REACTION OF CENTRIFUGAL NERVES IN THE HUMAN RETINA TWO WEEKS AFTER PHOTOCOAGULATION*

BY *J. Reimer Wolter*, M.D.,
AND (BY INVITATION) *O.-E. Lund*, M.D.

CENTRIFUGAL (EFFERENT, ANTIDROMIC) NEURITES are now well known to exist in the optic nerve and in the nerve-fiber layer of the retina of the human eye.[1-12] These centrifugal nerve fibers occur in great numbers and we have estimated that they represent about 10 per cent of the neurites in the normal human optic nerve and nerve-fiber layer.[9-11] At least two different types of centrifugal nerves have been recognized by differences of size, course, and reactions in man.[8-11] One type was shown to supply blood vessels in the optic nerve and retina.[3,7,12] It was also observed that some centrifugal neurites came from the lateral geniculate body; half of these crossed and the other half remained uncrossed in the chiasm, while another type of centrifugal neurite entered the chiasm from a posterior direction (hypothalamus, pituitary stalk) and appeared to be independent of the optic tracts.[8-10]

The reactions of centrifugal neurites in the retina after photocoagulation were first demonstrated by Okun and Collins[13] in the dog. Histologic study of the reactions of retinal neurites next to photocoagulation burns in man were done in one case twenty-four hours after photocoagulation.[11] This study showed interruption of the retinal neurites in the area of the photocoagulation burns. Nerve stumps with terminal swellings (axonal enlargements)[14,15] were demonstrated on both sides of the burns. Three types of interrupted neurites were found after twenty-four hours on the central aspect of the burns (toward the disk). Two of these were considered the stumps of centrifugal nerves. The third type of interrupted neurite on the central aspect of the photocoagulation burns exhibited only very small axonal

*From the Departments of Ophthalmology and Pathology of the University of Michigan Medical Center and from the Universitaets-Augenklinik, 43 Essen 1, Germany. This study was supported by Research to Prevent Blindness, Inc., N.Y.

enlargements and it appeared possible that these could be reactive nerve swellings which may occur soon after interruption on peripheral stumps of severed neurites which are no longer connected to their cell bodies.[16–18]

The reactions of the interrupted retinal nerve fibers on the central aspects of photocoagulation burns in the human eye fourteen days after their application are reported in the present paper.

CASE REPORT

This 51-year-old male was seen late in June 1967 in the University Eye Department, Essen, Germany, with a nodular, solid retinal elevation in the temporal aspect of the fundus of his right eye (Figure 1). Additional exudative retinal detachment was seen inferiorly. A choroidal tumor was suspected as the cause of the solid elevation. Enucleation was advised. The patient, however, refused to have his eye removed, but he permitted further testing with intravenous fluorescein injection, P32 uptake studies, and photocoagulation on and next to the tumor. A row of photocoagulation burns was applied to the retina superior to the tumor on 30 June 1967. The Zeiss photocoagulator was used and the settings were: normal load II, opening 0, degrees 4.5, 8 applications of 1/2–1 sec. A test with intravenous radioactive P32 was done and this was positive. Another row of photocoagulation burns with similar settings was applied nasally on 11 July 1967. Two weeks later the eye had become virtually blind, the patient agreed to have the eye removed, and the enucleation was done without difficulties on 14 July 1967. The globe was immediately fixed in a 10 per cent solution of neutral formalin and sent to Ann Arbor for histopathologic examination.

The eye was of normal size and no tumor was found on the outside. It was opened horizontally by cutting the tumor in two halves (Figure 2). The two rows of photocoagulation burns were visible through some milky exudate in the vitreous. Histologic study showed the tumor to be a choroidal melanoma of the spindle B cell type without evidence of direct extension into or through the sclera.

The retina, pigment epithelium, choroid, and sclera in the area of the first photocoagulation burns of 30 June 1967 had been isolated before the remainder of the eye was prepared for the routine histologic examination. This piece of the ocular wall was cut into flat sections on the freezing microtome. The Hortega silver stain for the demonstration of nerves[19] was used to stain the nerve-fiber changes in the region of the photocoagulation burns in these frozen sections.

There was total destruction of all neurites of the nerve-fiber layer in the center of the burns (Figure 3). Acellular granular debris was found in this zone (Figure 4) and the glia of the nerve-fiber layer was absent. The first zone

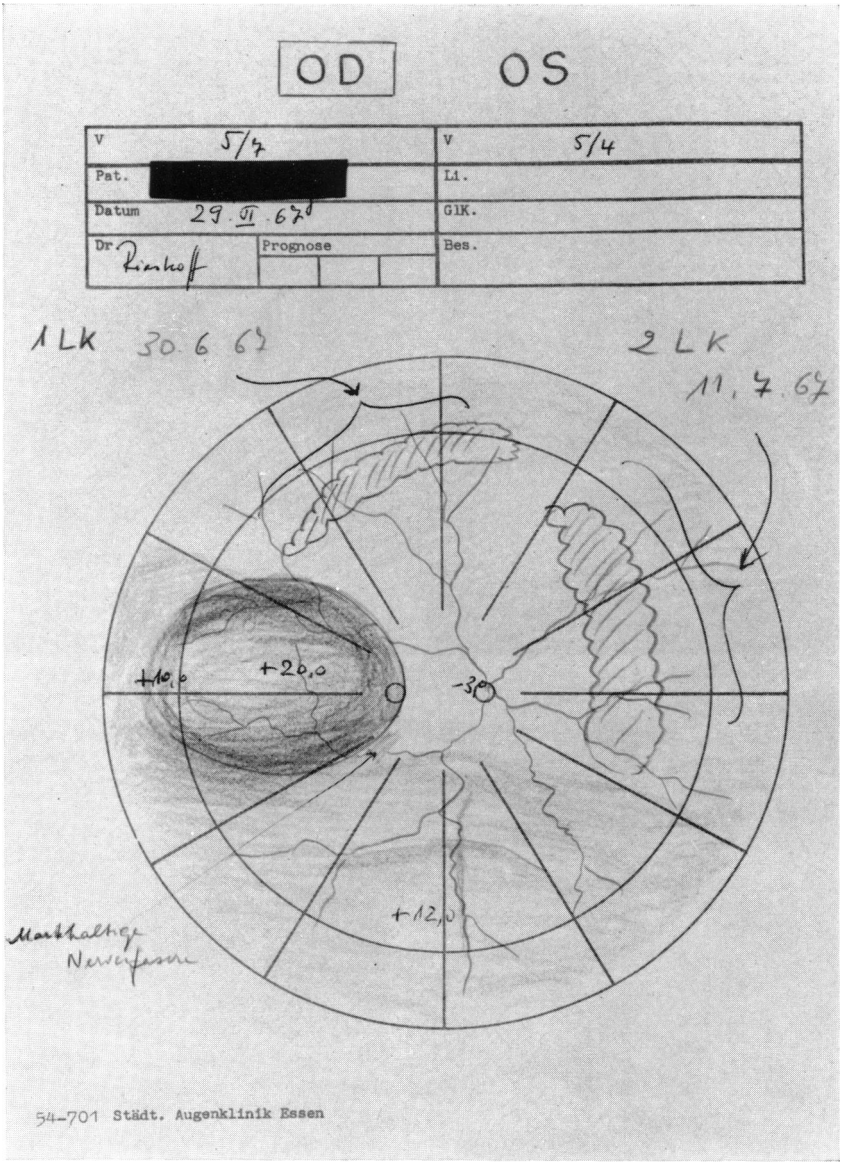
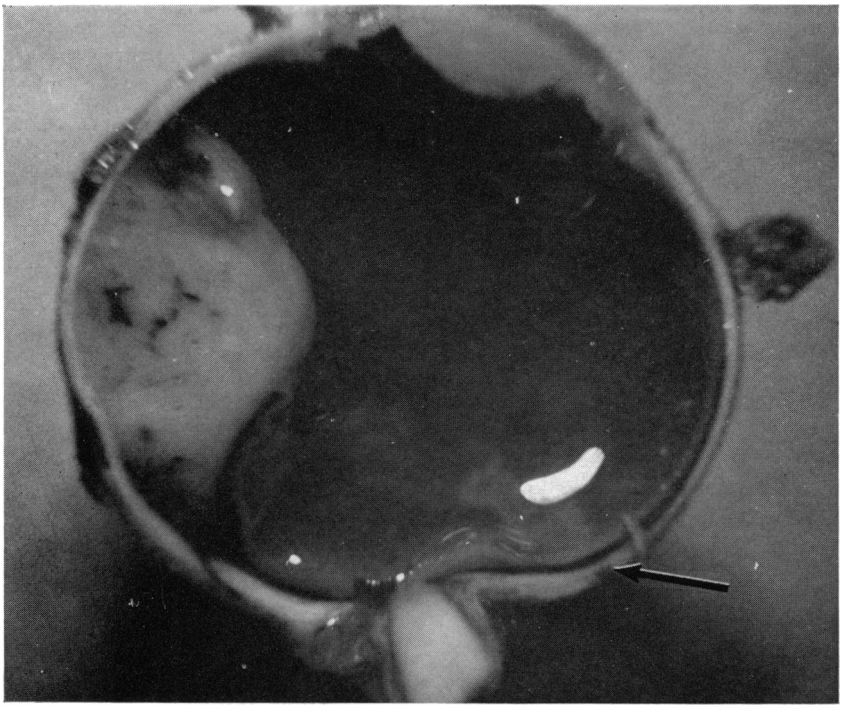
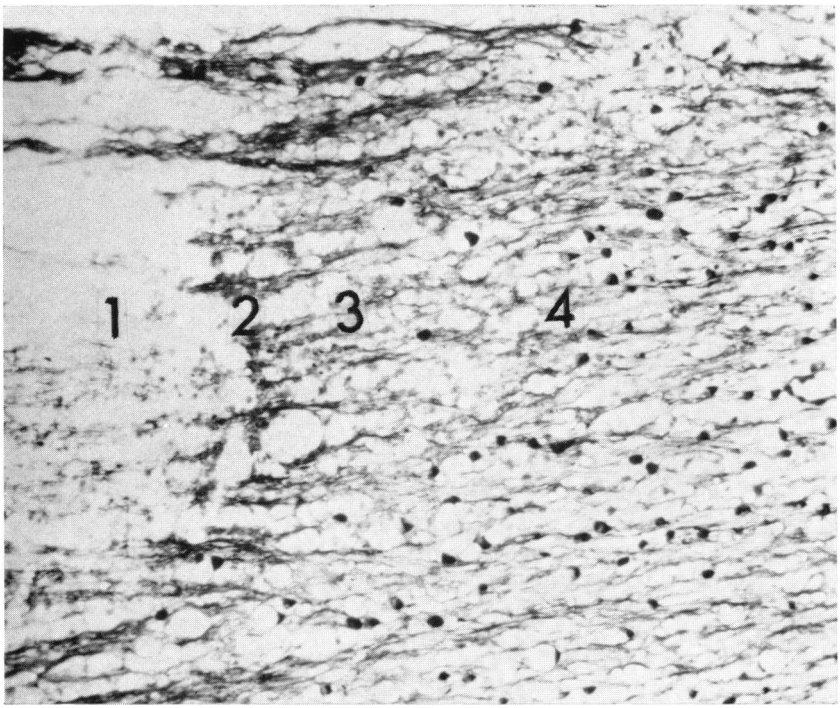


FIGURE 1

Drawing of fundus to show the choroidal melanoma as well as the two areas treated with photocoagulation on 30 June 1967 and on 11 July 1967.




1
2
3
4

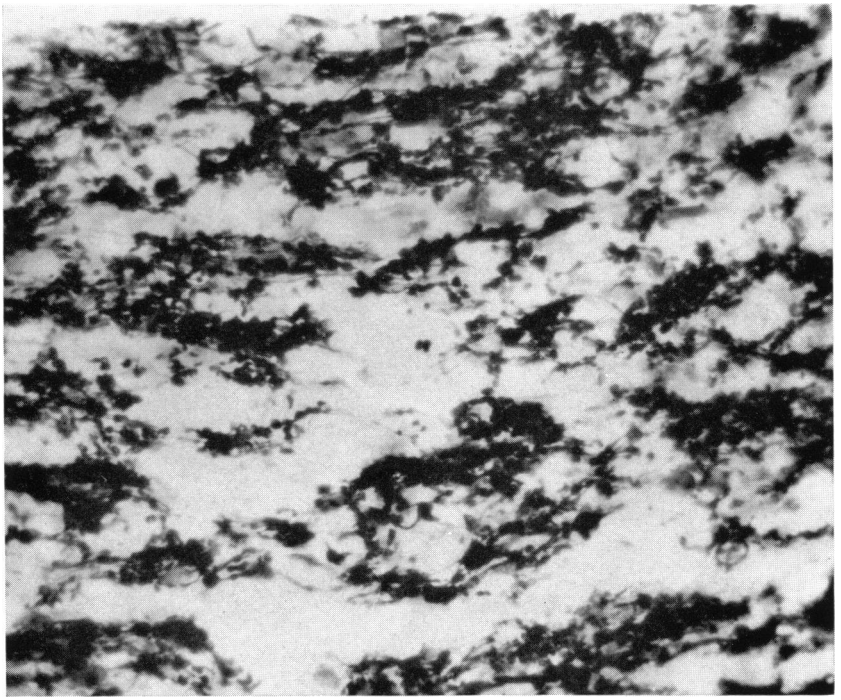


FIGURE 4

The granular debris of totally destroyed neurites and glia in the center of the burns (zone 1) at higher power. Frozen flat section, Hortega stain, photomicrograph, × 800.

FIGURE 2

Gross view of the superior half of the globe. The row of photocoagulation burns of 11 July 1967 is visible (arrow). The row of the earlier burns is covered by vitreous haze. Photograph, × 6.

FIGURE 3

Low-power view of a flat section of the nerve fiber layer at the central aspect of one of the photocoagulation burns applied on 30 June 1967. Zone 1 shows granular debris of totally destroyed nerve fibers and glia. Zone 2 exhibits larger pale-staining bodies. Zone 3 shows many small and a few large axonal enlargements. Zone 4 exhibits numerous thick nerve stumps with large axonal enlargements. The retinal periphery would be on the left while the optic disk would be on the right side of the picture. Frozen section, Hortega stain, photomicrograph, × 100.

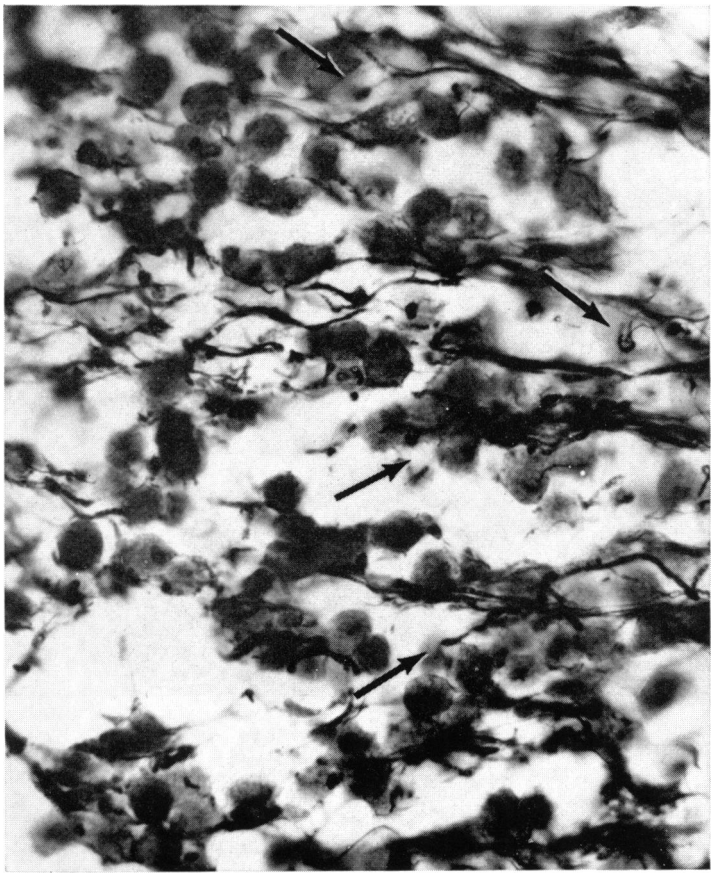


FIGURE 5

High-power view of zone 2 showing the large pale-staining bodies of this region as well as thin nerve-fiber stumps pointing to the periphery and exhibiting small terminal axonal enlargements at their ends (arrows). Frozen flat section, Hortega stain, photomicrograph, × 800.

of total nerve-fiber destruction in the center of the burns exhibited a second zone of larger pale-staining bodies (Figures 1 and 5) on its central aspect (toward the disk). Thin nerve-fiber stumps with small axonal enlargements (terminal swellings) were seen to end in the second zone among the larger round bodies as well as in a third zone next to it—in a direction toward the optic disk (Figure 6). Large axonal enlargements at the ends of thicker nerve-fiber stumps were found in a relatively broad fourth zone—in a direction toward the optic disk (Figures 7 and 8). Axonal enlargements of the thin nerve fibers were especially numerous next to the limit between the

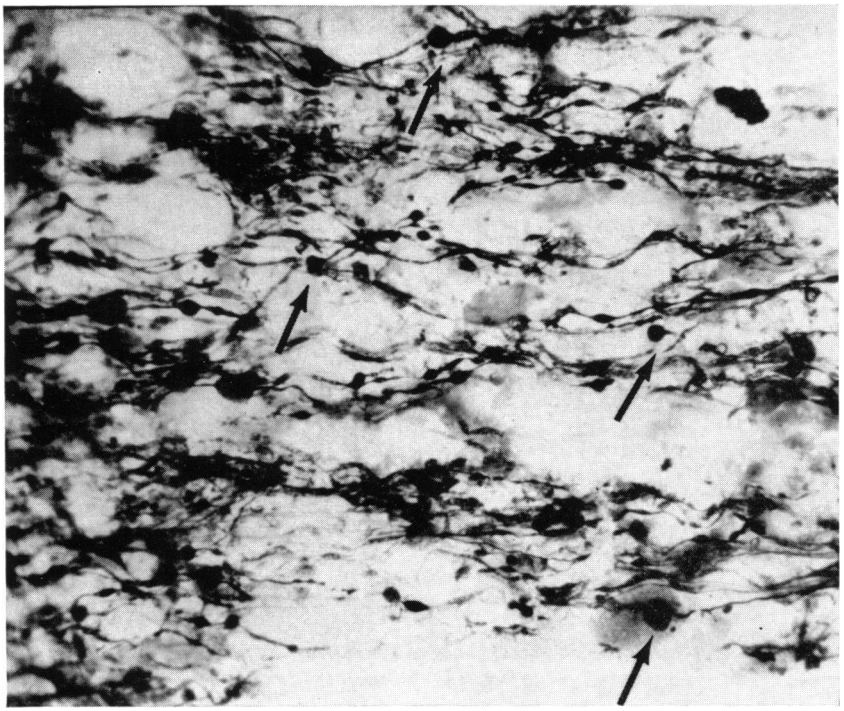


FIGURE 6

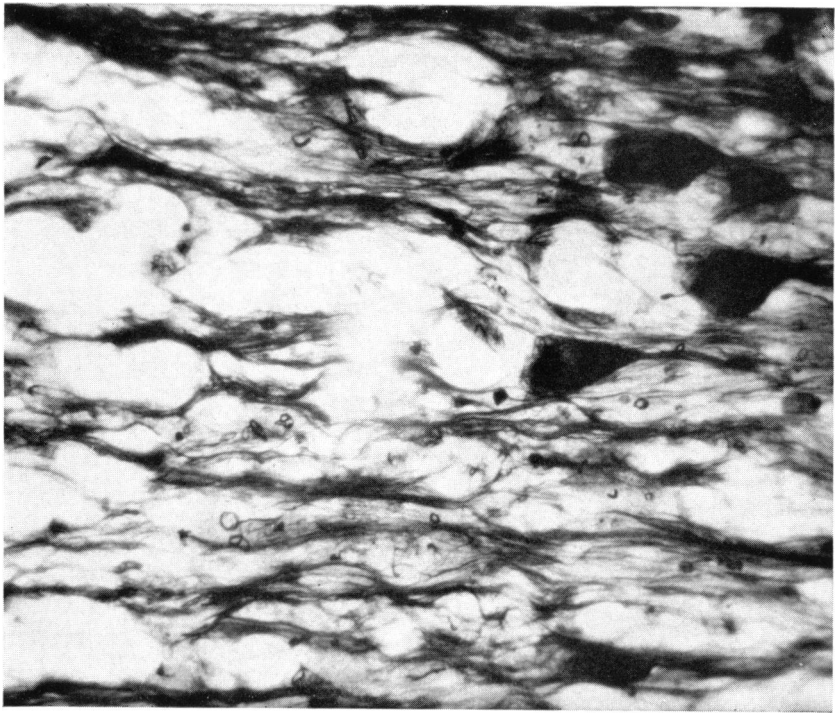
One area in the second zone on the central aspect of a 14-day-old photocoagulation burn with relatively few pale-staining bodies and with numerous, thin nerve-fiber stumps exhibiting small terminal axonal enlargements (arrows). Frozen flat section, Hortega stain, photomicrograph, × 800.

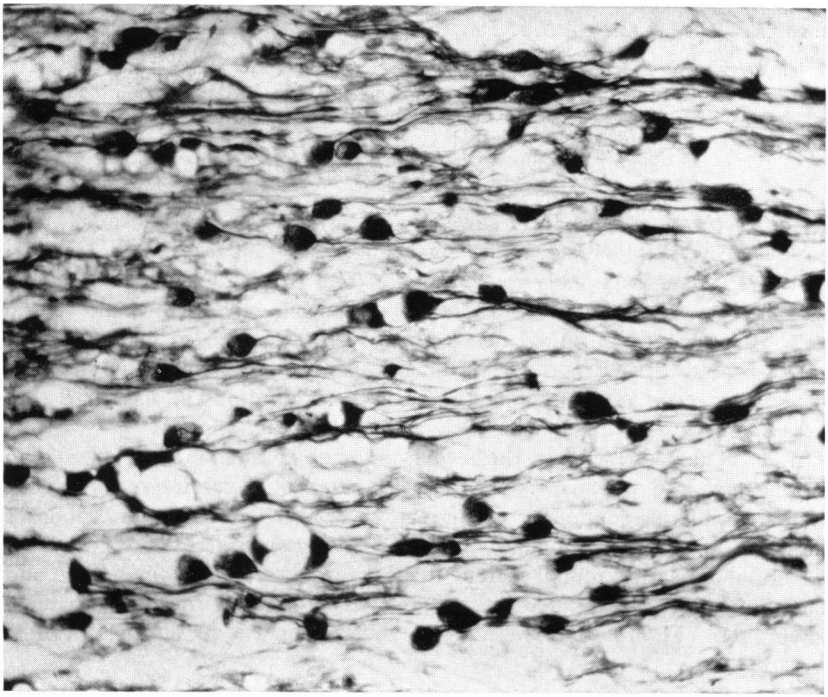
third and the fourth zones (Figure 7). The stumps of the thicker type of nerve fiber in the fourth zone with their large axonal enlargements (terminal swellings) were remarkably regular in size and shape (Figures 9 and 10).

Peculiar neurites of the nerve-fiber layer which ran at an angle to the main direction of the retinal nerve fibers were also seen to have survived on the central aspects of the photocoagulation burns. Small axonal enlargements on the end of some of these nerve fibers (Figure 11) indicated that these fibers were alive and most likely also centrifugal in nature.

Study of deeper layers of the retina, pigment epithelium, and choroid in and next to the photocoagulation burns revealed some interesting facts. Retinal capillaries containing erythrocytes were seen in the central zone of the burns next to the remnants of dead retinal ganglion cells (Figure 12).

Normal-appearing retinal ganglion cells were observed in zones three and four which contained the reactive axonal enlargements of the centrifugal nerve fibers (Figure 13). The pigment epithelium was totally destroyed in





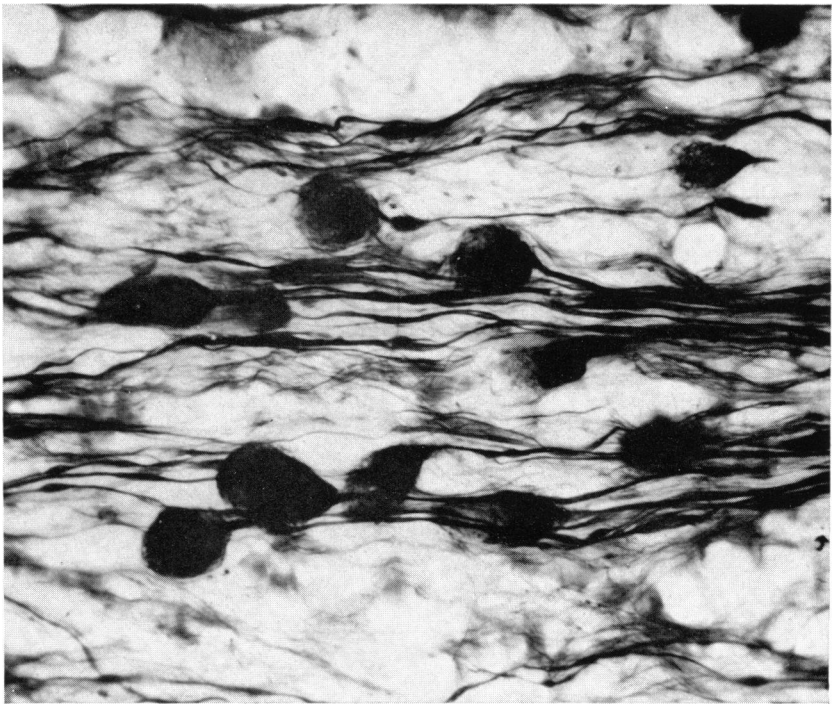


FIGURE 9

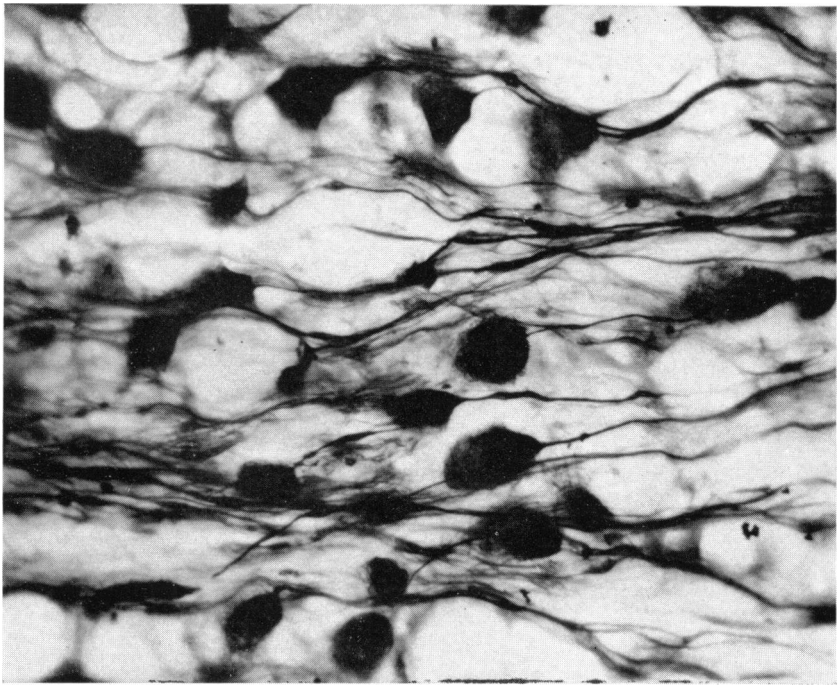
A bunch of stumps of the thicker type of interrupted centrifugal nerve fibers with large terminal axonal enlargements fourteen days after photocoagulation in zone 4. Frozen flat section, Hortega stain, photomicrograph, × 800.

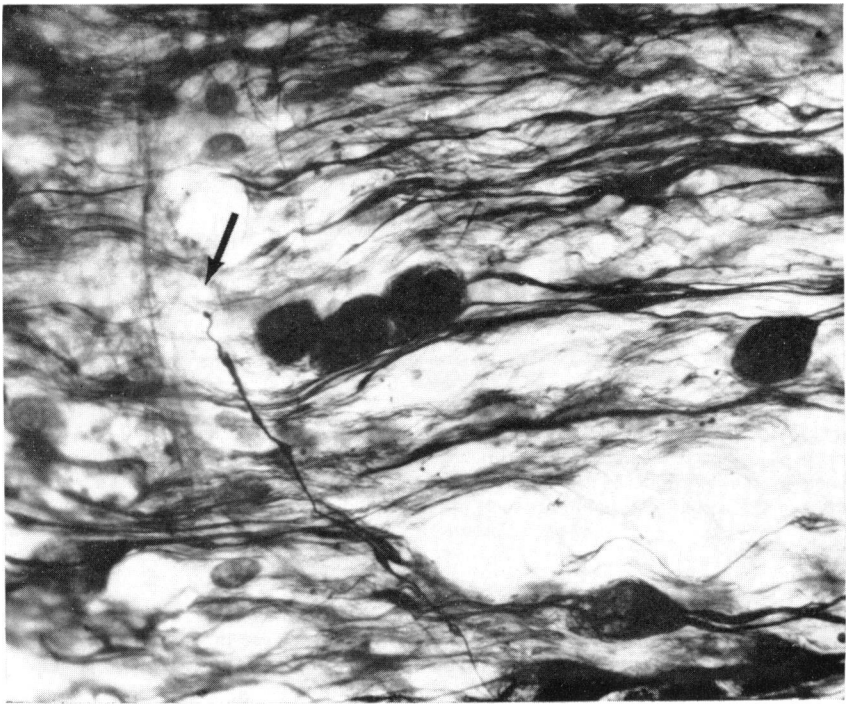
FIGURE 7

The limit between zones 3 and 4 on the central aspect of a photocoagulation burn after fourteen days. Thin nerve-fiber stumps with small terminal swellings are seen in the left half of the picture while there are seven thicker nerve stumps with larger axonal enlargements seen in the right half. Flat frozen section, Hortega stain, photomicrograph, × 800.

FIGURE 8

Medium power view of an area in zone 4 on the central aspect of a photocoagulation burn fixed fourteen days after its application gives an impression of the number of larger terminal enlargements at the ends of thicker nerve stumps. Frozen flat section, Hortega stain, photomicrograph, × 250.





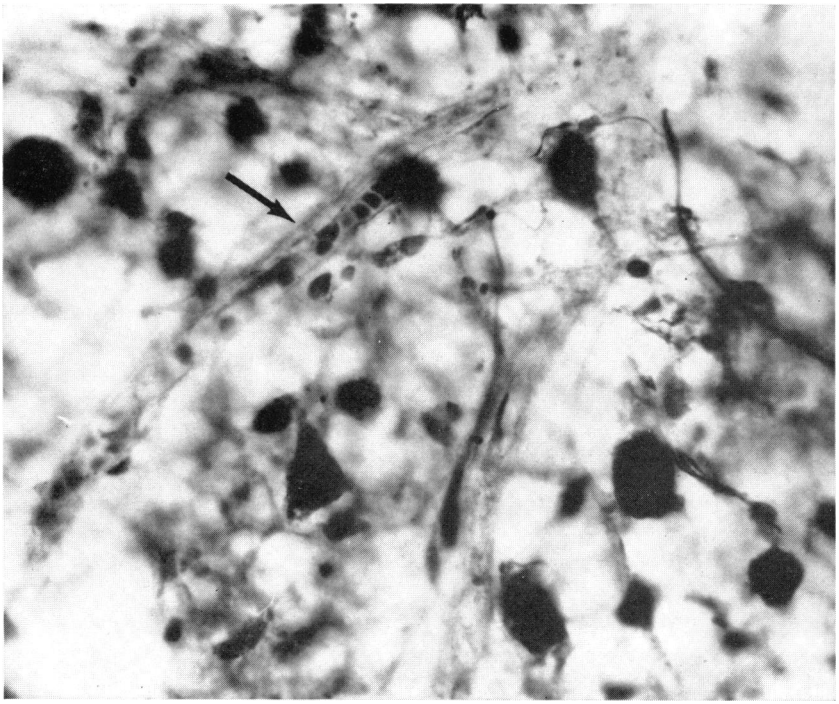


FIGURE 12

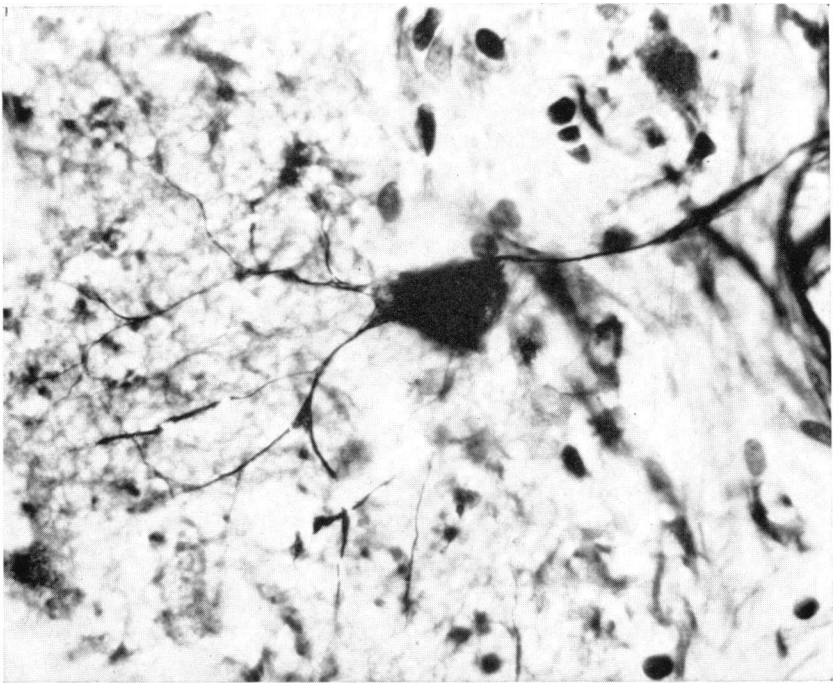
Remnants of ganglion cells and a capillary containing erythrocytes (arrow) of the ganglion-cell layer in the center of a 14-day-old burn. The neurites and dendrites of the ganglion cells are absent. Flat frozen section, Hortega stain, photomicrograph, × 800.

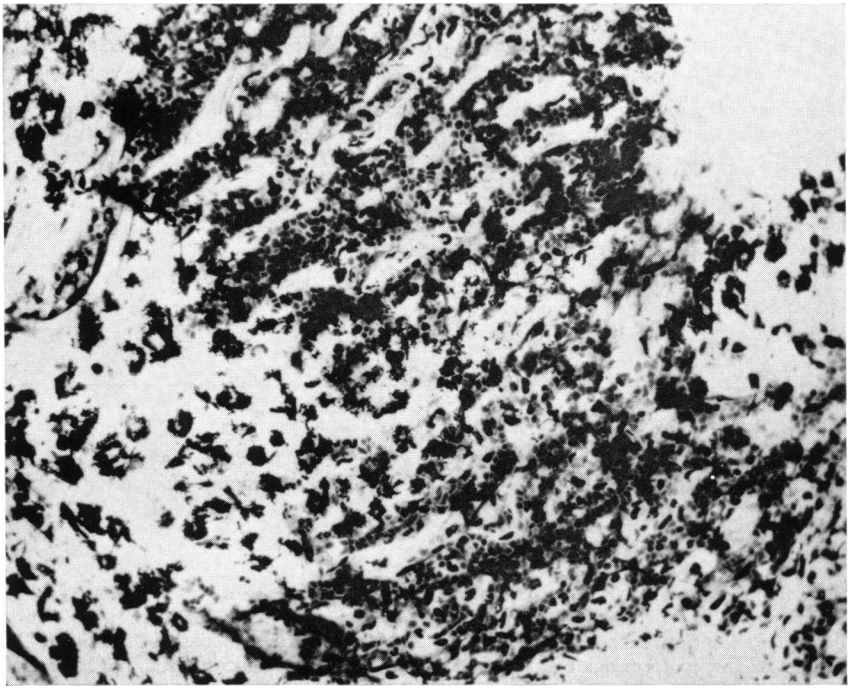
FIGURE 10

More diffusely arranged stumps of thicker nerve fibers in zone 4. Much edema is seen in the interspaces. Frozen flat section, Hortega stain, photomicrograph, × 800.

FIGURE 11

One thicker nerve-fiber stump running at an angle to the main direction of the retinal nerve fibers (arrow) shows a small terminal enlargement and perhaps some early regeneration in zone 4 central to a 14-day-old photocoagulation burn. A bunch of larger terminal enlargements is seen to its right. Frozen flat section, Hortega stain, photomicrograph, × 800.





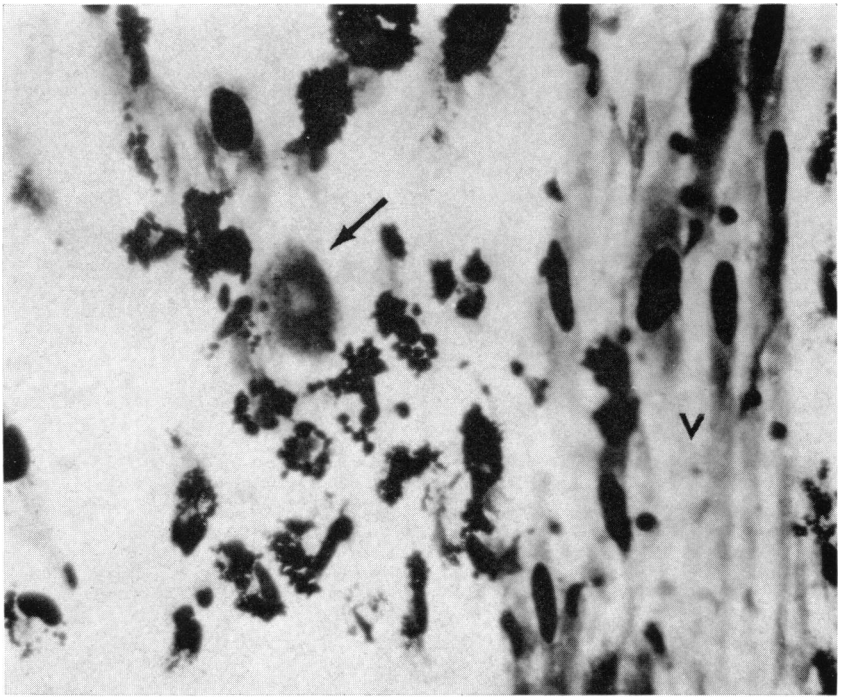


FIGURE 15

A blood vessel with normal endothelial cells (v), one normal-appearing primitive ganglion cell (arrow) and histiocytes laden with pigment in the choroid in the center of a 14-day-old photocoagulation burn. Flat frozen section, Hortega stain, photomicrograph, × 800.

FIGURE 13

A normal-appearing ganglion cell with neurite and dendrite in zone 3 for comparison. Frozen flat section, Hortega stain, photomicrograph, × 800.

FIGURE 14

Hyperemic choriocapillaris in the third zone fourteen days after photocoagulation. Damaged choroidal melanocytes on the left side of the picture. Flat frozen section, Hortega stain, photomicrograph, × 800.

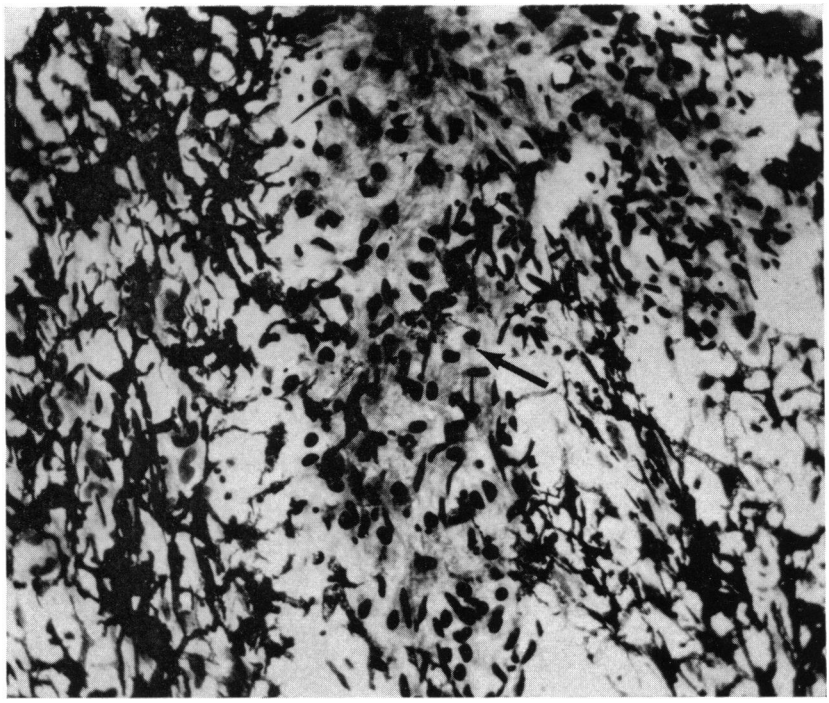


FIGURE 16

A cluster of many choroidal ganglion cells found in flat sections of non-involved choroid of the present eye (arrow). This is surrounded by normal melanocytes. Frozen section, Hortega stain, photomicrograph, × 250.

the central and first zones and this layer exhibited irregular reactive changes in the regions of the third and fourth zones (Figure 14). The choriocapillaris in the central and second zones contained no blood and appeared severely damaged. The choriocapillaris in the third and fourth zones had survived and showed extensive hyperemia (Figure 14).

The choroidal melanocytes were found to be destroyed in the center of the burns. Their pigment granules were seen, in part, in the protoplasm of histiocytes. The larger choroidal blood vessels had survived, with normal-appearing endothelium, in the center of the burns. Primitive choroidal ganglion cells also had survived in areas where the choroidal melanocytes were destroyed (Figure 15). These primitive ganglion cells occur as single cells or in groups in the normal human choroid and they appear to be increased in number in some eyes with choroidal melanoma.[20–23] The branching melanocytes as well as a group of the primitive choroidal ganglion cells are seen in their normal arrangement in the third and fourth

FIGURE 17

Extensive mononuclear infiltration in all layers of the choroid surrounding the photocoagulation burns after fourteen days. Frozen section, Hortega stain, photomicrograph, × 250.

zones in Figure 16. The choroid in these latter zones also exhibited areas of extensive mononuclear infiltration (Figure 17)—probably as a reaction to the necrosis caused by the photocoagulation burns.

DISCUSSION

The main purpose of this study was to demonstrate the reactions of the interrupted centrifugal (efferent, antidromic) neurites in the nerve-fiber layer of the human retina fourteen days after photocoagulation. The row of nasal photocoagulation burns which were set three days before enucleation of the eye was not studied histologically because of technical difficulties with flat sectioning in this region of the ocular wall.

The present study confirmed our earlier observation that photocoagulation in the dosage commonly used for treating human eyes locally

destroys and interrupts all neurites in the exposed area of the nerve-fiber layer.[11] The findings on the central aspects of the burns in the present case differ from those in the earlier case in that only two distinct types of nerve-fiber stumps with axonal enlargements (terminal swellings of Cajal) were found after fourteen days. Three types of interrupted nerves were seen on the central aspects of the burns after twenty-four hours, but one of these nerve stumps had virtually no axonal enlargement at its end. The present study seems to confirm the suspicion that these latter nerve-fiber stumps seen after twenty-four hours on the central edge of the burns must have been the severed afferent neurites. These were still preserved twenty-four hours after interruption by photocoagulation,[11] but they were found to be dissolved after fourteen days in the present case.

Two distinctly different types of nerve-fiber stumps with reactive axonal enlargements were seen on the central edges of the 14-day-old photocoagulation burns in the present case. One was a thin neurite with a small axonal enlargement at its end in the second and third zones of neuronal destruction described above. The other was a thicker neurite with a much larger axonal enlargement mostly found a little distance away from the total nerve-fiber destruction in the center of the burns (Figure 18). We have no doubt that these two types of nerve-fiber stumps represent two different kinds of centrifugal neurites which are normally present in the nerve-fiber layer of the human retina. The findings in the present case fit in well with our earlier observations of two types of centrifugal nerves in human optic nerve and retina under other conditions.[3,7–11,24]

The observations in the present case confirm our earlier estimate that about one-tenth of the number of neurites in the normal human nerve-fiber layer must be centrifugal in nature. We are waiting for a case that will allow for better estimates or actual counting.

The granular debris found in the nerve-fiber layer in the center (first zone) of the photocoagulation burns was a surprising finding. The granules appeared to be the coagulated remnants of the neurites and glia of this layer. Fourteen days after the photocoagulation treatment we would have expected to see absorption of these remnants by macrophages as well as early scarring. All this was absent. The best explanation for the surprising absence of macrophages and scarring in the necrotic areas of the retina of this case is the proximity of the large, fast-growing neoplasm. This could have exhausted the reserves of the local reticuloendothelial system.

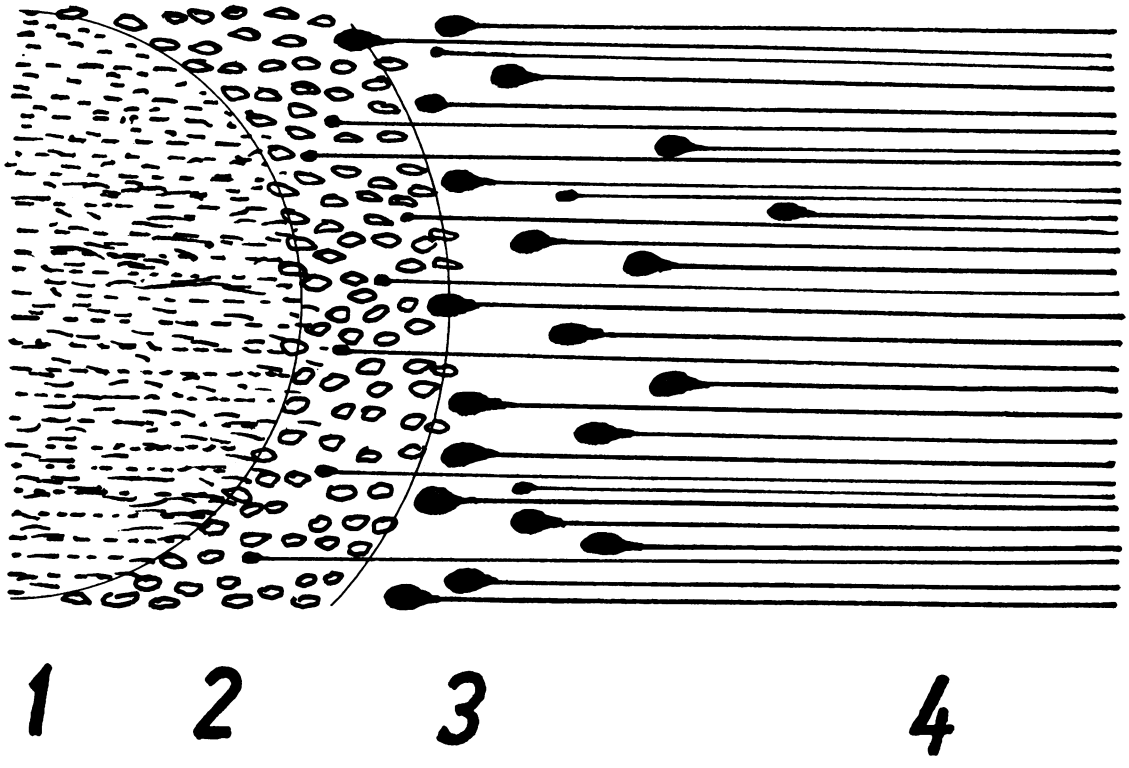


FIGURE 18

A drawing to summarize the observations demonstrated in Figures 3 to 11. It shows zone 1 with granular debris, zone 2 with pale-staining bodies and stumps of thin centrifugal nerves and, finally, zone 4 with the stumps of the thicker type of centrifugal nerves. The optic nerve should be imagined to be on the right side of the picture.

The larger, round, pale-staining globules next to the center of the burns in the second zone are believed to represent isolated axonal enlargements of the thicker type of nerve-fiber stump. Some retrograde degeneration must have occurred in these stumps after they formed their first terminal swellings and these remained as isolated bodies when the nerve stumps formed the second, more central, terminal enlargements seen in the sections. The process of the formation of such isolated bodies of nerve-fiber origin in the retina has been described elsewhere in detail[14] and Figure 19 explains its basic mechanism.

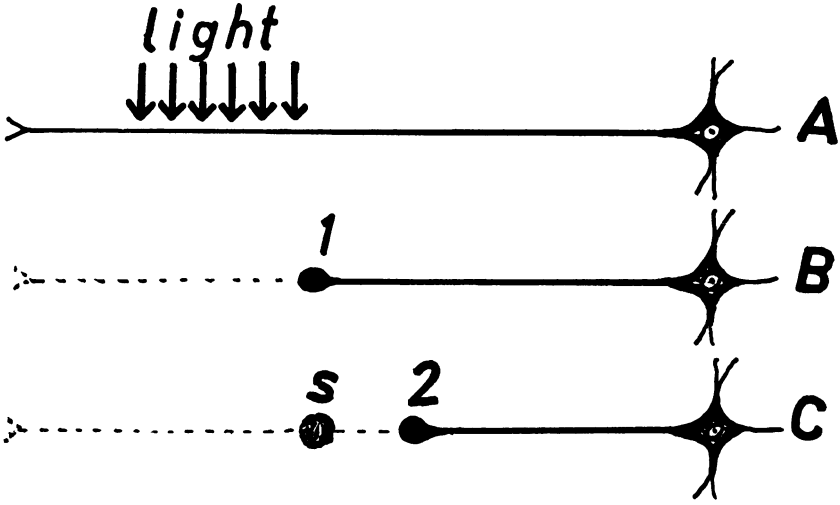


FIGURE 19

Drawing to explain our view of the nature of the larger pale-staining bodies found in zone 2 of the nerve-fiber layer centrally and next to the photocoagulation burns. The light beam causes interruption of neurites (A). A terminal axonal enlargement forms (B). With time, retrograde degeneration involves the end of the stump (C). A new axonal enlargement is formed by the living nerve stump and the first enlargement is left for some time resembling a pale-staining shadow (S).

Neurites that cross the direction of the main course of all retinal nerve fibers have had our special interest for many years. It seems that they are centrifugal in nature.[9,10] Terminal axonal enlargements on stumps of some of these crossing fibers next to photocoagulation burns in the present case (Figure 11) support this view.

Capillaries in the ganglion-cell layer of the retina either survived the photocoagulation or had regenerated. The ganglion cells them-

selves showed irreversible destruction in zones one and two. Again the proximity of the large neoplasm can be used to explain the fact that the necrotic cells were not as yet removed fourteen days after their destruction. The fact that the pigment epithelium and choriocapillaris are destroyed or severely damaged in the area of the burns is in line with the common understanding of the effects of photocoagulation. Hyperemia in the choriocapillaris and extensive chronic inflammatory reaction in the choroid around the burns are evidence of some remaining ocular reactions in spite of the adjacent neoplasm. The fact that the blood vessels and the primitive neuronal cells of the choroid[20–23] are less susceptible to photocoagulation injury than the choroidal melanocytes may be explained simply by the fact that the melanocytes are filled with pigment and, thus, absorb more light. This fact is very interesting, however, especially since the functions of the primitive choroidal neurons are as yet totally obscure.[20–23] These primitive ganglion cells of the choroid are greatly increased in number in the present case—as in many other cases of uveal melanomas.[22]

We certainly hope that this paper will stimulate more interest, not only in the nature and origin of the centrifugal nerves of the human retina, but also in the effects of photocoagulation in the human eye.

SUMMARY

The reactions of interrupted centrifugal neurites in the nerve-fiber layer of the human retina two weeks after photocoagulation were studied histologically with a silver stain. Two different types of surviving nerve stumps with terminal axonal enlargements found on the central aspects of the photocoagulation burns represented the two main types of centrifugal neurites of the human retina. A third type of centrifugal nerve which was observed to run at an angle to the main direction of the retinal nerve fibers was more rarely seen. Our earlier estimate that about one-tenth of all neurites in the human nerve-fiber layer originate in the brain is confirmed.

REFERENCES

1. Wolter, J. R., and L. Liss, Zentrifugale (antidrome) Nervenfasern im menschlichen Sehnerven, Graefes Arch. Ophth., 158:1, 1956.
2. Wolter, J. R., Ueber Endigungen zentrifugaler Nervenfasern an den Blutgefässen der menschlichen Netzhaut, Graefes Arch. Ophth., 158:524, 1957.
3. Liss, L., and J. R. Wolter, Zur Innervation der Blutgefässe des menschlichen Sehnerven, Klin. Monatsbl. Augenh., 129:793, 1956.
4. Wolter, J. R., Ein weiterer Beweis für die Existenz zentrifugaler Nervenfasern in der menschlichen Netzhaut, Graefes Arch. Ophth., 158:235, 1956.

5. Wolter, J. R., Regenerative potentialities of the centrifugal fibers of the human optic nerve, Arch. Ophth., 64:697, 1960.
6. Pfister, R. R., and J. R. Wolter, Centrifugal fibers of the human optic nerve, Neurology, 13:38, 1963.
7. Wolter, J. R., Diabetic retinopathy, Am. J. Ophth., 51:1124, 1961.
8. Wolter, J. R., and R. R. Knoblich, Pathway of centrifugal fibres in the human optic nerve, chiasm, and tract, Brit. J. Ophth., 49:246, 1965.
9. Wolter, J. R., The reactions of the centrifugal nerves of the human eye: after photocoagulation, occlusion of the central retinal artery and bilateral enucleation, In, Eye Structure, II, Symposium, Eighth Internat. Congress of Anatomy, Wiesbaden, Germany, 1965, p. 85.
10. Wolter, J. R., The centrifugal nerves in the human optic tract, chiasm, optic nerve, and retina, Tr. Am. Ophth. Soc., 63:678, 1965.
11. Wolter, J. R., and L. T. Moorman, Early effects of photocoagulation on the nerve fiber layer of the human retina, Arch. Ophth., 76:385, 1966.
12. Matsuyama, M., Existence of centrifugal nerve fiber in the retina, Jahresb. Kurashiki-Zentralhosp., Jg. 36:1, 1967.
13. 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.
14. Wolter, J. R., The cytoid body reaction of the human retina, Tr. Am. Ophth. Soc., 65:106, 1967.
15. Wolter, J. R., Axonal enlargements in the nerve-fiber layer of the human retina, Am. J. Ophth., 65:1, 1968.
16. Webster, H. de F., Transient, focal accumulation of axonal mitochondria during the early stages of Wallerian degeneration, J. Cell Biol., 12:361, 1962.
17. Kreutzberg, G., Enzymhistochemische Veränderungen in Axonen des Rückenmarks nach Durchschneidung der langen Bahnen, Deutsche Ztschr. Nervenh., 185:308, 1963.
18. Roessmann, U., and L. R. Friede, Early enzyme histochemical changes following transection of dorsal spinal funiculi, Exper. Neurol., 12:230, 1965.
19. Scharenberg, K., and W. Zeman, Zur Leistungsfähigkeit und zur Technik der Hortega'schen Silberkarbonatmethoden, Arch. Psychiat., 188:430, 1952.
20. Wolter, J. R., Melanoblasts of the normal human choroid, Arch. Ophth., 53:211, 1955.
21. Wolter, J. R., J. M. Bryson, and T. P. McKee, Ganglioneuromelanocytosis of the choroid, Arch. Ophth., 74:353, 1965.
22. Wolter, J. R., and J. M. Bryson, Overabundance of uveal ganglion cells: in eyes with choroidal melanoma, Am. J. Ophth., 62:1034, 1966.
23. Wolter, J. R., N. T. O'Keefe, and J. M. Bryson, Hyperplasia of uveal ganglion cells, J. Pediat. Ophth., 3:24, 1966.
24. Wolter, J. R., Centrifugal nerves at the optic disk (ten days after complete occlusion of the retinal artery), Excerpta Medica International Congress Series No. 146, 1966, p. 117.

DISCUSSION

DR. DAVID G. COGAN. Dr. Wolter has presented us with a fine example of retinal pathology investigated by silver techniques. Argyrologists, and Dr. Wolter is clearly ophthalmology's leading exponent of the group, know the advantages and limitations of these procedures better than those of us committed to conventional histopathologic techniques who must take what they

say on faith. For my part I think Dr. Wolter has shown beautifully and convincingly reactions of nerve fibers on both in the center and on the periphery of the photocoagulated area and I would have to agree with him that this implies centrifugal fibers coursing in the nerve-fiber layer of the retina. This is in keeping with what he and others have found previously in the optic nerve and retina.

This paper is of interest from several points of view. Surgeons will be interested to find that photocoagulation as done by Drs. Wolter and Lund causes destruction of the entire thickness of the retina and not, as has been claimed by others, of just the outer retinal layers. Anatomists and pathologists will be interested in the types of nerve-fiber reaction and will particularly want to know what is the destination and function of these centrifugal fibers. And those of us who have had tangential contact with electron microscopy will be curious to know what is the ultrastructural basis for these terminal enlargements.

I assume that cytoid bodies comprise focal nerve-fiber reactions similar to those induced by Dr. Wolter. Accordingly, I would like to show one of Dr. Kuwabara's electron micrographs of a cytoid body (from a patient with diabetic retinopathy). This shows beautifully the swelling of individual nerve fibers and mild increase in the number of mitochondria. I am not sure just what component or components of these ultrastructural abnormalities are staining by Dr. Wolter's technique, but the entire field depicted here would presumably be included in a single argyrophilic body.

I enjoyed reading Dr. Wolter's paper immensely. He is the one among us who has persistently and commendably kept a silver lining to ophthalmic histopathology.

Dr. Frederick C. Blodi. I also enjoyed Dr. Wolter's paper very much. His silver technique and gold technique impress us who use much cheaper metals.

I have two questions. One concerns the problem of ophthalmoscopic appearance of these lesions. Dr. Cogan alluded to this. It would seem to me that such a high concentration of Cajal's bodies in the retina should be ophthalmoscopically visible as something like the cottonwool patches. Dr. Wolter did not say what happened during the two weeks when the patient was blind. Maybe there was complete retinal detachment or the fundus was not visible. I think these Cajal's bodies should have been ophthalmoscopically visible.

My second question concerns the fact that the patient became blind. I did not hear the reason for this, but here again I would presume that, if you did light coagulation in the area opposite the melanoma, you not only interrupted the centrifugal but also a number of centripetal nerves, and therefore I would assume that you should have seen a number of these bodies attached to nerves running in the opposite direction. If you did see them I failed to recognize them in the pictures.

DR. ALBERT D. RUEDEMANN, JR. I thought Dr. Wolter's paper was extremely interesting. As a non-pathologist it has just occurred to me that this looks like a reverse amputation neuroma. I wonder if Dr. Wolter would comment on this and its possible relationship to a peripheral nerve type of amputation neuroma.

DR. J. REIMER WOLTER. First, I would like to thank Dr. Cogan. I agree with everything he has said, as I usually do.

I would like to say that not all centrifugal fibers go on into the optic tracts after they partially cross at the chiasm (Brit. J. Ophth., 49:246, 1965). Some of the fibers do, but others appear to come into the chiasm from the back. It seems to me that they come from the area of the pituitary stalk or hypothalamus.

Dr. Cogan's question as to what is stained by this silver method is difficult to answer. Part of the stain that we saw in the slides, where the stain was rather heavy, is an incrustation of cell membranes. This is due to the fact that the silver is deposited on the surface of these formations and makes them appear black. However, there are many other ways in which silver will stain many details of intracellular structures. The mechanism is not known to me.

In reply to Dr. Blodi's questions, I would like to state in the first place that, of course, the clinical part of this paper was done in Essen in Dr. Meyer-Schwickerath's clinic. I am not entirely sure what happened to the eye before it was removed. It is certain, however, that the area of the burns was not detached and that there was tremendous vitreous haze that made it difficult to find the burns in the enucleated and fixed eye after we received it in Ann Arbor.

Dr. Blodi also asked why photocoagulation burns look white. We don't really know what it is that makes the cottonwool spot or a photocoagulation burn look white. This could be due to the edema that develops between the nerve fibers, or it could be due to the accumulation of axonal enlargements. I would not be surprised if it were found that both the swollen nerve fibers and the intercullular edema contribute to the whiteness that we observe clinically in and next to the area of photocoagulation burns.

Dr. Blodi, we did see the centripetal nerve-fiber stumps with their terminal swellings pointing toward the disk on the other aspect of the burns. However, this fact was well demonstrated before (Arch. Ophth., 76:385, 1966) and because of limitation of time I didn't discuss and demonstrate this here again.

To answer Dr. Ruedemann, may I say that his question shows that he has entirely understood the basic nature of the nerve-fiber reaction discussed in this study. Amputation neuromas are, in principle, the same kind of reaction that we are talking about here. Peripheral nerves are involved there, however, whereas the retina is part of the central nervous system. In amputation neuroma, furthermore, these terminal swellings or Cajal's bodies

later undergo extensive regeneration. Such extensive regeneration has not as yet been seen in centrifugal retinal neurites. However, some regeneration has been demonstrated in children.

With the permission of the Chairman I would like to make one statement that, I believe, is of interest to all of us. I have recently had occasion to examine an eye that Dr. Lund treated with laser burns of a dosage commonly used for treatment of so-called leaks in Bruch's membrane. An AO Laser was used. My three slides show that there was interruption of neurites in the nerve-fiber layer seen in the human eye three days after application in the area of the laser burns. It has been stated on grounds of clinical observation as well as routine histologic study that laser burns can be applied in the human retina without causing interruption of axons in the nerve-fiber layer. This case shows that irreversible damage to these axons certainly may occur.

May I finally thank all discussers—and especially Dr. Cogan—for their kindness and interest in our study.