THE CENTRIFUGAL NERVES IN THE HUMAN OPTIC TRACT, CHIASM, OPTIC NERVE, AND RETINA

BY *J. Reimer Wolter*, M.D.*

CENTRIFUGAL (EFFERENT, ANTIDROMIC) FIBERS have been known to exist in the optic nerve of animals for a long time[1,2] and this fact is supported by recent physiological observations.[3,4] There can no longer be much doubt that a great number of centrifugal nerves also exist in the human optic nerve. Numerous nerve fibers remaining in 2 atrophic optic nerve stumps 11 and 16 years after enucleation were the first evidence.[5] Subsequently, the terminal branches of centrifugal nerves were demonstrated in the normal human retina and optic nerve[6,7] and it was concluded that at least some of the centrifugal nerves supply blood vessels. The observation of interrupted neurites in the diseased human nerve fiber layer of the retina with terminal swellings pointing away from the optic disk was further proof of the presence of centrifugal fibers.[8] Attempts at regeneration of centrifugal fibers were found in a child's optic nerve stump 11 days after enucleation[9] and later the reactions of these fibers could also be studied 4 days after enucleation in another case.[10] A peculiar proliferation (hyperregeneration) of centrifugal nerves was observed around blood vessels and microaneurysms in advanced diabetic retinopathy.[11]

This study presents the important progress that has been made in estimating the number and understanding the pathway of the centrifugal nerves in man. It is composed of two parts. In the first part the surviving centrifugal nerves in the human disk are examined after complete occlusion of the central retinal artery that caused necrosis of the ganglion cells and all centripetal (afferent) retinal nerves. The second part contains the description of the pathway of the centrifugal

*From the Department of Ophthalmology of the University Medical Center and from the Department of Surgery of the Veterans Administration Hospital, Ann Arbor, Michigan.

nerves as it has been studied in the optic nerves, chiasm, and tracts of a patient who had had both eyes enucleated 50 years earlier.*

I. CENTRIFUGAL NERVES AT THE OPTIC DISK 10 DAYS AFTER COMPLETE OCCLUSION OF THE CENTRAL RETINAL ARTERY

In the present case sudden complete occlusion of the central retinal artery occurred in an unusual combination with acute episcleritis and anterior hemorrhagic uveitis. Enucleation of the blind eye had to be done ten days after the arterial occlusion because of intolerable pain. The ten days of ischemia in the inner retinal layers caused all ganglion cells and centripetal (afferent) neurites to degenerate. All the centrifugal (efferent) nerves with their cell bodies in the brain were still present in the optic disk, however. Thus, this case allows us to observe for the first time how many centrifugal nerves there are in an adult optic disk and how these nerves react to ten days of complete ischemia in the inner retina.

HISTOLOGICAL TECHNIQUE

The eye was fixed in neutral ammonium bromide formalin (Cajal solution) immediately after enucleation. The globe was cut twice horizontally at a plane above and below the disk. The optic nerve, disk, and the retina around it were isolated and cut on the freezing microtome. Serial flat sections of the optic disk with the surrounding retina were obtained and stained for nerves with the Hortega silver carbonate technique.[12] The remaining parts of the eye were imbedded in paraffin, cut, and stained with hematoxylin-eosin.

CASE HISTORY

This 69-year-old white male came to the eye clinic of this V.A. Hospital on 6/3/63 with the complaint of having lost all vision in his left eye overnight. He had experienced an upper respiratory infection 6 weeks before which had been treated with intramuscular penicillin. At that time he also noted some non-specific discomfort in his left eye that disappeared after the respiratory infection cleared. The vision in the left eye had been perfect until he woke on the day of admission with pain, redness, and blindness.

The examination revealed an obese white male with a blood pressure of 176/104. The left eye exhibited superficial and deep pericorneal injection.

*This brain was obtained for this study by Dr. Roman R. Knoblich of Flint, Michigan.

The pupil was irregular in shape and there was no direct light reaction. Movements of the eye were painful and the upper sclera in particular was very tender to touch. Slit-lamp examination revealed slight corneal edema, wrinkling of Descemet's membrane, a 3+ flare, an inferior hyphema, and a posterior synechia at 1:00 o'clock. Gonioscopy showed the angle to be open and filled with blood. Fundus examination revealed complete occlusion of the central retinal artery, sheathing of the main blood vessels on the disk, retinal edema, and a cherry red spot.

The right eye was entirely normal and had 20/20 vision. The intraocular pressure was O.D., 17.3 mm.Hg and O.S. 20.6 mm.Hg. The pulse of the temporal and occipital arteries was present and about equal on both sides.

Laboratory tests included a negative bentonite flocculation, a total protein of 7.0 Gm.%, amuric acid of 3.7 mgm.%, a white blood count of 7,000, hematocrit of 46%, hemoglobin of 14.1 gm., and a corrected sedimentation rate of 21 mm. in 1 hour. Urinalysis revealed a 2+ albuminuria, specific gravity of 1.024, and creatinine of 1.07 mgm.%. The B.U.N. was 20 mgm.% and the F.B.S. 78 mgm.% Chest X-ray revealed mild pulmonary emphysema and X-rays of the hands showed hypertrophic arthritis only.

A refer to rheumatology for evaluation of the possibility of collagen disease as cause of the patient's scleritis revealed no indication of collagen disease. A refer to otology revealed an early bilateral presbycusis and a hearing aid was recommended.

Treatment with systemic prednisolone 10 mgm. q.i.d. and with local atropine 1% q.i.d. and local Neo-delta-cortef 0.25% q.i.d. to O.S. was started. However, the eye became increasingly painful. Four days after admission a complete hyphema developed spontaneously in the left eye and the pain increased even more. The patient asked for removal of the eye. Enucleation of the left eye was done on 6/13/63. The postoperative course was uneventful and all pain was gone with the eye.

HISTOPATHOLOGICAL DESCRIPTION

Grossly the globe is of normal shape and size. The anterior chamber is filled with blood. The branches of the occluded central artery can be recognized as white branching streaks on the swollen optic disk (Figure 1).

Microscopic study of the paraffin sections shows the cornea to be normal. The anterior chamber and the otherwise normal trabeculum contain blood. There is dense perilimbal lymphocytic infiltration. The iris exhibits diffuse infiltration with lymphocytes and plasma cells as well as a few newly-formed thin-walled blood vessels on the iris surface. The ciliary body is normal except for diffuse infiltration with lymphocytes and plasma cells. The lens is normal. There is rather extensive cystic degeneration in the peripheral retina. The central

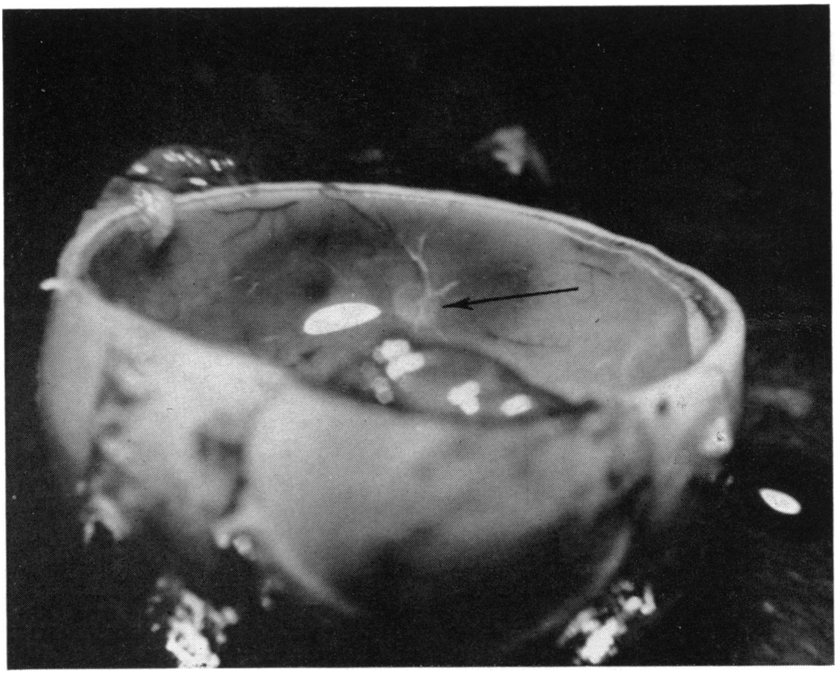


FIGURE 1
The globe after opening with the white obliterated arteries on the disk (arrow). The fovea is seen on the left side of the disk. (photograph, × 4)

retina shows total atrophy of its ganglion cells and of the nerve fibers. However, the spaces of these elements have not collapsed yet—which means that this atrophy occurred only recently. There is occlusion of the central retinal artery where it traverses the lamina cribrosa. The pigment epithelium is normal except for some senile changes in the periphery. Diffuse infiltration with lymphocytes is found in the choroid. The sclera itself is normal. However, lymphocytic infiltration is observed on the outside of the anterior portion of the sclera in the episcleral layers of loose connective tissue.

Silver staining of the optic nerve and central retina reveals the following facts. Cross-sections of the optic nerve directly behind the lamina cribrosa show a virtually normal pattern of nerve fiber bundles at low power (Figure 2). Higher power, however, reveals that these bundles are composed mainly of the myelin of degenerated nerves that has not been resorbed yet (Figure 3) and that the number of remaining nerves is greatly decreased. A cross-section through the optic nerve

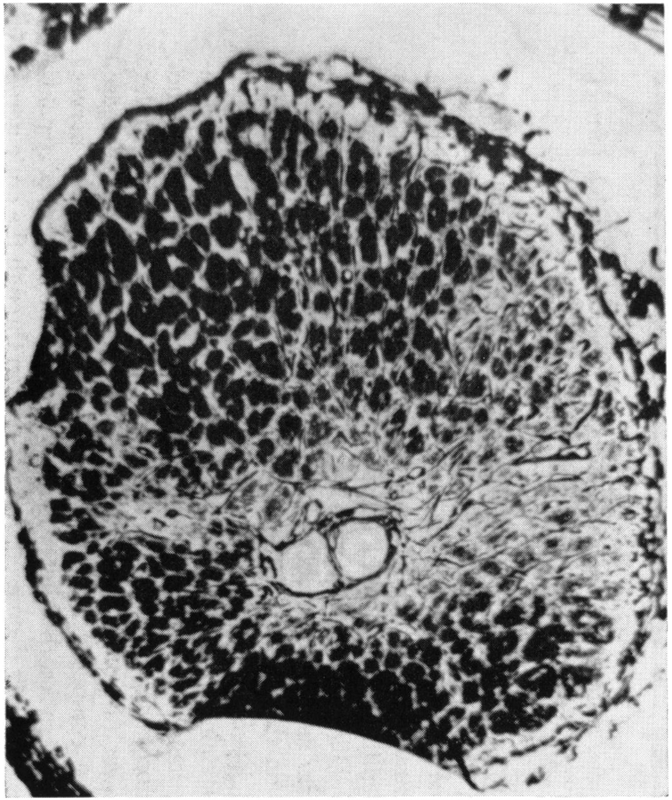


FIGURE 2

Cross-section of optic nerve behind lamina cribrosa with its dark-stained nerve bundles and central vessels. Frozen section, Hortega stain for nerves. (photomicrograph, × 50)

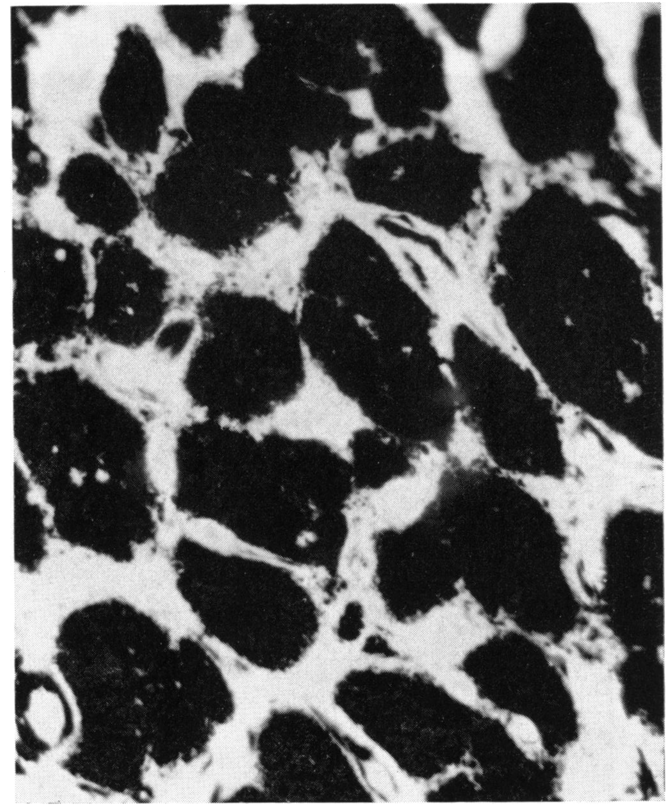


FIGURE 3

An area of cross-section in Figure 2 at a higher power shows that most of the nerve bundles are composed of disorganized myelin of degenerated nerve fibers. Frozen section, Hortega stain for nerves. (photomicrograph, × 400)

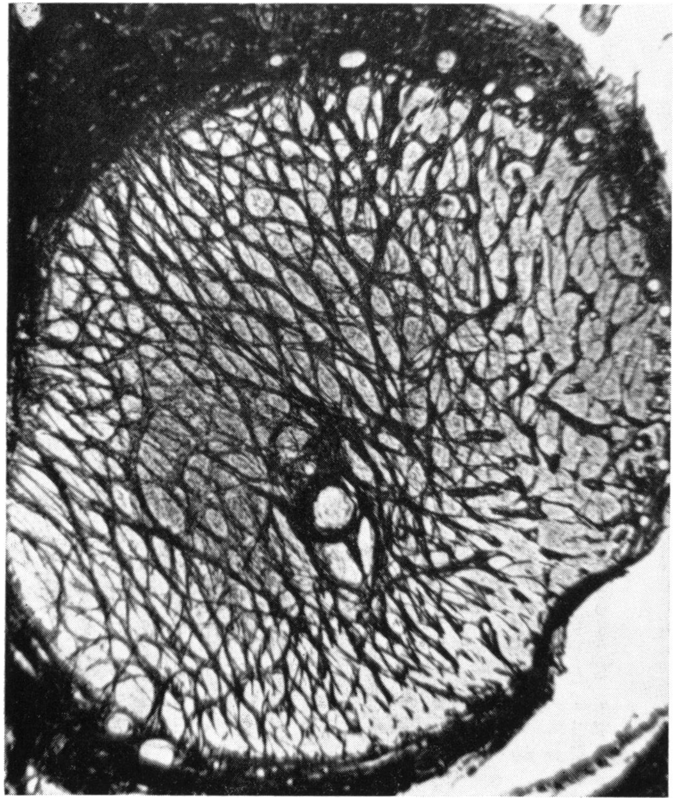


FIGURE 4

Cross-section of optic nerve through lamina cribrosa shows normal sieve-like mesodermal structure. Frozen section, Hortega stain for glia and connective tissue. (photomicrograph, $\times$ 50)

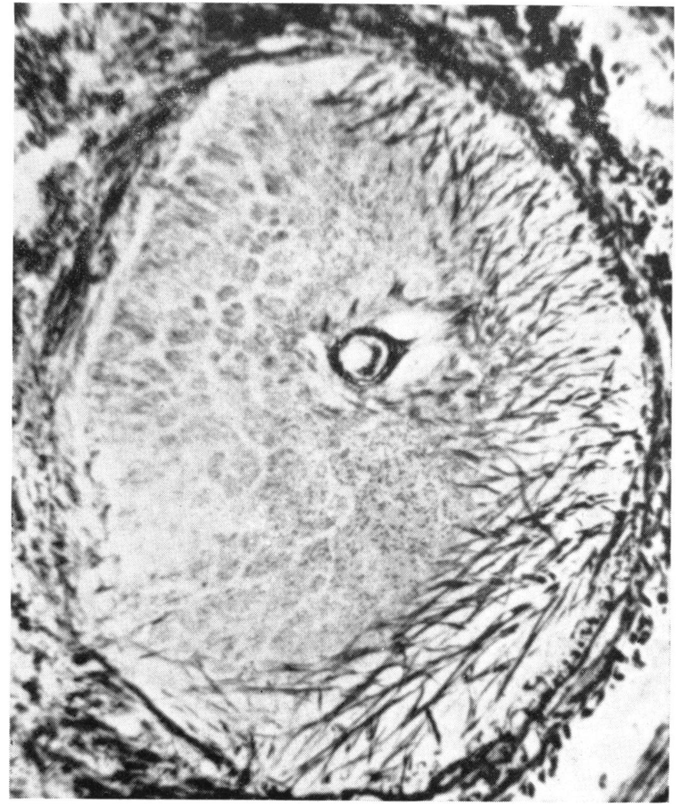


FIGURE 5

Cross-section through optic disk partly in and partly in front of lamina cribrosa showing remaining (unmyelinated) nerve fibers. Frozen section, Hortega stain for nerves. (photomicrograph, $\times$ 50)

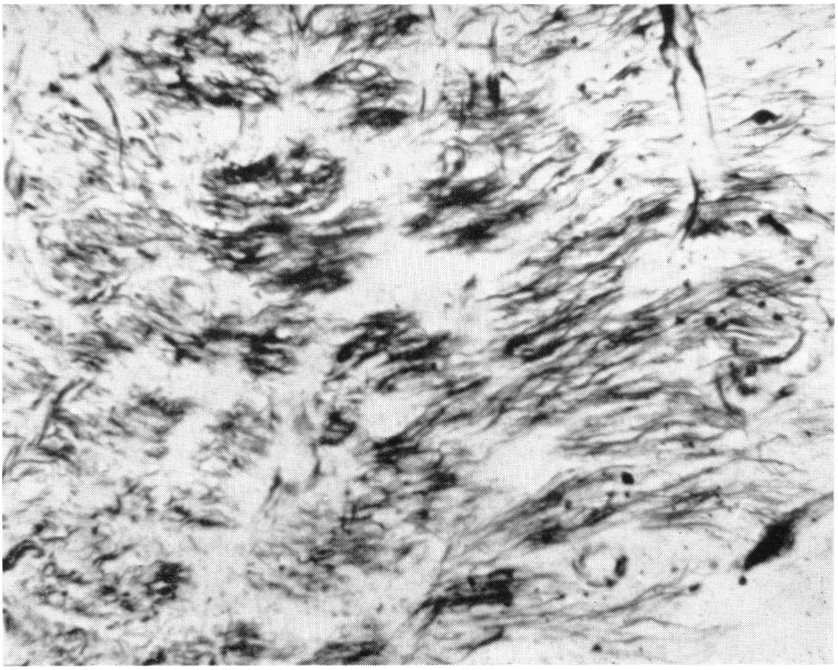


FIGURE 6
High-power view of remaining unmyelinated (centrifugal) nerves on optic disk in cross-section in front of lamina cribrosa. Frozen section, Hortega stain for nerves. (photomicrograph, × 800)

at the plane of the lamina cribrosa (Figure 4) shows the normal architecture of its mesodermal fibers. A nerve stain of a cross-section partly in and partly in front of the lamina cribrosa (Figure 5) reveals an extensive decrease in the number of nerves in this optic disk. The nerves are unmyelinated in this area. All remaining fibers are centrifugal, having their ganglion cells in the brain. All centripetal nerves have disappeared because of the total necrosis of all retinal ganglion cells. Figure 6 is a high-power view of an area with the remaining centrifugal nerves in the disk.

One of the four occluded main arterial branches at the optic disk is seen in Figure 7, a composite photograph. The muscle fibers around the artery next to the disk are seen in the lower part of the picture. The lumen is totally obstructed from the disk up to the first branching. After the first branching the arterial lumen is narrowed by extensive swelling of its endothelium. Many polymorphonuclear cells

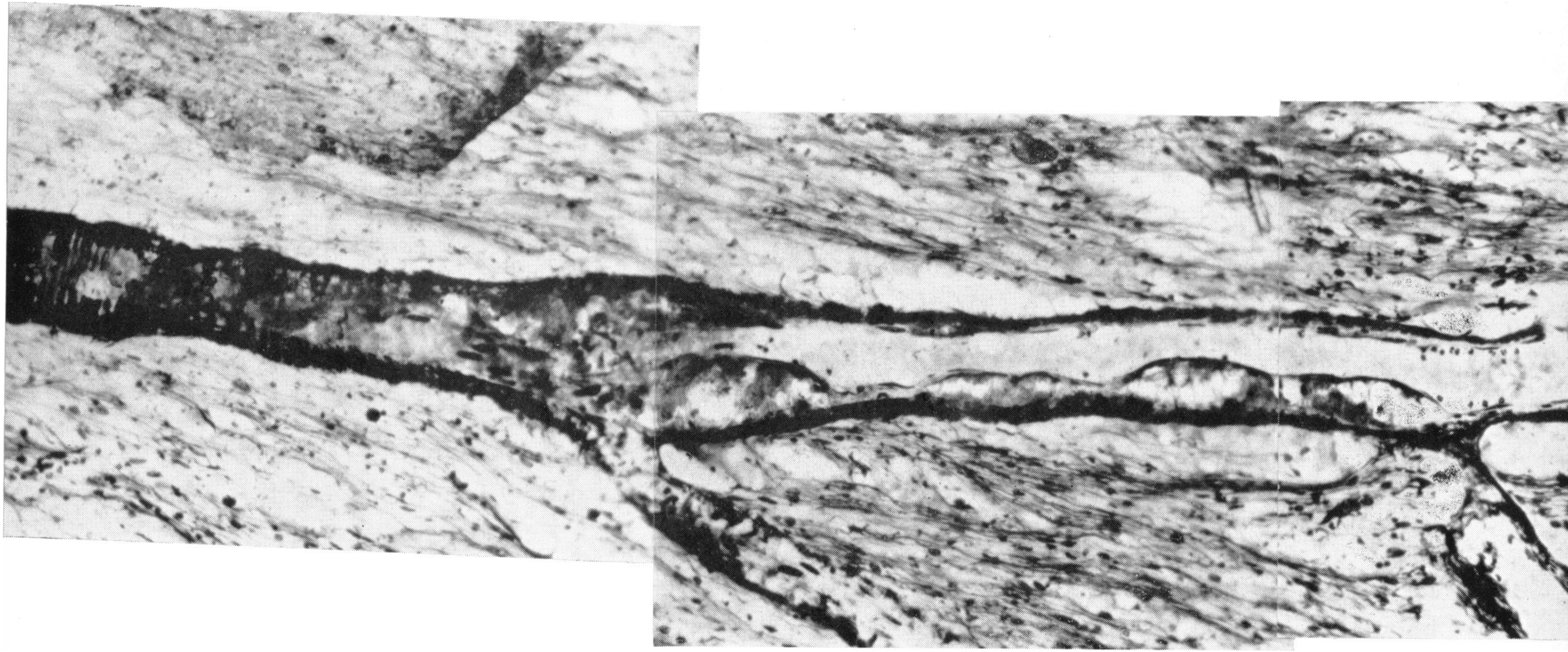


FIGURE 7

Composed photograph of an arterial branch next to the optic disk showing total occlusion in its central portion (left part of picture). The more peripheral portion of the artery has a small lumen, but shows extensive swelling of the endothelium. Frozen flat section, Hortega nerve stain. (photomicrograph, × 200)

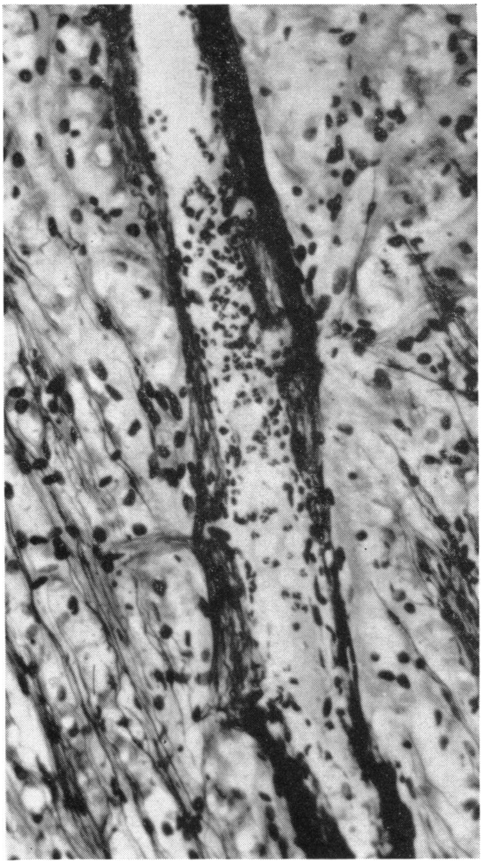


FIGURE 8
More peripheral portion of retinal artery without endothelial swelling and with many leukocytes in its lumen. Frozen flat section, Hortega nerve stain. (photomicrograph, × 200).

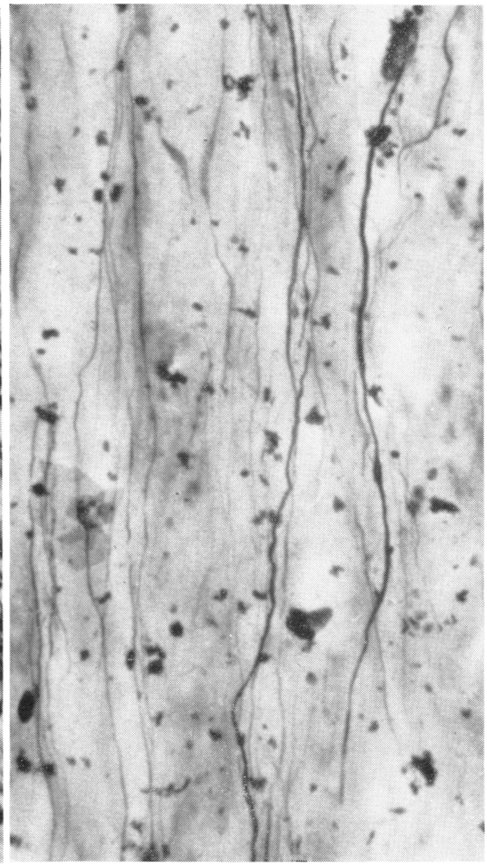


FIGURE 9
Centrifugal nerves of various thicknesses next to the disk. The thin fibers are seen to branch dichotomously. Frozen flat section, Hortega nerve stain. (photomicrograph, × 1000)

are seen peripherally in the arterial lumen (Figure 8). The absence of all retinal ganglion cells around the artery in all these photographs should be noted.

The nerves found in the retina next to the disk—just like those on the disk—must all be centrifugal fibers. The necrosis of the inner retina due to retinal ischemia has resulted in complete destruction of the centripetal elements. The remaining centrifugal fibers are quite different in thickness (Figure 9). Some are about the same size as most

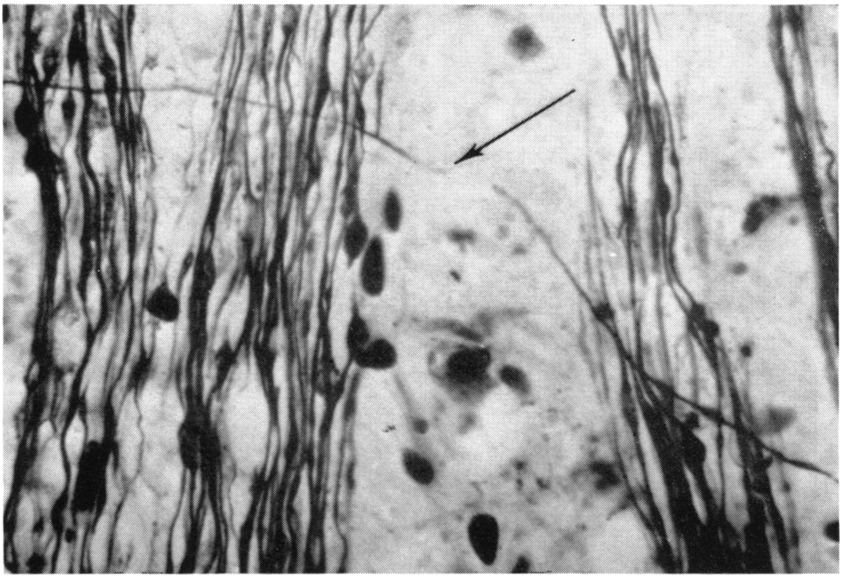
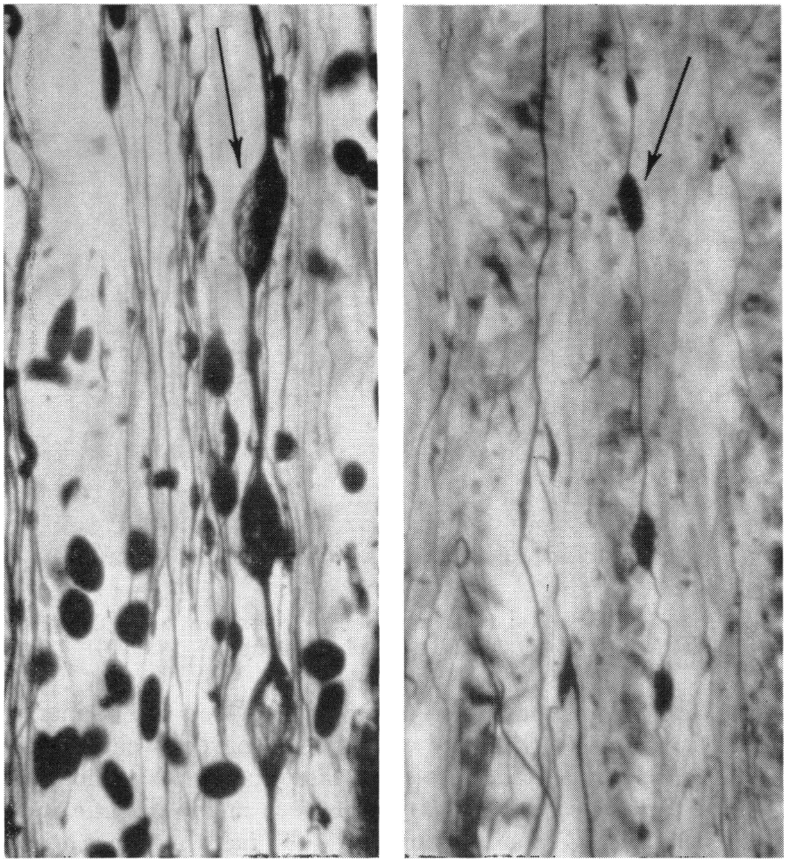


FIGURE 10
One nerve fiber running across the main nerve fiber course next to the disk. Frozen flat section, Hortega nerve stain. (photomicrograph, × 1000)

nerves in the normal human nerve fiber layer. Others are thinner and some are so very thin that they cannot be seen very well even in a × 1000 photomicrograph. However, these cobweb-like fibers are very distinctly stained and can be clearly seen under an optic system with oil immersion. We are fascinated by the fact that the particular nerves of the nerve fiber layer which run across the main direction of fibers in the nerve fiber layers have remained in the nerve fiber layer next to the optic disk in this case (Figure 10). Some of the thick as well as some of the thin remaining nerves show peculiar nodular bead-like swellings in their course (Figure 11). Nerves of all sizes are seen to branch dichotomously in a direction away from the optic disk, usually at an acute angle.

Nerves are found only in a small zone of nerve fiber layer of about 2 millimeters around the disk. All nerves are seen to end at the periphery of or somewhere within this zone. The endings that these interrupted centrifugal nerves exhibit fall into a few typical groups. However, in reality a great number of shapes and formations can be seen at the ends of these nerves. Most of the nerves run straight away from the disk and end suddenly, forming a large, round, so-called terminal

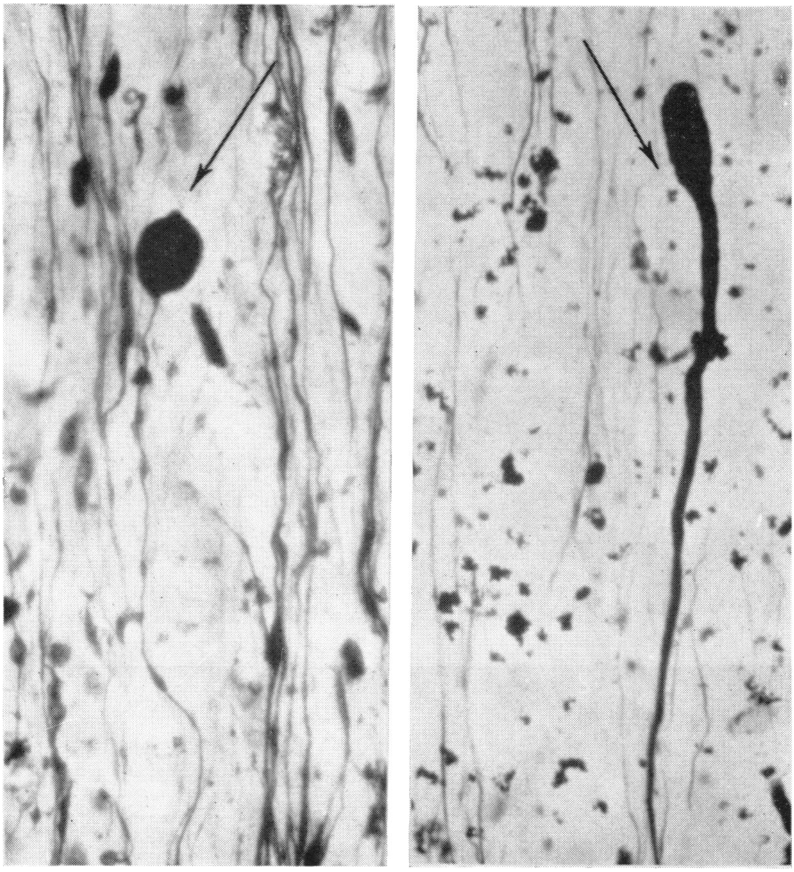


A B

FIGURE 11

A, bead-like swellings in the course of a thick centrifugal nerve next to the disk (arrow). B, bead-like swellings in the course of a thin centrifugal nerve next to the disk (arrow). Frozen flat sections, Hortega stains for nerves. photomicrographs, × 1000)

swelling of Cajal (Figure 12A). Some fibers show gradual thickening and end with a more club-shaped terminal formation (Figure 12B). Others run straight away from the disk, then turn sharply back towards the disk and form a large round terminal swelling (Figure 13). The thicker fibers usually form larger terminal bodies whereas the thin fibers form small terminal formations (Figure 14). All phases of the development of terminal swellings can be observed and accumulations



A B

FIGURE 12

A, round terminal swelling pointing away from the disk (arrow) at the end of a centrifugal nerve stump. B, club-shaped terminal swelling of similar nature. Frozen flat sections, Hortega stains for nerves. (photomicrographs, × 1000)

somewhat similar to those known from cotton-wool spots are seen—only in this case all end bulbs point towards the periphery (Figures 15 and 16). (In cotton-wool spots most terminal swellings are known to point towards the disk.[13]) Many round or oval terminal bodies are left in the nerve fiber layer of the present case and no longer show connections to any nerves (Figure 16). Swellings just like the terminal swellings may also occur in the course of still continuous nerves

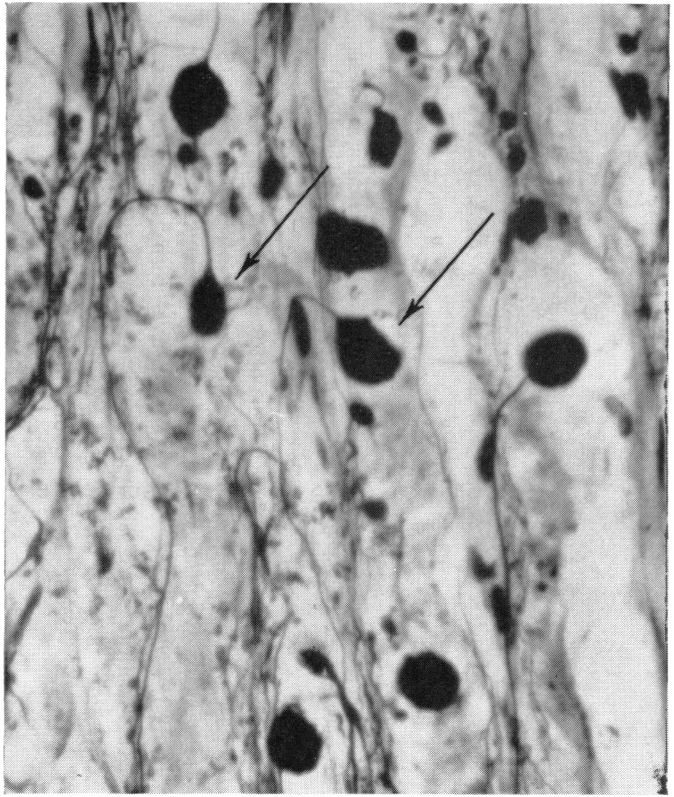


FIGURE 13

A number of terminal swellings at the end of centrifugal nerve stumps next to the disk. Several swellings have turned back towards the disk (arrows). Frozen flat section, Hortega nerve stain. photomicrograph, × 1000)

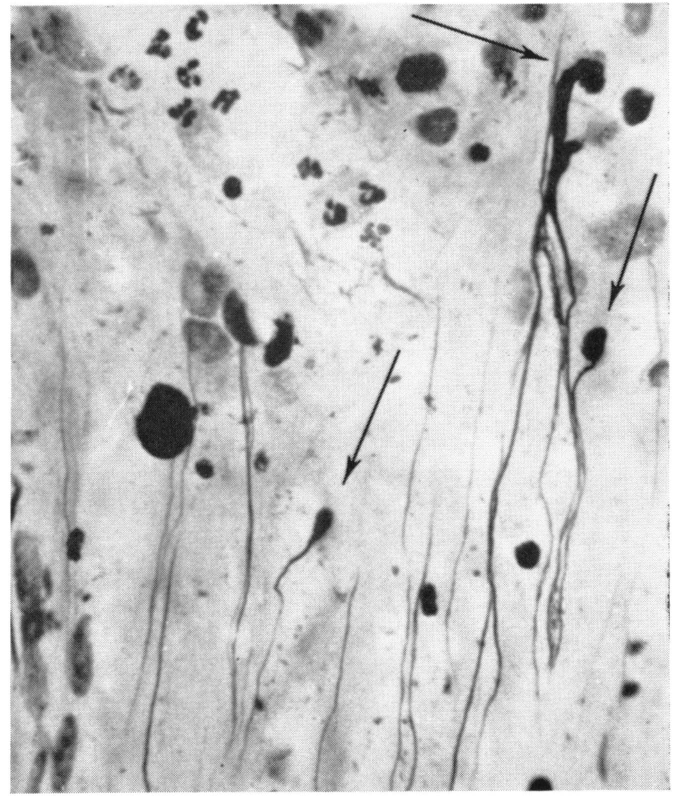


FIGURE 14

Large and small terminal bodies of thick and thin centrifugal nerves at the zone where all nerves end. Leukocytes are seen in the lumen of an artery (upper left). Frozen flat section, Hortega nerve stain. (photomicrograph, × 1000)

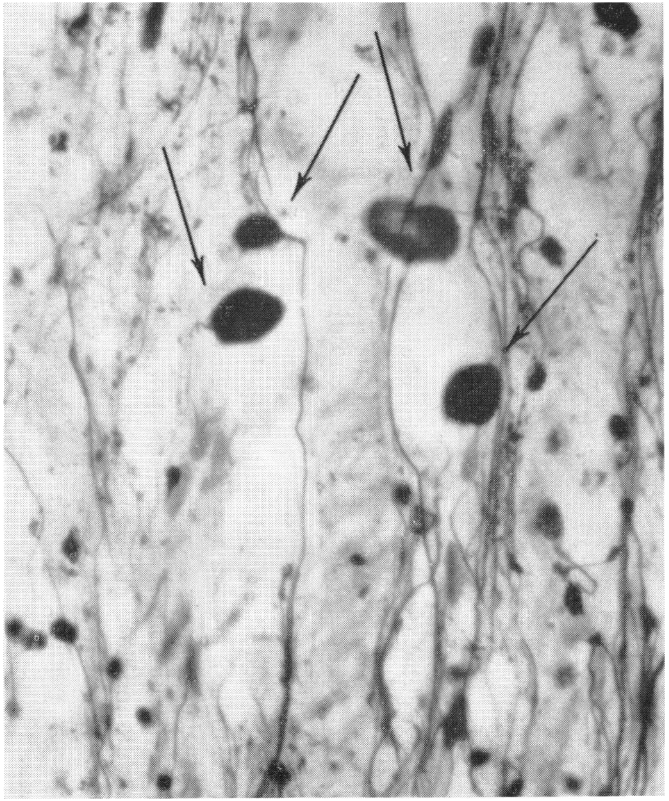


FIGURE 15

A group of terminal swellings at the end of centrifugal nerve stumps pointing away from the disk in a thin section. Frozen flat section, Hortega stain for nerves. (photomicrograph, × 1000)

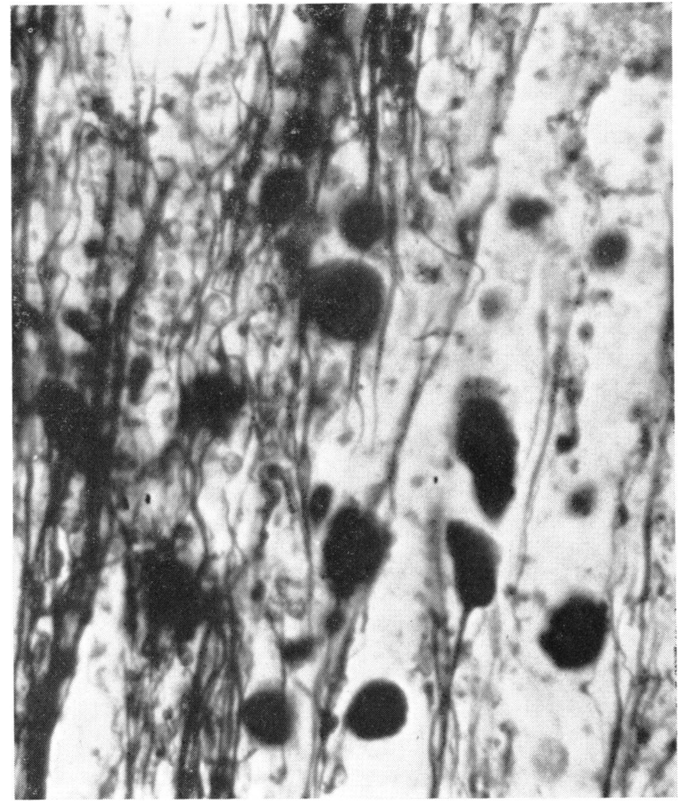


FIGURE 16

Thick section showing cotton-wool-spot-like accumulation of terminal swellings and isolated bodies—all pointing away from the disk. Frozen flat section, Hortega stain for nerves. (photomicrograph, × 1000)

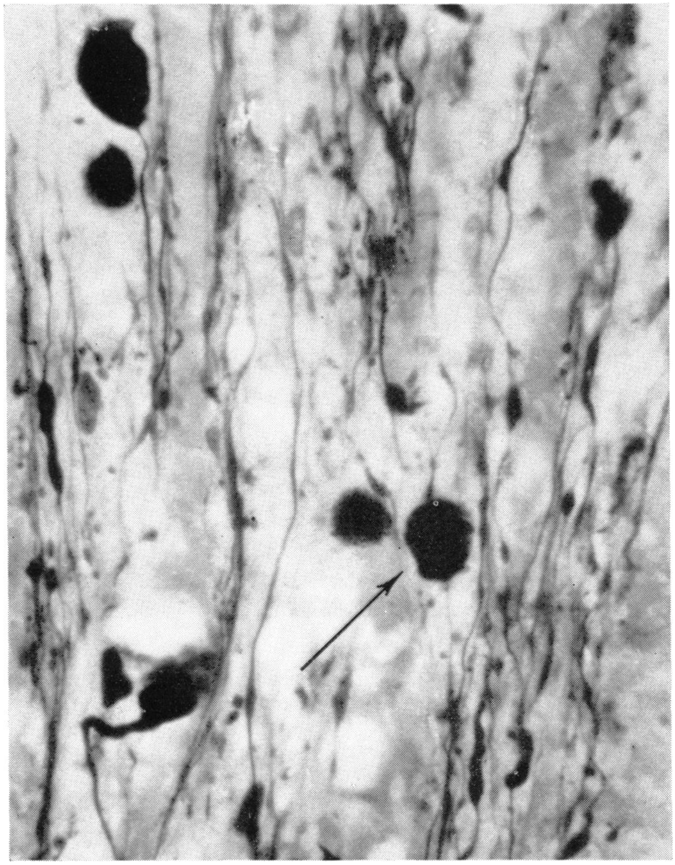


FIGURE 17

A large globular swelling in the course of a continuous centrifugal nerve next to the disk (arrow). There also are terminal and isolated swellings. Frozen flat section, Hortega stain for nerves (photomicrograph, × 1000)

(Figure 17). Such fibers with dark-stained bodies in their course are often seen to have another swelling at their distal end (Figure 18).

Of the other changes seen in this retina it may be mentioned that the layer of Henle's fibers in the fovea shows severe pathologic changes (Figures 19 and 20). These fibers show a wavy course, interruption, and formation of irregular globular bodies within their course or at interruptions pointing in both directions—towards and away from the fovea.

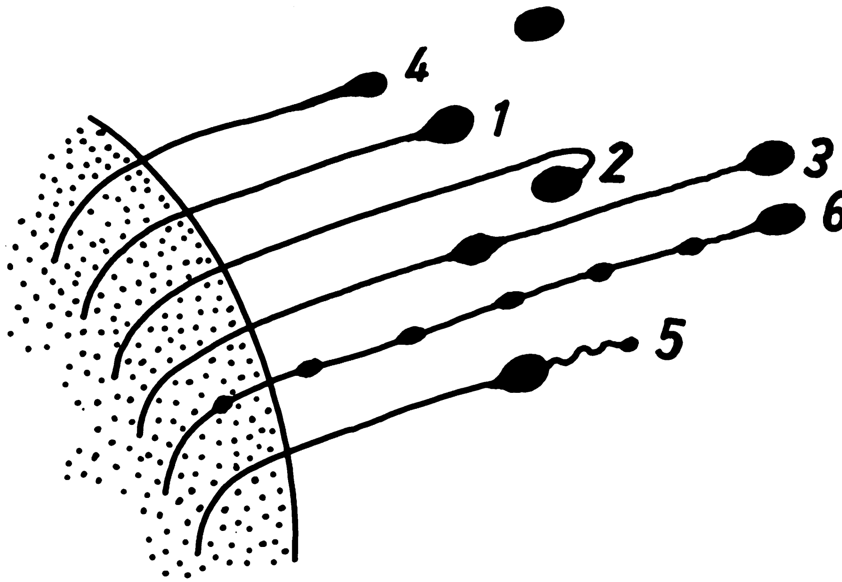


FIGURE 18

Simple drawing to demonstrate the different types of nerve changes observed after arterial occlusion in the stumps of the centrifugal nerves in the retina next to the disk. 1, simple terminal end bulb; 2, end of stump with terminal bulb bends backwards to the disk; 3, single globular swelling in the course of the nerve stump; 4, isolated terminal swelling peripheral to the nerve stump with another end bulb; 5, early attempt at regeneration starting out from a terminal swelling; and 6, bead-like swellings in the course of centrifugal nerve stumps.

DISCUSSION

The presence of centrifugal (antidromic, efferent) nerves in the human optic nerve is now well documented by morphologic studies.[5–11] The existence of these nerves is further supported by the neurophysiologic observations of Granit[3] and Dodt.[4] The functions of the centrifugal nerves are not known. However, we think these nerves to be important in ocular pathology and physiology. Some of the centrifugal nerves have been observed to supply blood vessels in the optic nerve and retina.[6,7,11] However, the present study shows that there are different types of centrifugal nerves morphologically and, thus, it is quite possible that the different nerve types may have different functions.

The present case gives the first impression of the number of centrifugal nerves on the human disk. There are many more of these nerves than we had thought before, thus answering the disturbing question

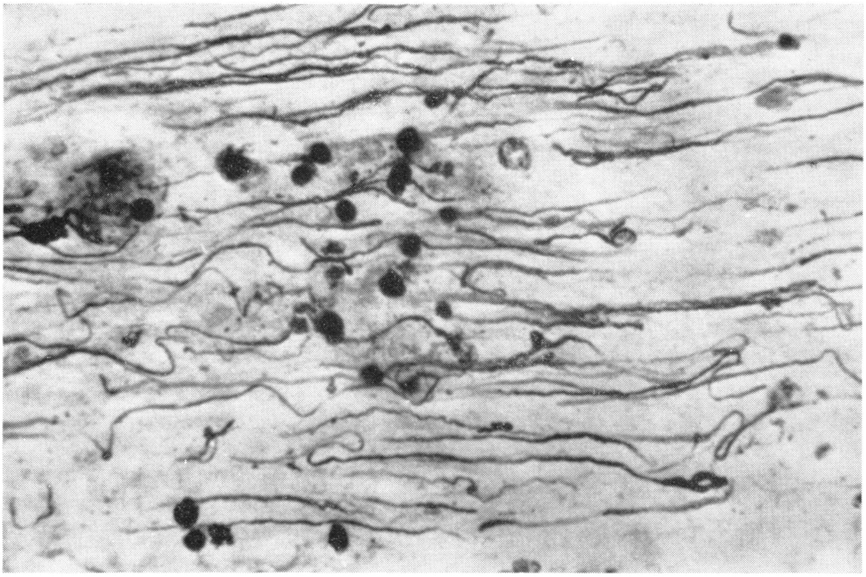


FIGURE 19

Henle's fibers are of irregular course and exhibit globular swellings. Flat frozen section, Hortega nerve stain. (photomicrograph, × 300)

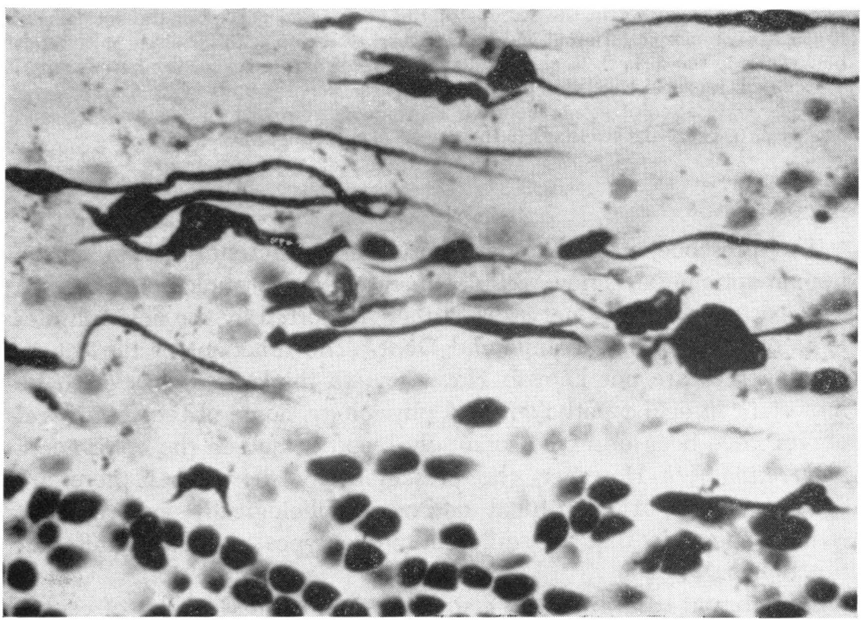


FIGURE 20

High-power view of bizarre changes found in Henle's fibers. Nuclei of the inner nuclear layer are seen below. Frozen flat section, Hortega stain for nerves. (photomicrograph, × 1000) that arose with Okun's and Collins' beautiful demonstration of terminal swellings of interrupted nerves (cytoid bodies) in the nerve fiber layer of the dog next to localized experimental photocoagulation.[14] Okun found that most of these swellings pointed away from the disk, while most of the terminal swellings in cotton-wool spots of the human retina had been seen to point towards the disk.[13] It seemed at the time of Okun's studies that there could not possibly be enough centrifugal nerves in the retina to account for all the terminal swellings pointing away from the disk that he found. However, after seeing how numerous the centrifugal nerves are in man it is clear that Okun was actually the first to observe the reactions of interrupted centrifugal fibers. We have now seen ourselves terminal swellings pointing away from the disk in the human retina in cotton-wool spots and after occlusion of the central retinal vein.[15]

It is not possible to count the remaining nerves in the present disk. Our guess is, however, that in the present case about one-tenth of the normal number of nerves has remained. That would mean that about one-tenth of the nerves in the normal human optic disk must be centrifugal in nature.

For an understanding of the nerve fiber changes of the present case three basic neuropathologic concepts have to be kept in mind: (1) that destruction of ganglion cells soon results in degeneration and disappearance of its neurites (nerves) and dendrites; (2) that nerves soon degenerate after they become separated from the cell body of their ganglion cell by a cut or after separation by compression, freezing, or ischemia, for example; and (3) that the stumps of interrupted neurites which are still connected to their ganglion cell bodies form reactive bulb- or club-shaped terminal swellings (Cajal bodies) at their distal ends. The terminal swellings are a reaction of the living nerve stump and regeneration starts out from them.

That the centrifugal nerves in this case have remained in the disk is due to the blood supply of the disk from the ciliary system. Soon after entering the retina, however, the fibers show interruption and most of their retinal portion has undergone necrosis along with the retinal ganglion cells and their centripetal (afferent) neurites as a result of the ischemia caused by the arterial occlusion. Typical terminal swellings of different shapes and arrangements are seen at the ends of the centrifugal nerve stumps. There also are nerve swellings within the terminal course of these stumps. At the end of some nerve stumps the very earliest signs of attempts at regeneration are seen. The terminal swellings that are found on nerve stumps which are bent backwards towards the optic disk (Figure 13) are a most bizarre and fascinating finding that we cannot yet fully explain. It seems as if these stumps have moved their end with the swelling back towards the disk and towards the better blood supply. It is hard to believe that nerve stumps should be able to move their ends actively. However, much about the reactions of retinal nerves is not yet known.

The observation of extensive pathologic changes in Henle's fiber layer in this case of acute arterial occlusion is most interesting and somewhat surprising. This finding would indicate that not only the innermost but also some of the deeper retinal layers are directly involved in occlusion of the central retinal artery. It has to be emphasized at this point, however, that the present case is not that of a simple arterial occlusion, a fact which must be considered not so much in regard to the reactions of the centrifugal nerves at the disk as in connection with the changes in the fovea, for example.

In conclusion it can be stated that the findings in this case allow for the following conclusions.

1. The human disk contains centrifugal (efferent) nerves.
2. These are very numerous and it seems that about one-tenth of the fibers in the human optic nerve are centrifugal.
3. There are different sizes of centrifugal nerves and this as well as the somewhat different reactions suggest that there actually are different types of centrifugal nerves.

It is realized that this unique case gives us only a first impression of the centrifugal nerves on the disk and their reactions to retinal ischemia in man. More cases of this kind are hard to obtain and the stains to demonstrate nerves do not always work. Thus, it seems worthwhile to report the observations in this one case.

II. PATHWAY OF CENTRIFUGAL FIBERS IN THE HUMAN OPTIC NERVE, CHIASM, AND TRACT

The course of the centrifugal nerves has been demonstrated histologically in the optic nerve stumps, chiasm, and optic tracts of a patient who had had both eyes enucleated 50 years previously.

CASE HISTORY

This 79-year-old negro male died on 12/12/63 of cachexia and liver cirrhosis with ascites and hydrothorax at Hurley Hospital in Flint, Michigan. Surgical absence of both eyes was observed at autopsy—along with many other pathologic changes that are of no interest in this study. The history revealed that in 1913 the patient injured his right eye with a branch while hunting. Removal of this eye was advised, but the patient refused. Sympathetic ophthalmitis developed and involved the fellow eye. Finally, both eyes had to be removed.

Fifty years after the bilateral enucleation the brain with the atrophic chiasm and optic nerve stumps (Figure 21) was obtained for this study.

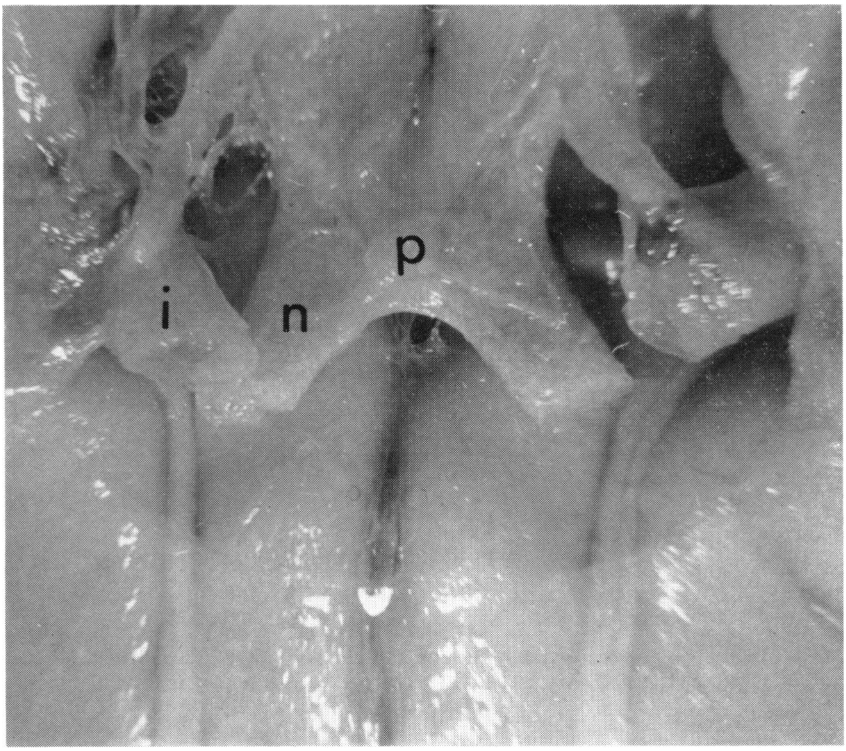


FIGURE 21

Gross view of the chiasm with the atrophic optic nerves (n), the pituitary stalk (p) and the internal carotid artery (i). (photograph, × 6)

PATHOLOGICAL FINDINGS

The brain was fixed in formalin. Frozen sections were cut of the optic nerve stumps, the chiasm (Figure 22), and the optic tracts. The Hortega silver carbonate technique for staining nerves[12] was used.

Both optic nerve stumps still contained many nerve fibers (Figures 22 and 23). The axons of these nerves were continuous and stained

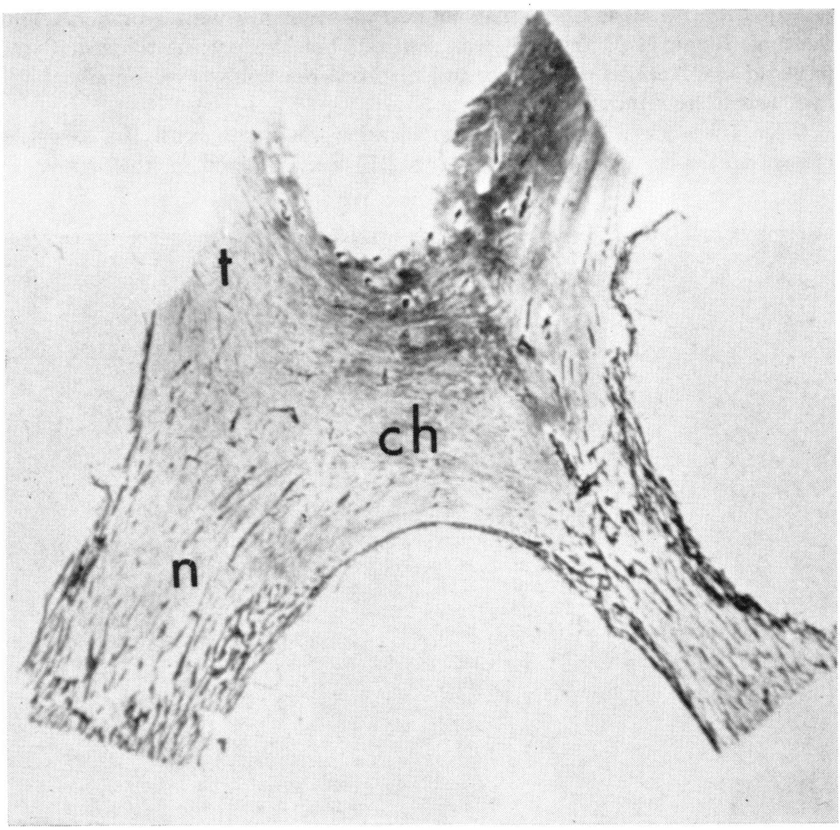


FIGURE 22

(One of the serial frozen sections through the chiasm (ch) with end of the optic nerves (n) and the optic tracts (t). Frozen section, Hortega stain. (photomicrograph, × 20)

well. Their myelin sheath, however, was of irregular distribution, nodular swellings alternating with areas of attenuation. In the areas of the nodular myelin swellings the axon usually also exhibited some swelling and an irregular course (Figures 24, 28 and 29). This degenerative change of optic nerve fibers with nodular myelin swellings has been recognized before and has been called "pearl-string-like nerve degeneration."[16] Other nerves—fiber tracts next to the optic tract, for example—did not show this pearl-string-like change. There also were numerous hyaline bodies of nerve fiber origin all through the optic nerves, chiasm, and optic tracts. Mixed with the majority of

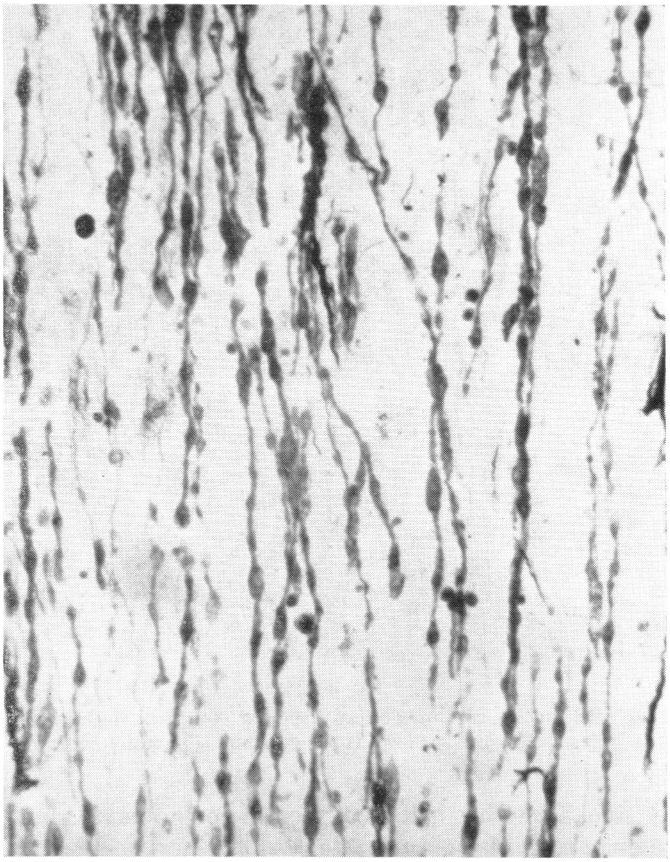


FIGURE 23
Nerve fibers with pearl-string-like myelin swellings on a parallel course in the right optic nerve stump. Frozen section, Hortega stain. (photomicrograph, × 600)

nerve fibers with pearl-string-like degeneration were a few neurites that had virtually no myelin sheath. These "unmyelinated" neurites seemed to increase in number as one progressed from the distal ends of the optic nerve stumps towards the chiasm. All nerves of the optic nerve stumps were arranged in the regular pattern of fibers on a parallel course (Figure 23).

The pattern of the nerve fibers with nodular myelin swellings became more irregular next to the chiasm (Figure 24). At the chiasm about half of these neurites were seen to cross from the optic tract of

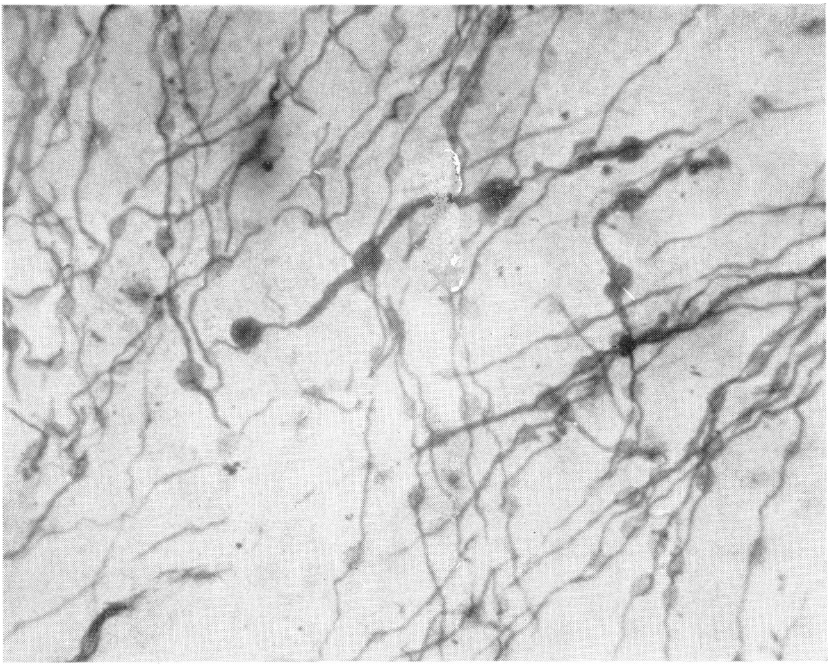


FIGURE 24

Nerve fibers with myelin swellings on an irregular course in the right optic nerve next to the chiasm. Frozen section, Hortega stain. (photomicrograph, × 800)

the other side. The other half were seen to come more or less directly from the optic tract of the same side.

In back of the chiasm there were some thin "unmyelinated" nerve fibers criss-crossing and extending into the chiasm from behind (Figure 25). A reconstruction showed that these nerves came from the direction of the pituitary stalk. A few of the thin fibers which were seen to come from the direction of the pituitary stalk and to join the chiasm were interrupted and showed rather large terminal swellings (Figure 26). All these terminal swellings pointed towards the optic nerve stumps. In the optic nerve stumps the same thin "unmyelinated" nerves could be recognized (Figure 27).

Most of the nerves of the optic nerve stumps—and all fibers with the pearl-string-like myelin swellings—could be traced into the optic tracts. They were still present in the optic tracts in a region right next to the lateral geniculate bodies (Figures 28 and 29). Figure 30 shows the course of the centrifugal nerves as found in this case.

FIGURE 25

Thin "unmyelinated" nerves criss-crossing between chiasm and pituitary stalk. Frozen section, Hortega stain. (photomicrograph, × 800)

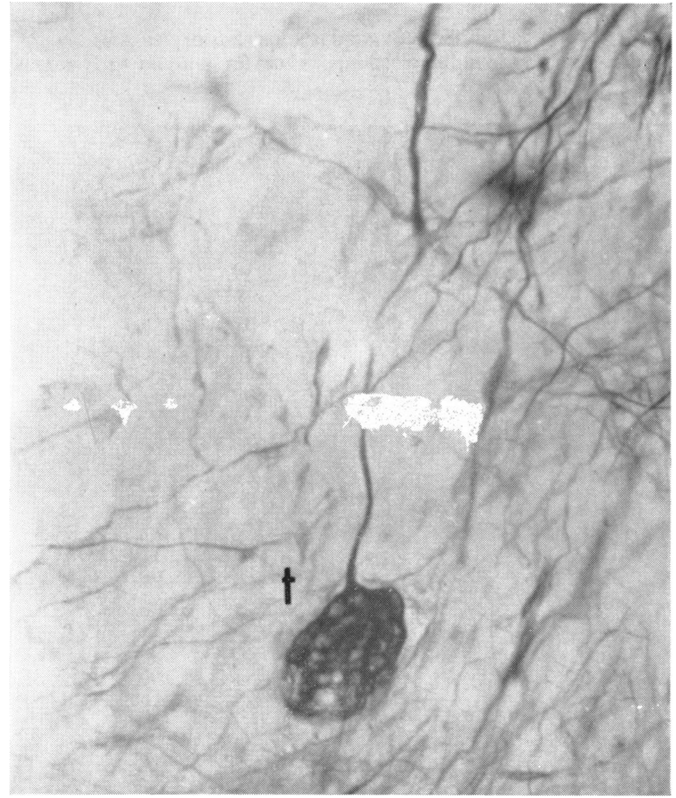


FIGURE 26

Terminal bulb of interrupted thin nerve (t) in the chiasm pointing towards the optic nerve stump. Frozen section, Hortega stain. (photomicrograph, × 800)

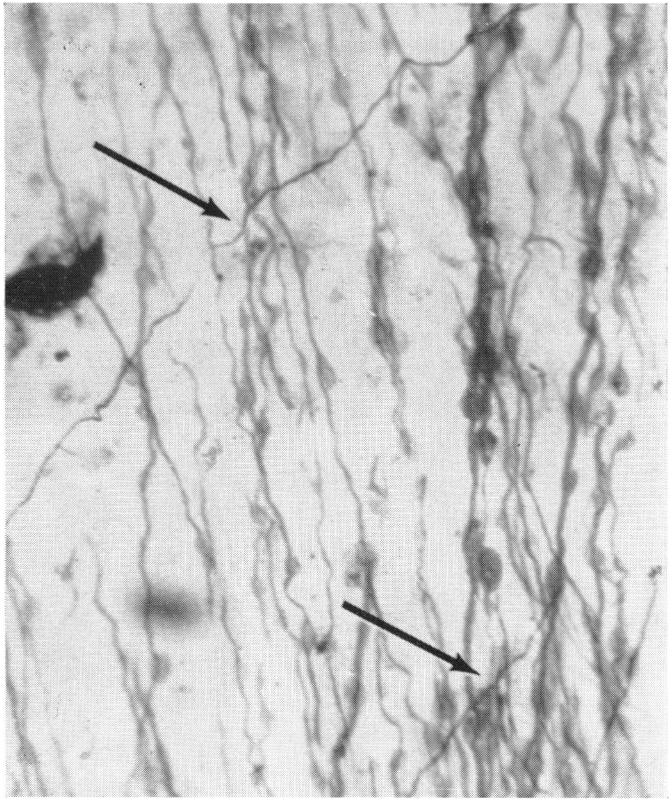


FIGURE 27

Two thin "unmyelinated" nerves (arrows) joining the other fibers of the left optic nerve stump. Frozen section, Hortega stain. (photomicrograph, × 800)

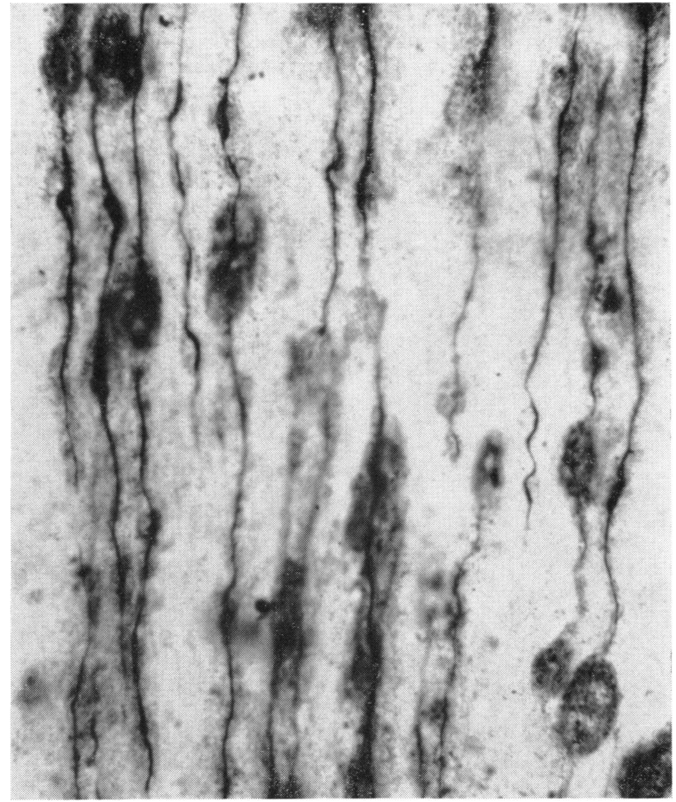


FIGURE 28

Nerves with nodular myelin swellings in right optic tract. Frozen section, Hortega stain. (photomicrograph, × 800)

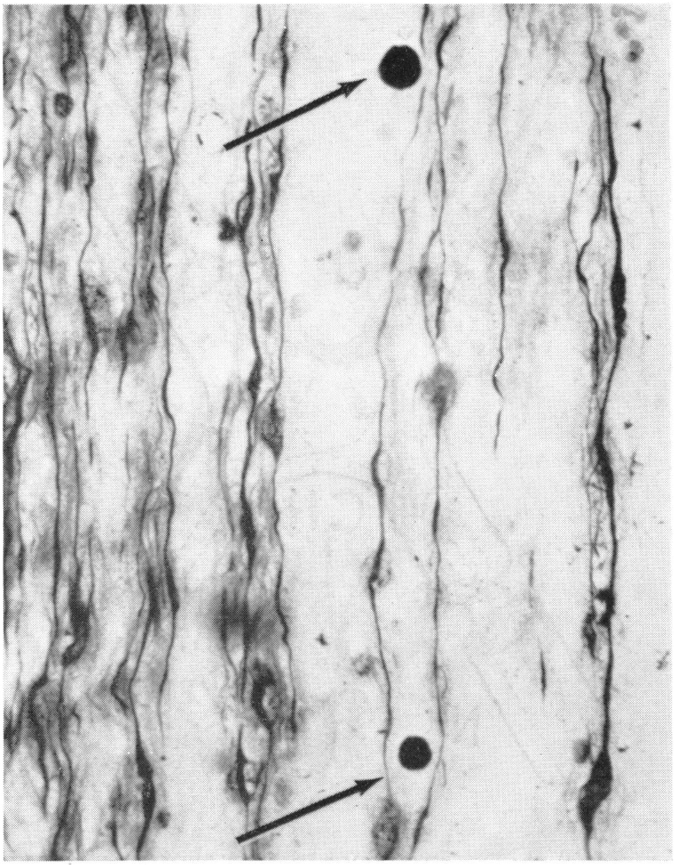


FIGURE 29
More distinct stain of axons showing irregularities within the areas of nodular swellings of nerves in the left optic tract next to lateral geniculate body. Two hyaline bodies (arrows) are also seen. Frozen section, Hortega stain. (photomicrograph, × 800)

DISCUSSION

The centrifugal (efferent) and centripetal (afferent) fibers of the normal human optic nerve, chiasm, and tract look alike in a histologic section. Therefore, it is impossible with present-day techniques to find the pathway of the centrifugal nerves in a normal human brain. The period of 50 years after bilateral enucleation in the present case must have caused complete atrophy of all centripetal nerves. All remaining nerves in the optic nerves, chiasm, and tracts must therefore be centrifugal in nature. It is already known that the centrifugal nerves show

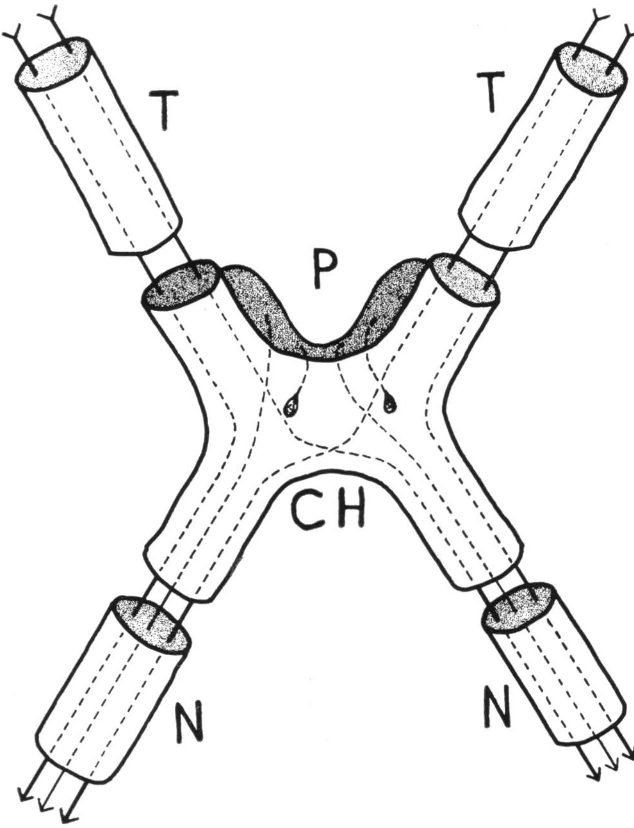


FIGURE 30. DRAWING TO GIVE IMPRESSION OF THE COURSE OF THE TWO TYPES OF CENTRIFUGAL NERVES.

One type (with myelin nodules) goes from optic tracts (T) by way of chiasm (CH) to the optic nerves (N). The other thin nerve type comes into the chiasm from pituitary stalk (P). The location of numerous degeneration bulbs of interrupted thin nerves is indicated.

only partial or no retrograde degeneration.[5] Thus, this case represents an unique opportunity to study the pathway of the centrifugal fibers of the human optic nerve.

At first, this study revealed that continuous centrifugal nerve fibers survived in the optic nerve stumps 50 years after bilateral enucleation. Most of the remaining fibers in the optic nerve stumps of the present case showed a peculiar pearl-string-like degenerative change of their myelin sheath that also involved the axon. This change is recognizable from atrophic optic nerves of other causes[16,17] and it serves very well in this study for an easy recognition of the remaining optic nerve fibers all the way up to the lateral geniculate body.

All fibers with the pearl-string-like myelin change could be traced to the optic tracts next to the lateral geniculate bodies. It cannot be said as yet whether the fibers originate there or whether they just pass through the lateral geniculate body and really have another origin. About half of the fibers with the pearl-string-like change were seen to cross in the chiasm while the other half remained uncrossed. In the optic nerve these fibers formed no distinct bundle, but were distributed evenly.

Additional thin fibers virtually without a myelin sheath were found in both optic nerve stumps. These fibers could be traced into the chiasm. All these "unmyelinated" fibers, however, were seen to come into the chiasm from behind—from the region of the pituitary stalk—and not from the optic tracts. No fibers of this type were found in the optic tracts. In this case it has not been possible to trace the thin centrifugal nerves which come from the pituitary stalk to the origin. These nerves are of great interest, of course. Extensive hyperregeneration of terminal centrifugal nerves around blood vessels and microaneurysms was demonstrated several years ago as "the only specific pathologic change of diabetic retinopathy."[11] The presence of such fibers connecting pituitary stalk and eye could perhaps also be important in relation to the removal of the pituitary gland or pituitary stalk section which has been found to improve advanced diabetic retinopathy.

COMMENTS

The observations of the present study indicate that the human optic nerve and retina contain numerous centrifugal nerves. This is an important and new insight. It may be recalled that Polyak,[18] in the new edition of his book on the retina, wrote: "Whether all axis cylinders of the optic nerve, in man and other primates belong to the category of afferent nerves—that is those conveying impulses generated in the retina to the brain—or whether there are efferent axons, or those originating in the brain and terminating in the retina, by means of which central influences may reach the photoreceptors, is a problem still to be solved. From the investigations of Ramon y Cajal, Bouin, Dogiel, Weber and others, the presence of such fibers is fairly certain in birds and axolotl, but they have not yet been definitely shown to exist in mammals."

The following facts support the existence of centrifugal (efferent) nerves in the human optic nerve and retina.

1. Survival of nerve fibers in the central stump of the optic nerve up to 50 years after cutting (enucleation).
2. Observation of normal retinal nerves which branch away from the optic disk and supply blood vessels.
3. Observation of nerve fiber stumps with terminal swellings pointing to the eye in the optic nerve and towards the periphery in the retina.
4. Abortive regeneration at the distal end of interrupted nerve fibers in optic nerve stumps of children.
5. Survival of nerve fibers at the disk with terminal swellings pointing towards the periphery after complete necrosis of the ganglion cell layer due to occlusion of the central retinal artery.

Other interesting morphological facts are that the centrifugal nerves were estimated to represent about 10 per cent of the nerve fibers of the normal human optic nerve and that they appear to be of varying thickness, course, and origin.

It is hoped that the morphological findings reported in this study will soon be supported and extended by physiological observations in man. To the morphologist remains the taks of classifying and understanding the different endings of centrifugal fibers in the retina and optic nerve and of tracing the different nerve types to their origins. We have no doubt that an understanding of the centrifugal nerve system in the visual apparatus will prove to be important for an exact insight into normal function and ocular disease.

SUMMARY

In the first part of this study the surviving centrifugal (efferent) nerves were examined after complete occlusion of the central retinal artery. It was estimated that about one-tenth of the nerves in the normal human optic disk are centrifugal. The second part contains a description of the pathway of the centrifugal nerves in the chiasm and optic tract as it was observed in a patient who had had both eyes enucleated fifty years earlier.

REFERENCES

1. Cajal, S. R., Die Retina der Wirbeltiere, p. 168, Wiesbaden, Bergmann, 1894.
2. Dogiel, A. S., Die Retina der Vögel, Arch. mikr. Anat., 44:622, 1895.
3. Granit, R., Centrifugal and antidromic effects on ganglion cells of the retina, J. Neurophysiol, 18:388, 1955.

4. Dodt, E., Centrifugal impulses in rabbit's retina, J. Neurophysiol, 19:301, 1956.
5. Wolter, J. R., and L. Liss, Zentrifugale (antidrome) Nervenfasern im menschlichen Sehnerven, Graefes Arch. Ophth., 158:1, 1956.
6. Wolter, J. R., Ueber Endigungen zentrifugaler Nervenfasern an den Blutgefässen der menschlichen Netzhaut, Graefs Arch. Ophth. 158:524, 1957.
7. Liss, L., and J. R. Wolter, Zur Innervation der Blutgefässe des menschlichen Sehnerven, Klin. Monatsbl. Augenh., 129:793, 1956.
8. Wolter, J. R., Ein weiterer Beweis für die Existenz zentrifugaler Nervenfasern in der menschlichen Netzhaut, Graefes Arch. Ophth., 158:235, 1956.
9. Wolter, J. R., Regenerative potentialities of the centrifugal fibers of the human optic nerve, A.M.A. Arch. Ophth., 64:697, 1960.
10. Pfister, R. R., and J. R. Wolter, Centrifugal fibers of the human optic nerve, Neurology, 13:38, 1963.
11. Wolter, J. R., Diabetic retinopathy, Am. J. Ophth., 51:1124, 1961.
12. Scharenberg, K., and W. Zeman, Zur Leistungsfähigkeit und zur Technik der Hortega'schen Silberkarbonatmethoden, Arch. Psychiat., 188:430, 1952.
13. Wolter, J.R., Pathology of a cotton-wool spot, Am. J. Ophth., 48: 473, 1959.
14. Okun, E., and E. M. Collins, Histopathology of experimental photocoagulation in the dog eye, II, Production of cytoid body lesions, Am. J. Ophth., 54:786, 1962.
15. Wolter, J. R., Retinal pathology after central retinal vein occlusion, Brit. J. Ophth., 45:683, 1961.
16. Wolter, J. R., Perlschnurartige Nervenfaserdegeneration im menschlichen Sehnerven, Graefes Arch. Ophth., 159:384, 1957.
17. Wolter, J. R., and L. Liss, Hyaline bodies of the human optic nerve, A.M.A. Arch. Ophth., 61:780, 1959.
18. Polyak, S. L., The Vertebrate Visual System, p. 292, Chicago, University of Chicago Press, 1957.