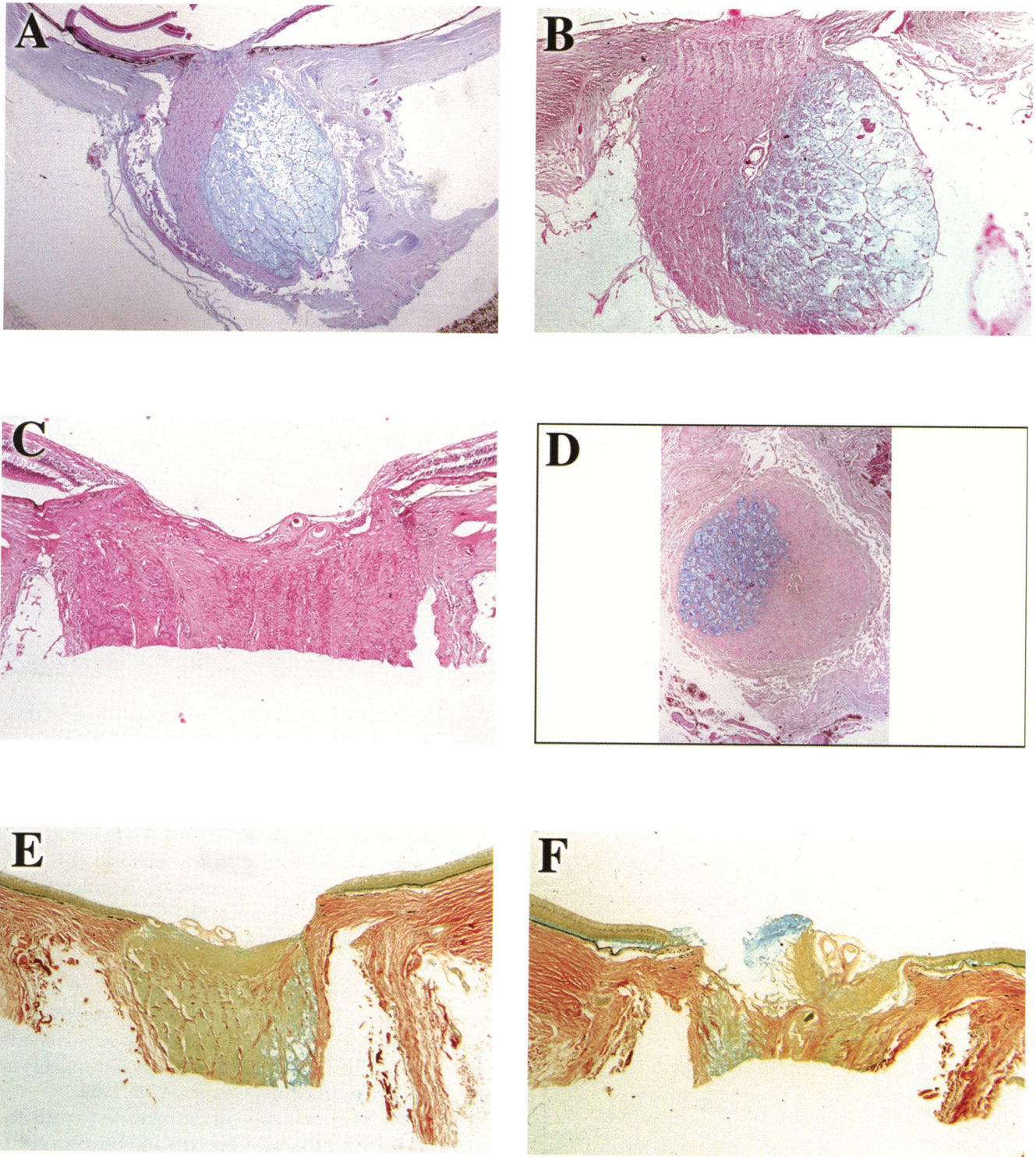
Same case as in Fig 19. Higher-power view of lymphoma infiltration of fibrovascular pia septae (hematoxylin-eosin: A, original magnification x300; B, x400).

without staining for MPS (Figs 17, 18, and 20).

Knox and Duke<sup>24</sup> were the first to present histopathologic evidence of an ischemic process that had caused an initial loss of vision and then progression of further vision loss. That case is included in this series (Fig 13).

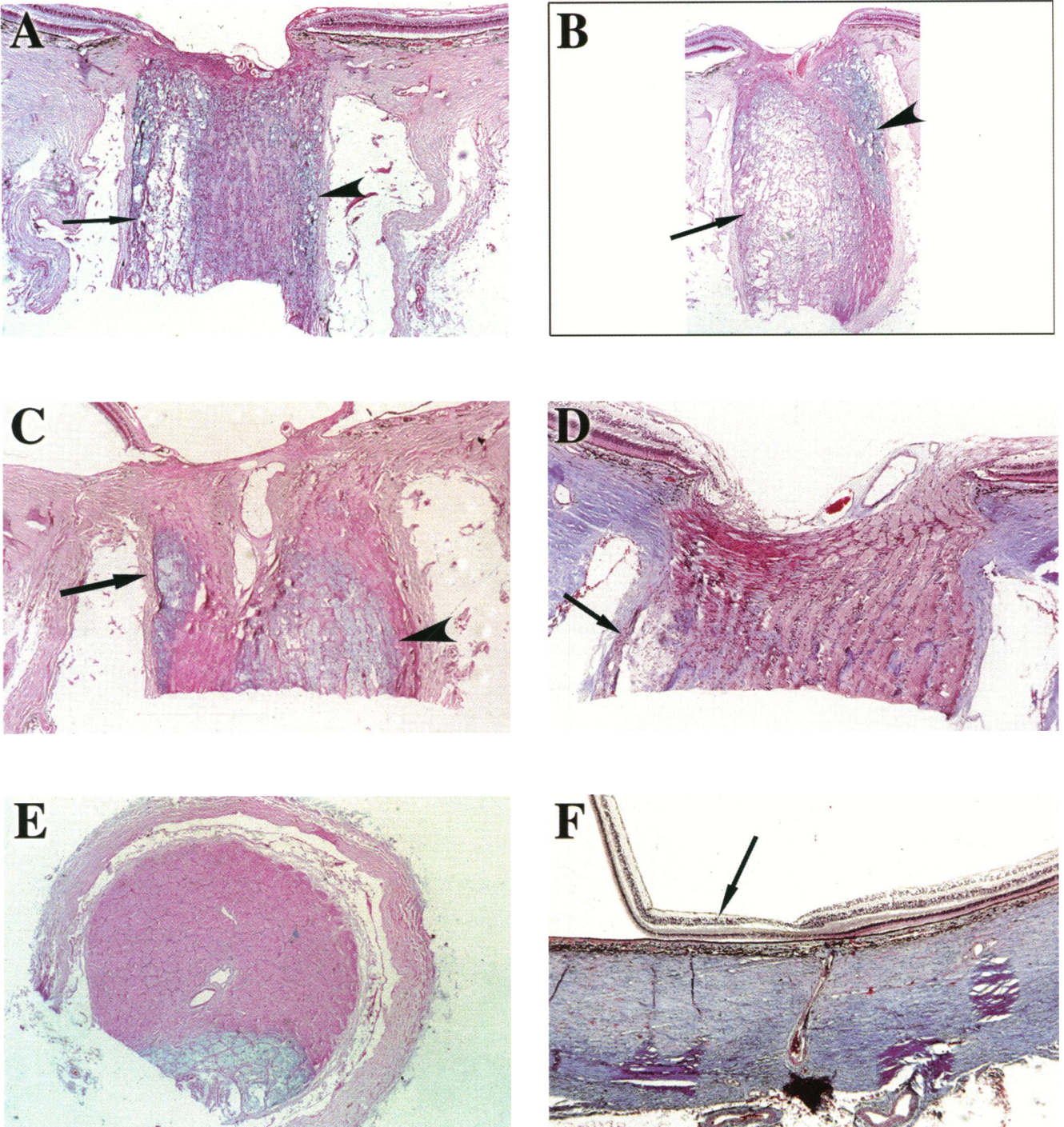
Clinicopathologic correlation of fatal cases of giant cell arteritis with ischemic optic neuropathy have provided insights into the histopathologic features of recent-onset ischemia. Better recognition of the syndrome of giant cell (temporal) arteritis and vision loss led to reports of the ocular pathology of that disorder by Greenfield<sup>15</sup> in 1951, Kreibitz<sup>16</sup> in 1953, and Crompton<sup>17</sup> in 1959.

The first American report of the optic nerve pathology of giant cell arteritis was by Spencer and Hoyt<sup>18</sup> in 1960, which described the details of a 77-year-old man with extensive giant cell arteritis who lost all vision in both eyes 14 days before dying. An area of cellular ischemic necrosis was present immediately behind the lamina cribrosa of the right eye, and vasculitis involved the coronary, iliac, internal carotid, and temporal arteries; the aorta; both ophthalmic arteries; and the short ciliary arteries near the left optic nerve. A mural thrombus was believed to be the



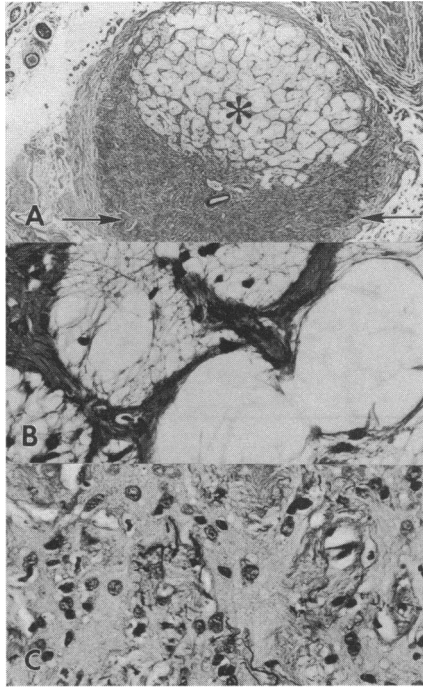
**FIGURE 24**

A and B, Examples of large areas of cavernous degeneration with extensive mucopolysaccharide accumulation in eyes with no clinical or histopathologic features of glaucoma (A, EP 21764; B, EP 66939) (Alcian blue: A&B, original magnification x30). C and D, Cavernous degeneration with dense mucopolysaccharide in eye with neovascular glaucoma and severe glaucomatous atrophy (EP 108206) (B, hematoxylin-eosin; x30; E, Alcian blue, x30). E and F, Example of tracking of MPS from vitreous, through lamina cribrosa and into retrolaminar area of cavernous degeneration in right (E) and left (F) eyes with large optic nerve heads and normal intraocular pressure (15 mmHg) (EP 69433) (colloidal iron: C and F, x30).



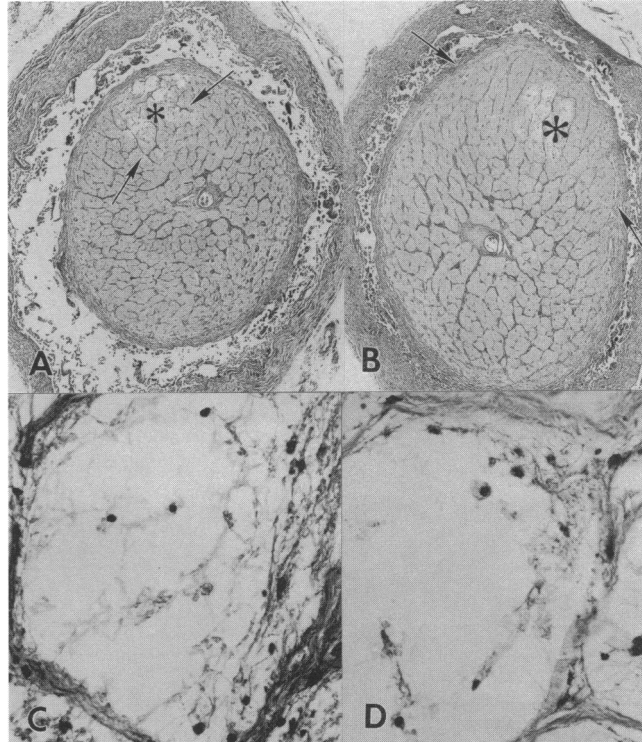
**FIGURE 25**

Glaucoma and cavernous degeneration. A, Long temporal area of cavernous degeneration with mild deposition of mucopolysaccharide (MPS) deposition is present in right (A) and left eyes (B) (arrows). Both eyes have large cavernous lesion with little MPS and small peripheral cavernous lesions with prominent deposition of MPS (arrowheads) in 69-year-old man with 20-year history of glaucoma (EP 66646) (Alcian blue: A and B, original magnification x30). C, Eye with two areas of cavernous degeneration: small area adjacent to lamina cribrosa (arrow) with prominent MPS deposition and large area with minimal MPS (arrowhead) (EP 68227) (Alcian blue, x30). D, E and F, Left amblyopic eye of pituitary dwarf who lost vision and field 3 years earlier and had an inferior peripapillary nerve fiber hemorrhage. Eye was enucleated because of sinus carcinoma with orbital involvement (EP 48729). D, Apparent glaucomatous cupping with compression of lamina cribrosa and small retrolaminar infarction with only trace MPS (arrow) (Masson trichrome, x30). E, Sectorial area of infarction with cavernous degeneration and MPS accumulation (Alcian blue x30). F, Typical loss of nerve fiber and ganglion cell layers in temporal aspect of macula (arrow) is present (EP 48729) (Masson trichrome, x30).



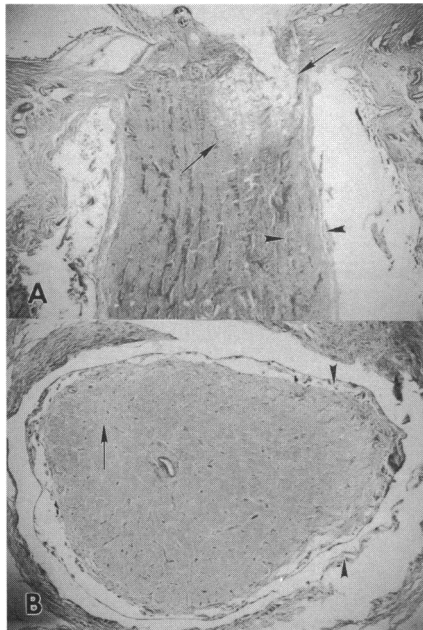
**FIGURE 26**

A, Large, mostly acellular cavernous lesion (asterisk and B) in optic nerve with marked atrophy elsewhere (between arrows and C) in 78-year-old woman following central retinal vein occlusion and neovascular glaucoma (EP 108206) (Verhoeff van Gieson: A, original magnification x35; B and C, x 475).



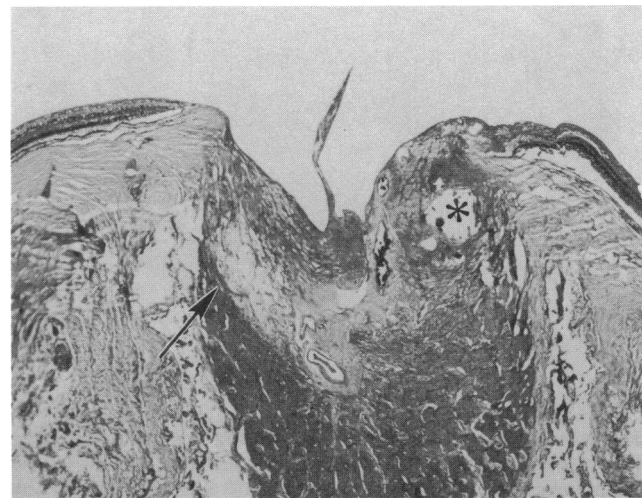
**FIGURE 28**

Ischemic infarctions (between arrows) with small central areas of cavernous degeneration (asterisks) with MPS in right (A and C) and left (B and D) eyes of 68-year-old woman with chronic obstructive pulmonary disease (EP 75623) (Verhoeff van Gieson: A and B, original magnification x18).



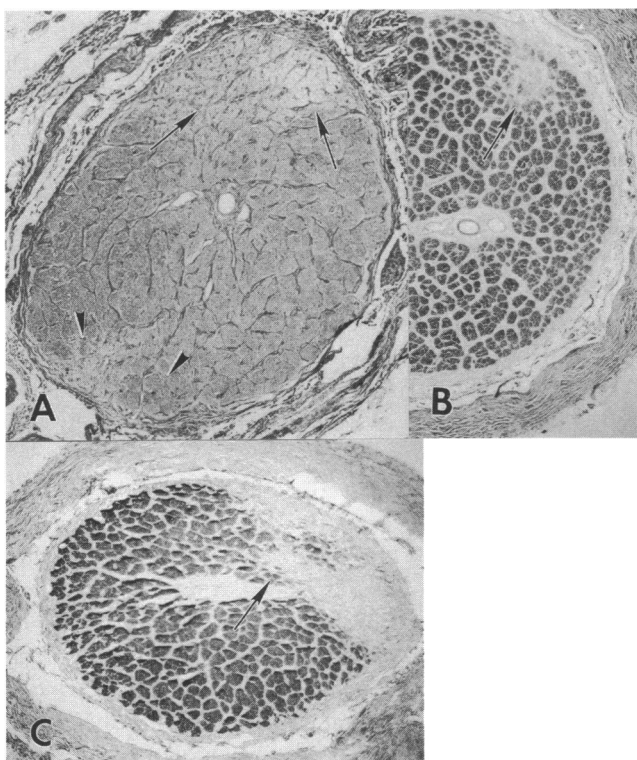
**FIGURE 27**

A 90-year-old woman with no history of glaucoma had been observed to have a splinter hemorrhage of left optic nerve head, 6 months before death. A, 0.8 mm area of infarction involving optic nerve head and lamina and retrolaminar areas of optic nerve (between arrows) was present. Area of infarction extended posteriorly for several millimeters (arrowhead). B, Area of posterior extension (between arrowheads). A second, smaller area of atrophy is present on opposite side (arrow) (EP 71103) (hematoxylin-eosin: A, original magnification x25; B, x20).



**FIGURE 29**

Drusen in nasal aspect of optic nerve head (asterisk) and small, temporal area of retrolaminar cavernous degeneration (arrow) in eye of 58-year old woman who died of emphysema with chronic obstructive pulmonary disease (EP 57159) (hematoxylin-eosin, original magnification x35).



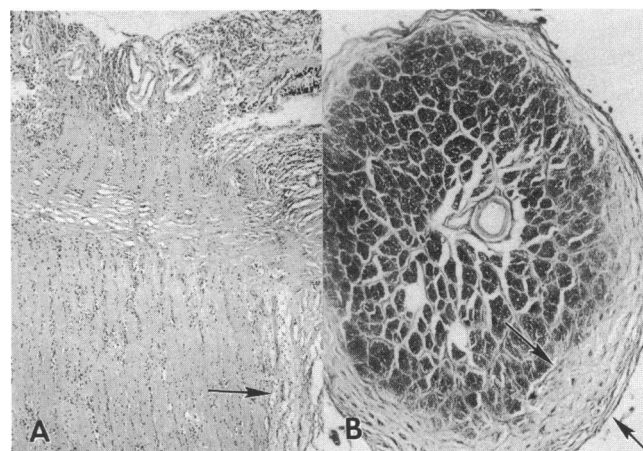
**FIGURE 30**

Examples of patterns of optic atrophy include sectorial (A, superior, arrows, A, inferior, between arrowheads), peripheral focal (B, arrow) and sectorial with slab configuration (C, arrow). (A: EP 45857, hematoxylin-eosin, original magnification x25) (B: EP 62934 and C: EP 88904: Verhoeff van Gieson, x20).

source of emboli to liver, spleen, and brain.

In 1964, Rodenhauser<sup>19</sup> published clinical and histopathologic details of ischemic optic neuropathy in a 79-year-old man with giant cell arteritis who died 3 weeks after losing vision. Manschot's report<sup>20</sup> in 1965 was followed by that of Henkind and associates<sup>21</sup> in 1970, who described the pathologic findings of the blind left eye of a 67-year-old woman with a clinical diagnosis of giant cell arteritis. The patient died 16 weeks after losing all vision in the left eye. The ischemic lesion located just posterior to the lamina cribrosa had gitter macrophages. No vasculitis of blood vessels in and around the eye was found.

The earliest we observed gitter macrophages was in a patient who died 9 days after loss of vision from gastrointestinal hemorrhage and systemic hypotension,<sup>35</sup> in a patient who died 14 days after ligation of jugular veins<sup>39</sup> (Fig 15), and in a patient who died 18 days after beginning a progressive loss of vision from internal carotid occlusion<sup>24</sup> (Fig 13). In these cases, gitter macrophages were most evident in ischemic tissue adjacent to more normal nerve, as evidence that these macrophages had come into the infarction from intact blood vessels. These 3 cases can also be interpreted as occurring because of a generalized reduction of blood supply, not a discrete local occlusion.



**FIGURE 31**

Peripheral concentric area of atrophy in longitudinal (A, arrow) and cross (B, between arrows) sections (EP 76489) (A, hematoxylin-eosin, original magnification x50; B, Verhoeff van Gieson, x45).

The reports of Spencer and Hoyt,<sup>18</sup> Kreibig,<sup>16</sup> and Hinzpeter and Naumann<sup>22</sup> document gitter cells at 14, 15, and 18 days, respectively, from giant cell arteritis. Kreibig described the presence of these cells at the periphery of lesions.

In contrast, early lesions caused by multiple emboli (Fig 2)<sup>31</sup> had neither adequate time nor competent blood vessels to allow immigration of macrophages into the necrotic tissue.

We believe that these observations support the concepts of Russell<sup>55</sup> and Konigsmark and Sidman<sup>56</sup> that gitter macrophages come from general circulation through adjacent, relatively intact vessels.

We observed cavernous lesions, which appeared to occur 4 weeks or longer after vision loss. An extensive literature has accumulated on the significance of those lesions, beginning with Schnabel's report describing a group of anterior optic nerve changes, which he attributed to glaucoma.<sup>1-3</sup> Because there were no illustrations by either photography or artists drawings, we found his early articles to have very limited value for comparison with the present study.

In his most detailed report, Schnabel<sup>3</sup> did not document which cases had clinical details, although 2 cases were credited to Elschnig. Schnabel did not quantitate the level of elevated intraocular pressure as measured by any tonometric device. "Sehr hart" (very hard) was used to describe certain eyes, leaving the reader to assume that tactile methods were the means of assessment.

In 1905, Schnabel<sup>3</sup> described 3 morphologic variations. The first was microcystic changes in the center of the anterior optic nerve of 3 patients—one with an iris melanoma and glaucoma, a second with postcataract extraction iridocyclitis, and the third who had had

penetrating trauma. These optic nerve head changes are similar to those seen in 4 eyes with iris melanoma and secondary glaucoma (W. Richard Green, unpublished data).

The second variation of Schnabel was seen in eyes that had loss of vision, thin temporal rim of nerve tissue, and "Glaucom ohne Hochsteigerung" (glaucoma without high pressure). Pathology in these eyes was characterized by small to medium sized areas of loss of axons and myelin.<sup>3</sup>

The third variation described by Schnabel has become the entity known as "Schnabel cavernous optic atrophy." These were large acellular lesions of the optic nerve. The first patient was a 69-year-old man who had a sudden loss of vision, 14 months before high pressure and pain in the eye requiring enucleation. Cloudy cornea, deep anterior chamber, and dilated pupil were clinically described features. Schnabel did not give any clinical details of the fellow eye, nor did he describe pathologic features of the anterior segment of the enucleated eye. Atrophy of the optic nerve not affected by the large acellular cavernous lesion was seen in the figure presented by Schnabel.

In the second case of Schnabel,<sup>3</sup> a large cavernous lesion occurred in an 84-year-old woman who had experienced slowly progressive loss of vision for 1 year before her first visit in July 1887. The clinical description was glaucomatous excavation without changes in the anterior chamber angle and normal ocular pressures. Vision deteriorated, and both eyes were enucleated. The large lesion, depicted in Schnabel's article, is similar to cases in this series (Figs 24D, 25E, and 26).

Illustrations from articles published in Germany from 1904 to 1914 demonstrate that in eyes with glaucoma or high myopia, cavernous types of lesions were present both immediately behind the lamina cribrosa and more posteriorly.<sup>4,8</sup>

Following Schnabel's reports, different investigators addressed the issue of whether these lesions had anything to do with glaucoma. Goerlitz,<sup>12</sup> in 1920, presented the details of a 57-year-old man who lost vision 10 days after losing a large amount of blood from a gastrointestinal hemorrhage. The patient died 20 days after losing vision and was found to have mild cellular edema anterior to the cribriform plate and a small retrolaminar infarction.

In 1925, LaGrange and Beauvieux<sup>13</sup> reported eyes with large areas of acellular atrophy, which they attributed to vascular disease. Loewenstein,<sup>9,10</sup> in 2 articles published in 1945, concluded that "all these degenerative changes are the result of vascular damage with impairment of nutrition rather than the effect of increased intraocular pressure."

In 1947, Wolff<sup>11</sup> presented clear arguments against the primary role of glaucoma in cavernous optic atrophy.

Wolff emphasized that chronic glaucoma produced glial proliferation in the optic nerve, not empty spaces. In 1949, Radnot<sup>14</sup> described a case of cavernous degeneration associated with secondary glaucoma from an iris melanoma. All investigators have acknowledged that high-ocular-pressure glaucoma and narrowed vessels often occur in the same eye.

Duke-Elder and Scott<sup>54</sup> and Giarelli and colleagues<sup>25</sup> noted the histopathologic features of cavernous lesions. The interval between loss of vision to death was noted in only 1 of 14 patients.<sup>25</sup> Neither report<sup>25,54</sup> noted when gitter macrophages begin to appear. In 1968, Cogan<sup>59</sup> illustrated an example of an optic nerve infarction with cavernous degeneration.

In 1977, Giarelli and coinvestigators<sup>25</sup> described 14 cases of cavernous degeneration of the optic nerve that had been found by histopathologic study of the optic nerves of 1,381 autopsies. In only 3 of these 14 eyes had there been a diagnosis of glaucoma prior to death. All of the eyes had evidence of "aging of the vessels of the optic nerve." In 2 of Giarelli's illustrations, swelling produced by the cavernous degeneration distended overlying pia. In 1 of these eyes, there was distortion of adjacent more normal optic nerve similar to that shown in 2 of our cases (Fig 24A and B). The third illustration in this article documented a small cavernous lesion posterior to the lamina cribrosa. This lesion is similar to the lesion shown in figs 25C and 27 of this series. Giarelli also described the presence of MPS in these lesions.<sup>25</sup>

Further evidence against Schnabel's thesis was presented by Kubota and associates<sup>46</sup> in 1993. They found multiple arteriosclerotic lesions in an eye with bilateral cavernous degeneration.

In 1983, Isayama and Takahashi<sup>26</sup> presented the pathologic features of a group of 12 cases of optic nerve ischemic lesions that were found in a series of 53 autopsies of patients dying of cerebrovascular diseases. Their classification of acute, subacute, and chronic stages of infarctions was apparently based on type of systemic or neurologic disease. They did not present chronologic data defining time from loss of vision or cerebrovascular event, to death and autopsy. Isayama and coinvestigators<sup>27</sup> also described the patterns of visual field loss in 14 patients with the clinical diagnosis of "posterior" ischemic optic neuropathy.

Twenty-six small cavernous and 133 atrophic lesions from this study, plus the 12 lesions of Isayama and Takahashi, reinforce the concept that small infarctions may be a cause of loss of central vision and visual field.

The bilateral small acellular, cavernous lesions shown in Figs 28A, B, C and D present evidence that such lesions can occur relatively posterior to the lamina cribrosa. Careful study of longitudinal sections did not



reveal that these lesions seen in cross sections were the posterior ends of more anterior lesions. These lesions were either superiorly or inferiorly located in the nerves. Both stained with alcian blue for MPS. The left eye lesion (Fig 28B and D) had intense staining of the cavernous cavity and of the adjacent nerve tissue. This tissue staining provides evidence that this MPS material was generated in the wall of such lesions and not driven from the vitreous.

Many reports have documented the presence of MPS, particularly in cavernous lesions. MPS was not demonstrated 10 days after loss of vision in 1 case (Fig 8) and 18 days after loss of vision in another case (Fig 13). MPS was present in 1 patient whose loss of lower visual field was documented 1 month before death, although the onset of vision loss was not known (EP 78342).

In 1 reported case with giant cell arteritis, ischemic changes with MPS were present anterior and posterior to the lamina cribrosa 18 days after loss of vision.<sup>22</sup> Hinzpeter and Naumann<sup>22</sup> suggested that normal ocular pressure drove MPS from vitreous into the damaged nerve in a manner similar to the MPS seen early after induction of experimental glaucoma in owl monkeys.<sup>47-51</sup> Similar features are also seen in iris melanoma with secondary glaucoma (W. Richard Green, unpublished data).

Dense concentrations of MPS were seen in small (Fig 25) and large cavernous lesions (Figs 24 and 25). In nerves with 2 lesions, different densities of MPS staining were considered evidence that the 2 lesions had occurred at different times before death (Fig 10B). In some nerves, 1 lesion stained and the other did not (Fig 25). Since development of MPS requires weeks to months, different intensity of staining implies that the 2 lesions occurred at different times. We conclude that dense accumulation of MPS indicates a duration of weeks or longer. The presence of MPS posteriorly and medially suggests local production.<sup>52,53</sup>

The changing and expanding criteria for the diagnosis of glaucoma have led to many optic neuropathies being included under the umbrella of glaucoma. Current emphasis of "low" or "normal tension" glaucoma as a cause of loss of visual acuity or field may lead clinicians to discount the possibility of an ischemic mechanism.<sup>59</sup>

Peripapillary nerve fiber hemorrhages had been observed clinically in 3 patients in this series. All had sudden loss of vision and were found to have small cavernous lesions in the affected optic nerves (Figs 25D and 27). These 3 cases support the concepts of Lichter and Henderson<sup>60</sup> and others<sup>61-64</sup> that peripapillary hemorrhages may represent ischemic optic neuropathy.

On the basis of the findings in this study, consideration must be given to improving both clinical diagnosis and therapy for different forms of ischemic optic

neuropathy. A diagnosis of progressive ischemic edema should be considered when an eye with partial loss of vision has early (days) progression of vision and field loss and when ophthalmoscopy demonstrates hyperemic edema of the nerve head, particularly in a segment of the nerve that does not correspond to the original field defect. Ultrasound or fine-cut magnetic resonance imaging should be developed to confirm clinical suspicion.

Systemic corticosteroid therapy for ischemic edema has rationale based on the beneficial effect of steroids in reducing cerebral edema after trauma or stroke or during intracranial surgery. Currently, steroids have not been used for most cases of ischemic optic neuropathy.

A diagnosis of cavernous optic atrophy compressing adjacent, more normal nerve should be considered when, weeks to months after initial loss, vision and visual field deteriorate slowly. Ultrasound and magnetic resonance imaging have the potential to demonstrate the enlarged nerve as shown in Figs 24A and B.

Two forms of therapy for large caverns may be considered. The first of these would be surgical incision of the pia mater to relieve intracavernous tension. This approach will be possible if imaging techniques are developed. The second approach would be to develop biochemical-based pharmacologic agents that reduce the amount of MPS in cavernous lesions in an effort to reduce swelling. Other strategies might include antiapoptotic and neuroprotective agents.

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## **DISCUSSION**

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DR RALPH C. EAGLE, JR. This retrospective review attempts to characterize and define the histopathologic features of Ischemic optic neuropathy. The authors identified 3 types of lesions attributable to ischemic damage in 193 eyes. These included acute edematous lesions, foci of cavernous degeneration and areas of optic atrophy. Focal areas of optic atrophy were most common, comprising 66.8% of the lesions. Unfortunately, most of the atrophic lesions were found incidentally during the postmortem examination of eyes from patients who had no clinical history of visual loss. 36% of the 193 optic nerves had cavernous degeneration consistent with Schnabel's cavernous optic atrophy. A small number (13.5%) of relatively acute cases had focal ischemic edema that showed progressive infiltration by foamy macrophages called gitter cells.

The major limitation of this, and many other large retrospective histopathological studies, is a lack of correlative clinical data. Only 27 of the 193 cases had a detailed history of abrupt visual loss. The latter included 15 cases reported by other institutions; histopathologic material from only 3 of these cases was available for review. The 27 cases with historical data included 8 cases of giant cell arteritis. The rest comprised a wide variety of other severe systemic pathologies including other vasculitides, emboli, fungal and bacterial infection, lymphoma, acute blood loss and cerebrovascular accidents. The 193 eyes included very few cases of clinically documented "garden variety" anterior non-arteritic ION. It certainly is possible that the 133 atrophic lesions found during the routine screening of postmortem eyes may have included such lesions, but without clinical data, this must remain speculative.

More than a third of the 193 eyes had Schnabel's cavernous optic atrophy. Based on its regular occurrence on OKAP and Board examinations, one might conclude that Schnabel's cavernous optic atrophy ranks in frequency and importance with conditions like cataract and myopia. In this regard, however, it must be noted that a recent Medline search retrieved only three articles that had Schnabel's Cavernous Optic Atrophy as subject or title words.

This paper does shed some light on Schnabel's cavernous optic atrophy. Confirming the results of prior reports from other authors, this study indicates that Schnabel's cavernous optic atrophy can, and does, occur in eyes that are not glaucomatous, and can be caused by ischemia. About half of the cavernous spaces found in this study contained mucopolysaccharide. In addition, the intensity of MPS staining observed in presumed sequential lesions suggests that the hyaluronic acid may be produced locally, and is not derived from the vitreous as several experimental studies of acute glaucoma have concluded. The authors estimate that it takes at least 4 weeks

for hyaluronic acid to accumulate.

I had hoped that this study might highlight differences between the arteritic and non-arteritic variants of anterior ischemic optic neuropathy. One interesting clinical feature that difference between these 2 disorders is the frequent occurrence of disk cupping in patients with endstage optic neuropathy secondary to giant cell arteritis compared to those with anterior non-arteritic ION. A retrospective masked review of optic nerve photographs by Drs Helen V. Danish-Meyer, Peter R. Savino and Robert C. Sergott from the Neuro-ophthalmology service at the Wills Eye Hospital showed that cupping developed in 92% of 92 eyes with arteritic anterior ION compared to only 2% of 113 eyes with non-arteritic ION. Danish-Meyer's paper currently is in press in *Ophthalmology*.

Some have questioned whether the development of disk cupping in patients with giant cell arteritis might be related to Schnabel's cavernous optic atrophy. Schnabel originally suggested that the formation of cavernous spaces in the retrolaminar part of the optic nerve played a role in the pathogenesis of glaucomatous cupping by pulling the optic disk posteriorly or by allowing the optic disk to collapse posteriorly. Unfortunately, the data in this study do not support this conclusion, as only 1 of the 8 cases of giant cell arteritis showed cavernous degeneration. This probably should not be unexpected since caverns filled with hyaluronic acid are space occupying lesions that typically cause lateral displacement of the residual normal parts of the optic nerve.

In conclusion, I would like to commend the authors for their extremely well-referenced and scholarly work, and I thank them for providing me with an illustrated manuscript 2 months prior to the meeting.

DR ALFREDO A. SADUN. I too would like to congratulate David Knox for his excellent presentation and for acquiring a collection of cases which I suspect will lead to many other excellent studies. One issue we should keep in mind is to not confuse anterior ischemic optic neuropathy (AION) with ischemic optic neuropathy. David was very careful to use the term ischemic optic neuropathy. When as neuro-ophthalmologists we talk about AION, we are not talking about a disease which is thought to be due to thrombotic or embolic events. We are talking about a disease which we feel has something to do with the configuration of the disk (as Ron Burde calls it: disk at risk) and is triggered after many years by a very subtle vasculopathic process such as hypertension or diabetes. AION does not have a high risk factor for sudden death. It is true that hypertension or diabetes will shorten your life span, but this does not lead to death within 2 weeks of the time your optic nerve atrophies. On the other, patients with thrombotic and embolic disease are more likely to die at the

time of the visual loss. Therefore in this collection of cases there is a selection bias towards patients with the more serious systemic diseases which led to the death of the patient and the availability of the eyes for histopathologic evaluation. We must be careful how we extrapolate this data because we do not have exact clinical-pathologic correlation. One of the greatest values of this material is to look at and understand the tissue reaction to ischemia. I have found gitter cells as long as 40 years after an acute event; I find it hard to believe they survive that long. Maybe these diseases, which we think occur at a single time, have a long-term persistent process so that gitter cells keep forming. What is the longest you believe a gitter cell can be found after an acute event?

DR GEORGE A. CIOFFI. This is an amazing collection of cases which I hope can be exploited much more. In the laboratory we have developed an ischemic optic neuropathy in a primate eye. One of the earliest changes we see is activation of astrocytes within the optic nerve and even extending into the retina. In your material can you determine if activated astrocytes actually exist and are possibly the precursors of the mucopolysaccharide deposits?

PAUL R. LICHTER. I am pleased that Dr Knox has confirmed what John Henderson and I discussed at this meeting in the late 1970's. We talked about a specific hemorrhage at the infero-temporal margin of the disk which was followed by the development of a notch in the optic cup and a field defect, an arcuate defect coming very close to fixation. This often gave the patient a positive scotoma, which they noticed. Were you able to determine where these infarcts occurred in the optic nerve? Many clinicians observe these notches and field defects and begin treating these patients vigorously for normal tension glaucoma; in fact, they do not have glaucoma. We postulated a watershed type of circulation making this area of the nerve susceptible to these hemorrhages and infarcts. It is important for clinicians not to panic because, as Dr. Knox pointed out, most of these patients do not have a second event. Therefore, I prefer to watch and wait; if a patient has a second event, then I may think the intraocular pressure has some role in the process and attempt to lower the pressure.

DR DAVID L. KNOX. I would like to thank the discussors for their positive reactions and support.

We acknowledge the limitations of materials which are obtained through eye banks. By the time the slides get to microscopic evaluation, it is a long time, when the patient died in another city, to find the ophthalmologist and to search things out. It is difficult.

Alfredo reinforced a comment that Ralph gave on Sergott's paper that is going to be published. Part of the diagnosis of non-arteritic anterior ischemic optic neuropathy is the fact that it occurs in a tight optic nerve head without a physiologic cup. It is a reinforcing diagnosis both prospectively and retrospectively. It is my opinion that the diagnosis of anterior ischemic optic neuropathy is being over made by general ophthalmic practitioners in the country today. There are other reasons for changes in acuity, sudden or slow progressive.

Schnabel himself wrote his most definitive paper in 1905, where he described basically 3 different morphologic entities, pathologically. A few of these one could extrapolate his data and say that they were clearly ischemic events.

Alfredo, I don't know the exact way to answer your question about the progression of gitter cells, except that studies have reported that gitter cells appear in the central nervous system about 8 to 14 days after infarction and by about 6 weeks they are gone. Gitter cell origins are explained by 3 theories: converted astrocytes, pericytes in the vessel walls or travel through vessel walls that are damaged. I think all 3 theories have validity and it is a question of what percentage, in any given circumstance. I guess that answers Dr Cioffi's question concerning the activation of histiocytes in the primate model. Dick Green and I do not agree exactly on the cellularity that can be seen in these optic nerves. He says these are variations of normal but in some specimens, a lot of cells get into the retina near the optic nerve head.

Regarding Paul's question about the optic nerve head: in the first case I showed, that had a sudden loss of acuity, there was a notch in the area of the infarction, which may have been either primary or secondary. We don't have a good clinical description of the exact location, other than that the hemorrhage was lower temporal.

Regarding normal tension glaucoma, David Cogan, in his book on the Neurology of the Visual System, raised the issue that infarctions could produce a syndrome which would be labeled normal tension glaucoma, when it had nothing to do with elevation of intraocular pressure.

Thank you for your attention.