EXPERIMENTAL CENTRAL RETINAL VEIN OCCLUSION: A COMPARISON OF INTRAOCULAR AND EXTRAOCULAR OCCLUSION*

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IN REVIEWING FLUORESCEIN ANGIOGRAPHY of cases of central retinal vein occlusion at the Bascom Palmer Eye Institute, we have observed that venous filling always occurs even though it usually is delayed. Also, arterial filling is not prolonged. These findings do not correlate well with those observers[1-3] who postulate that arterial insufficiency plays the predominant role in this disease. In an excellent report,[4] Hayreh summarized the controversy of the last seventy-five years concerning the arterial and venous components of this disease. In addition, he produced retinal hemorrhages in the rhesus monkey only when he diathermized both the central retinal artery and vein external to the optic nerve, and not when he diathermized the central retinal vein alone. The conflict in these observations with our interpretation of fluorescein angiography stimulated us to compare venous occlusion in the region of the optic disk to venous occlusion outside the optic nerve in the owl monkey. This study reports fundus appearance, fluorescein angiography, and pathology in these two groups of animals.

METHOD AND MATERIALS

The central retinal vein was occluded in 27 owl monkey (*Aotus trivirgatus*) eyes. In 17 eyes, neoprene was injected into the central retinal vein to occlude this vessel in the optic nerve and disk (Group I). In 10 eyes, the central vein was tied and cut as the vessel emerged

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from the optic nerve (Group II). The monkeys were anesthetized by intraperitoneal injection of 10 mg of pentobarbital sodium. The operation was performed *via* the Krönlein approach. The lateral rectus, inferior rectus, and inferior oblique muscles were cut. The central retinal vein and artery were exposed on the inferior side of the optic nerve (Figure 1). An 8–0 silk suture was placed around the vein. The Zeiss operating microscope provided the magnification needed in this technique.

In Group I eyes, an incomplete incision into the wall of the central retinal vein was made central to the suture. A fine cannula was prepared by stretching a piece of PE50 polyethylene tube, heated above a candle flame. Pure neoprene 842-A was injected into the cannula and the larger end was sealed with a hot forceps. The cannula was then inserted into the central retinal vein and the suture was tied around it. Neoprene was introduced into the central retinal vein by gently squeezing the end of the cannula with a hemostat until neoprene was first seen in the veins of the disk by direct ophthalmoscopic visualization. The cannula was removed and the suture was tied. Technically, great care was necessary to reach this objective whereby only the central vein and its immediate branches contained neoprene. Other-

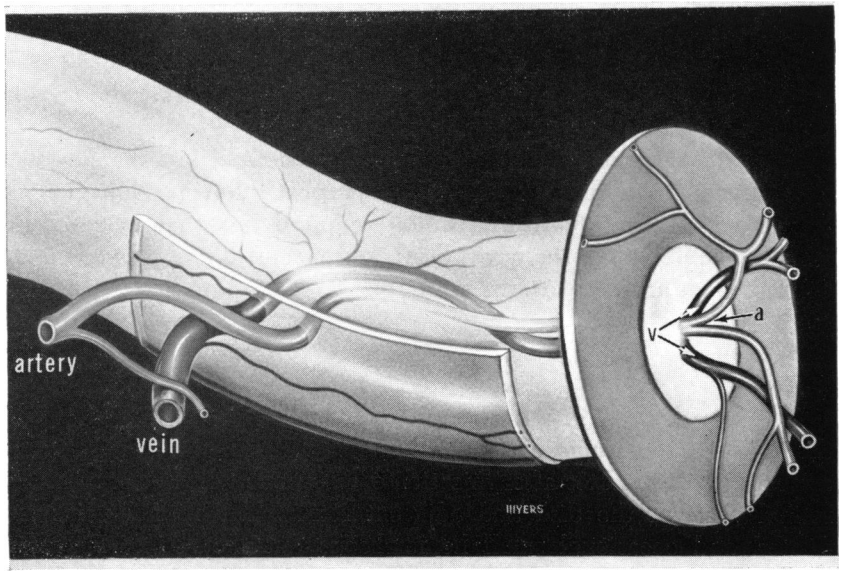

FIGURE 1

Diagram of central retinal artery and vein of owl monkey eye. Site of ligation was at the entrance of vessel into optic nerve.

wise, too much neoprene entered the vein. The neoprene latex solidified after injection.

In Group II eyes, the silk suture about the vein was tied and the vein was cut central to the suture along with superficial branches of the central retinal vein at its entrance into the optic nerve. In all animals, the surgical wound was closed.

Fundus photographs were taken in all eyes and fluorescein angiography was performed in 6 eyes of Group I and in 8 eyes of Group II by injecting 0.3 cc of 5 per cent fluorescein into a surgically exposed femoral vein of the anesthetized animal. The fluorescein technique at the Bascom Palmer Eye Institute has been previously described.[5] These photographs were taken from twenty minutes to four weeks following the procedure.

The eyes were enucleated under general anesthesia at intervals from two hours to three months after operation. Before enucleation in 9 eyes (6 from Group I and 3 from Group II), 20 cc of India ink was injected at 130 mm Hg pressure into the left ventricle after the descending aorta was clamped.

Twenty-five eyes (17 from Group I and 8 from Group II) were fixed either in 10 per cent formalin or Kolmer's solution (1 eye). The eyes were sectioned and the central part was embedded in paraffin. Cross sections were prepared and stained with hematoxylin and eosin, PAS, and Verhoeff's elastic stain. A segment of the retina in 20 eyes (14 from Group I and 6 from Group II) was prepared by the trypsin digestion technique of Kuwabara and Cogan.[6]

The rate of retinal circulation time in the normal owl monkey was determined from fluorescein cinematography following injection of dye into the atrium.[7] Arterial filling required less than one second after dye appeared in the nerve head, and venous filling was complete three seconds after the arterial stage.

RESULTS

In Group I eyes, in which neoprene occluded the venous system, the sequence of change was consistent. Figure 2 illustrates the fundus appearance 20 minutes after injection of neoprene which is seen in the retinal veins of the disk and adjacent retina. The retinal veins are dilated and occasional small hemorrhages dot the retina. Figure 3 shows the same eye one day later. The venous system is engorged and many hemorrhages extend along the veins. Retinal edema obscures the underlying choroidal pattern. Fluorescein angiography in this eye

one day after operation demonstrates dye in the artery just at the nerve head (Figure 4). At two minutes, arterial filling occurs only adjacent to the disk and the veins contain no dye (Figure 5). The dye has diffused outside the arterioles in the posterior pole. Five minutes after injection, no dye is visible in the veins and intravitreous fluorescein obscures further angiography.

Figures 6 through 11 illustrate a similar change in which the initial insult is more severe. At two hours (Figure 6), retinal edema and hemorrhages, dilated veins, and localized detachment inferior to the disk portray a fundus picture of severe damage. Three days later (Figure 9), the damage has progressed to a more severe degree. Extension of the hemorrhage into the vitreous obscures some of the fundus detail. Fluorescein study in this eye two hours after operation reveals incomplete arteriolar filling eight seconds after the dye has reached the disk (Figure 7). Thirty-two seconds later, the veins are incompletely filled (Figure 8). The blurred margins of the vessels indicate extravasation of the dye. At three days, arterial flow is more stagnant. Figure 10 illustrates the first arterial phase. Figure 11 shows incomplete arteriolar filling seventy seconds later and is analogous to Figure 5. No dye enters the veins in ten minutes, after which intravitreous fluorescein obscures the retinal vessels.

In some eyes of Group I, vitreous hemorrhage completely obscures the fundus. In the later stages, the retinal and vitreous hemorrhages resorb to some degree, but an atrophic hemorrhagic retina with attenuated vessels characterizes the final appearance of the fundus of the eyes observed for two months and three months.

In one case in Group I, fluorescein study reveals an incomplete venous occlusion. One day after operation, the venous system is engorged and a few round hemorrhages are scattered about the fundus (Figure 12). After injection of fluorescein, the arterial tree fills rapidly (Figure 13), but complete venous filling requires twelve seconds (Figure 14) after arterial filling. Eight minutes later (Figure 15), considerable fluorescein has leaked from the vessels of and adjacent to the disk.

An entirely different sequence of events occurred in Group II in which the central retinal vein was ligated and cut outside the optic nerve. Two hours after venous ligation (Figure 16), the retinal veins are dilated and one small intraretinal hemorrhage is present adjacent to the inferior nasal vein. Fluorescein study two hours after operation reveals unimpaired arterial filling (Figure 17). Venous filling requires eight seconds (Figure 18) to complete. At twenty minutes (Figure

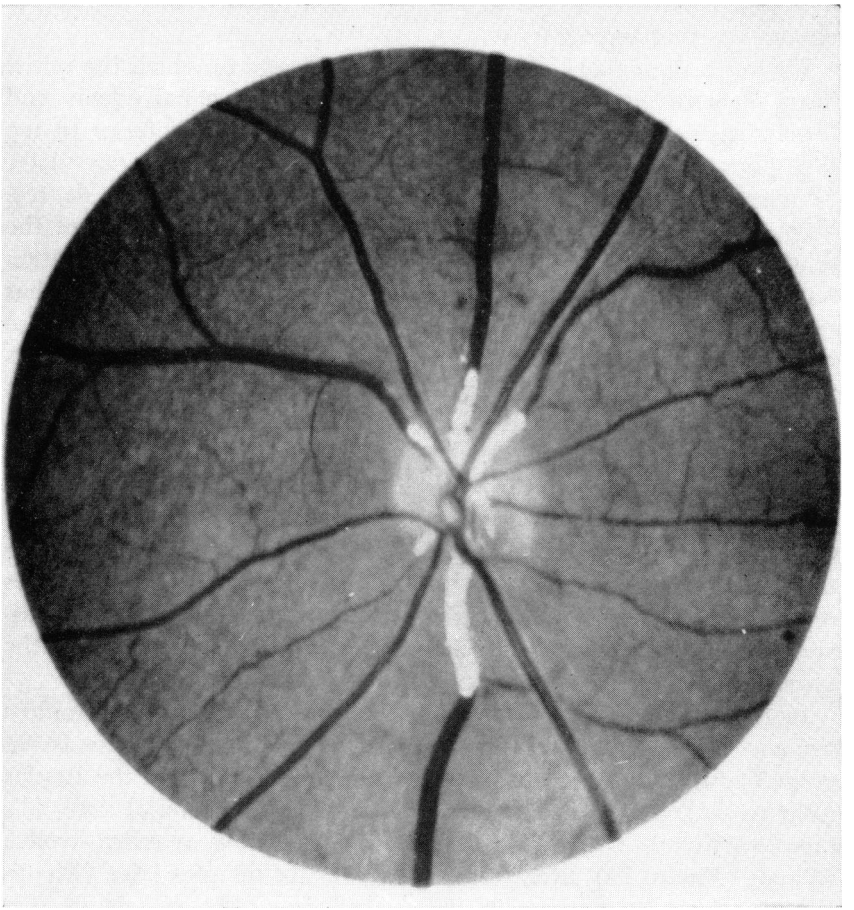

FIGURE 2

(Monkey 26 L) Fundus appearance twenty minutes after injection of neoprene into central retinal vein. Neoprene is white opaque material in veins.

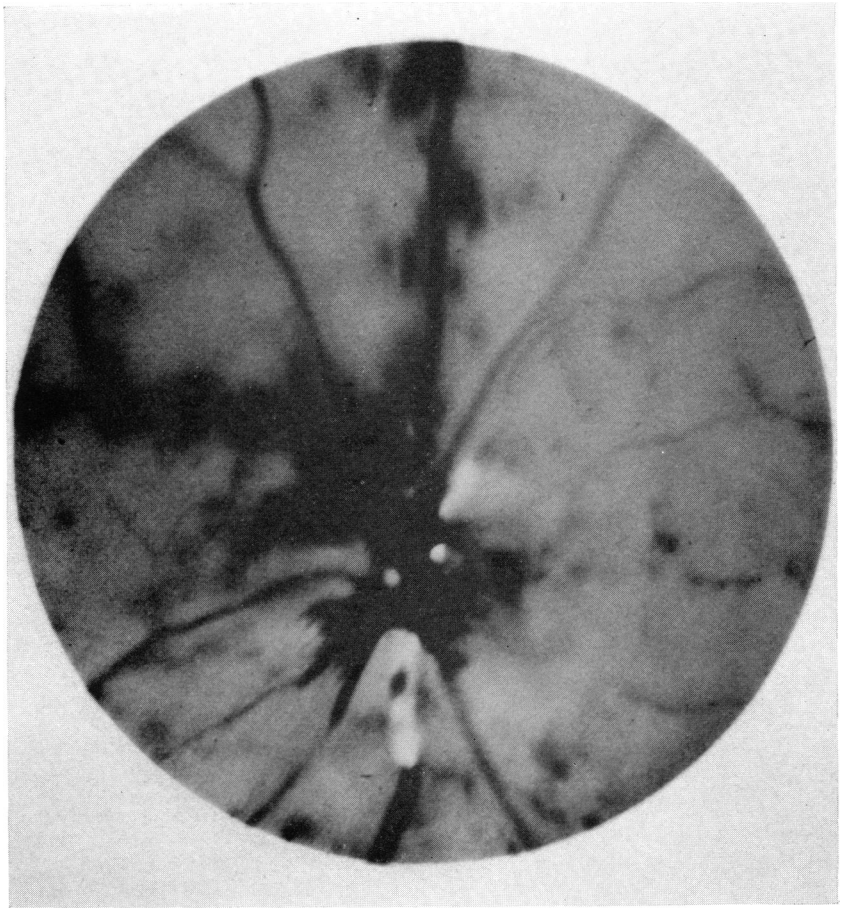

FIGURE 3

(Monkey 26 L) Same eye as Figure 2 one day later with venous distention and extensive retinal hemorrhages along veins.

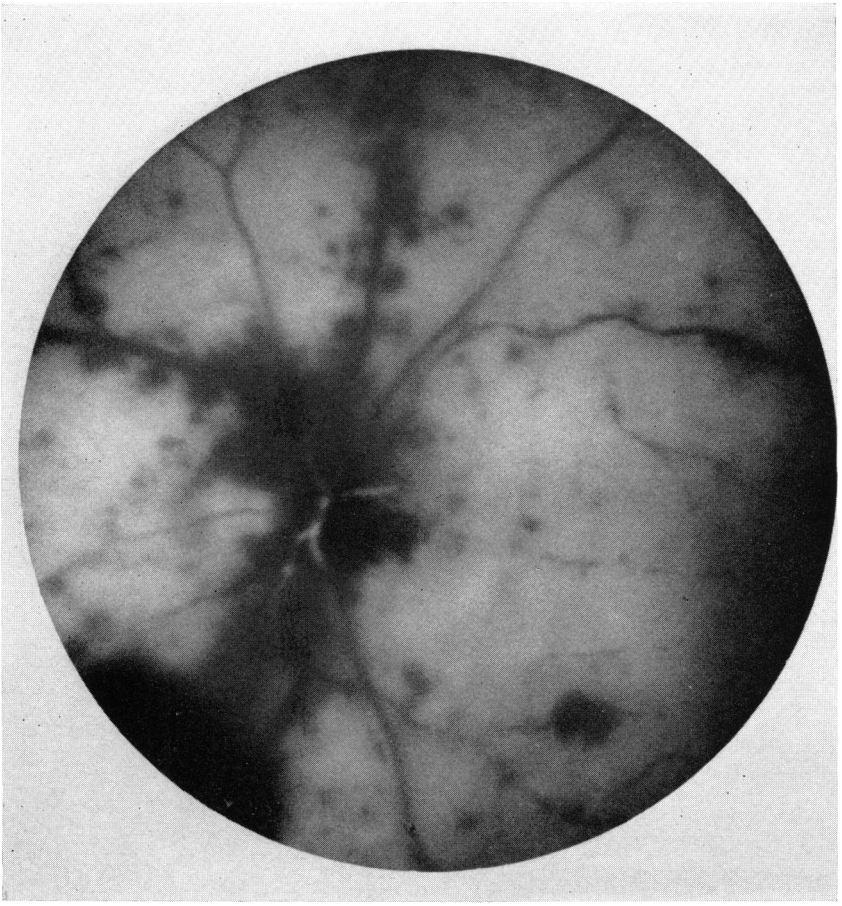

FIGURE 4

(Monkey 26 L) One day after neoprene injection. First appearance of dye in disk.

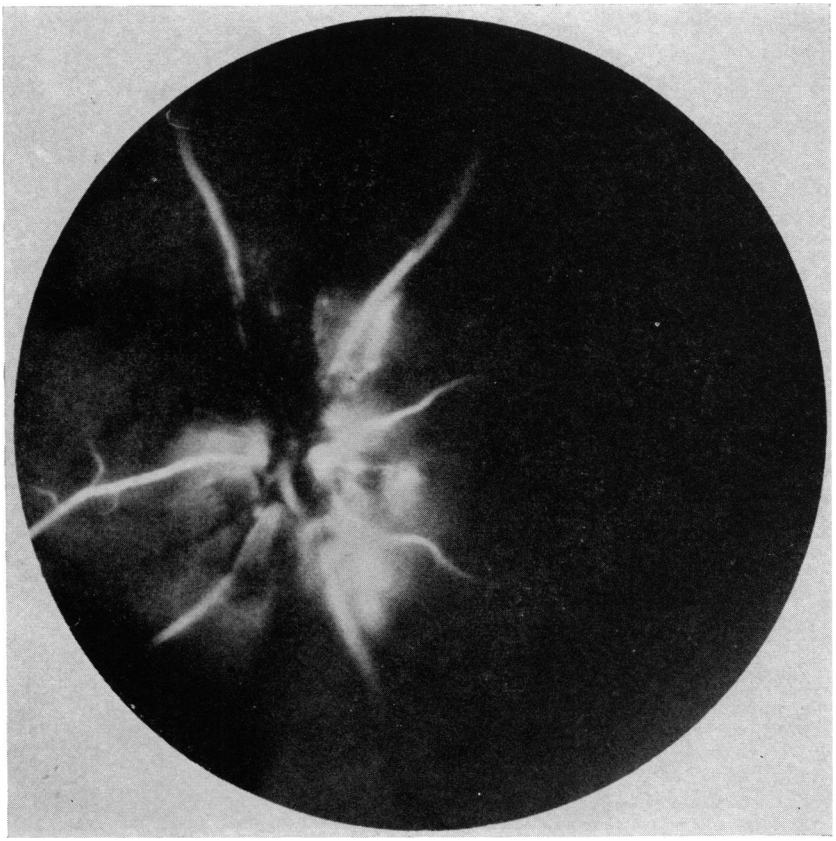

FIGURE 5

(Monkey 26 L) Two minutes after Figure 3. Arteries are incompletely filled and no dye is visible in veins. A considerable amount of dye is extravascular.

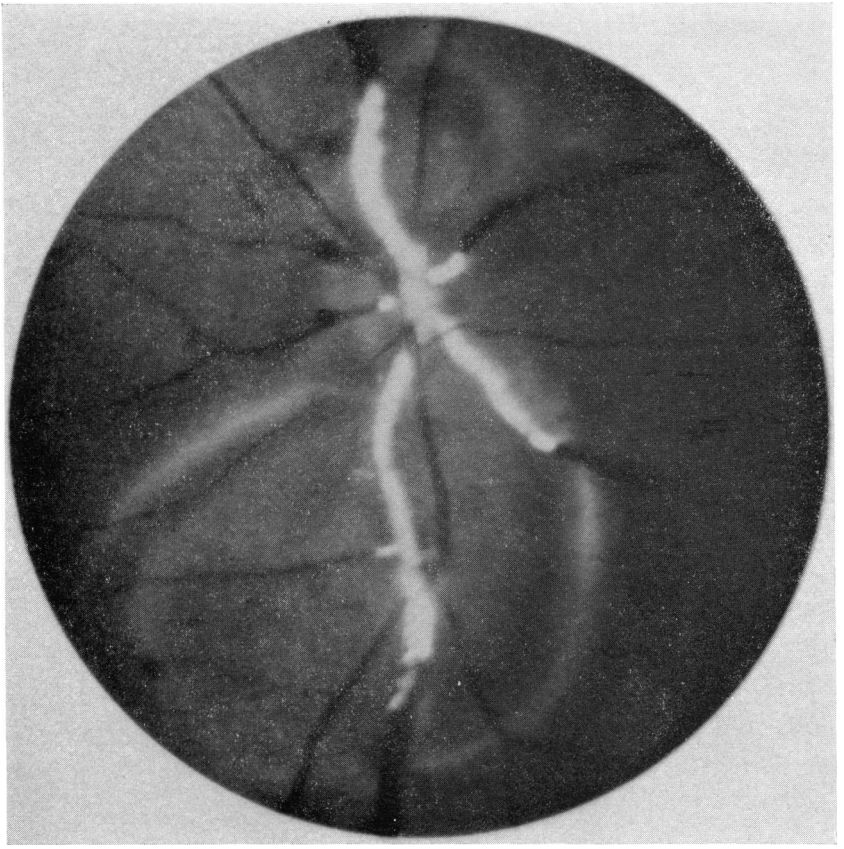

FIGURE 6

(Monkey 23 R) Two hours after injection of neoprene into central retinal vein. A localized retinal detachment presents inferior to the disk.

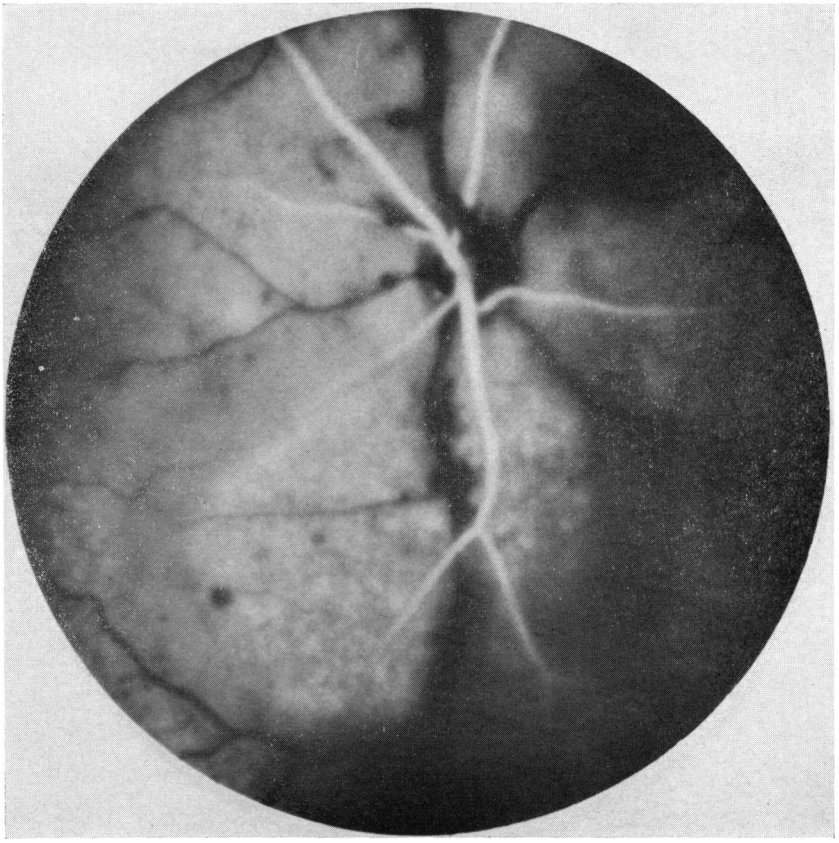

FIGURE 7

(Monkey 23 R) Fluorescein angiogram two hours after injection of neoprene into central retinal vein. Eight seconds after dye appeared at disk, retinal arteries are still incompletely filled.

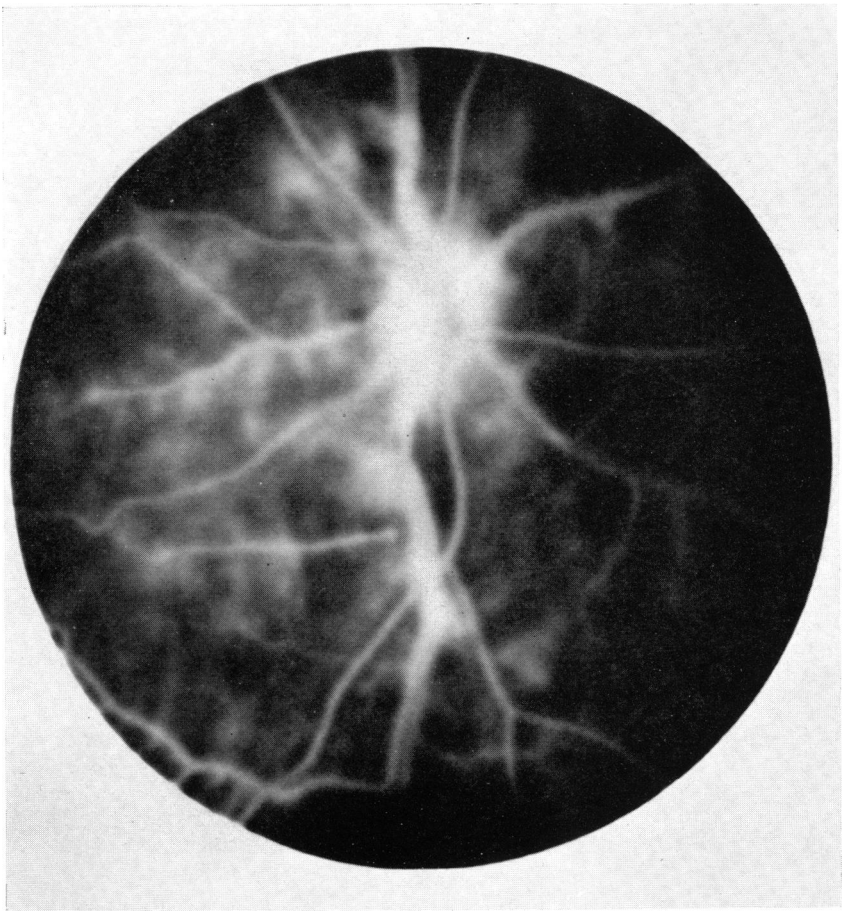

FIGURE 8

(Monkey 23 R) Thirty-two seconds later, veins are only partially filled. Blurred vessels and splotchy areas indicate leakage of dye from vessels.

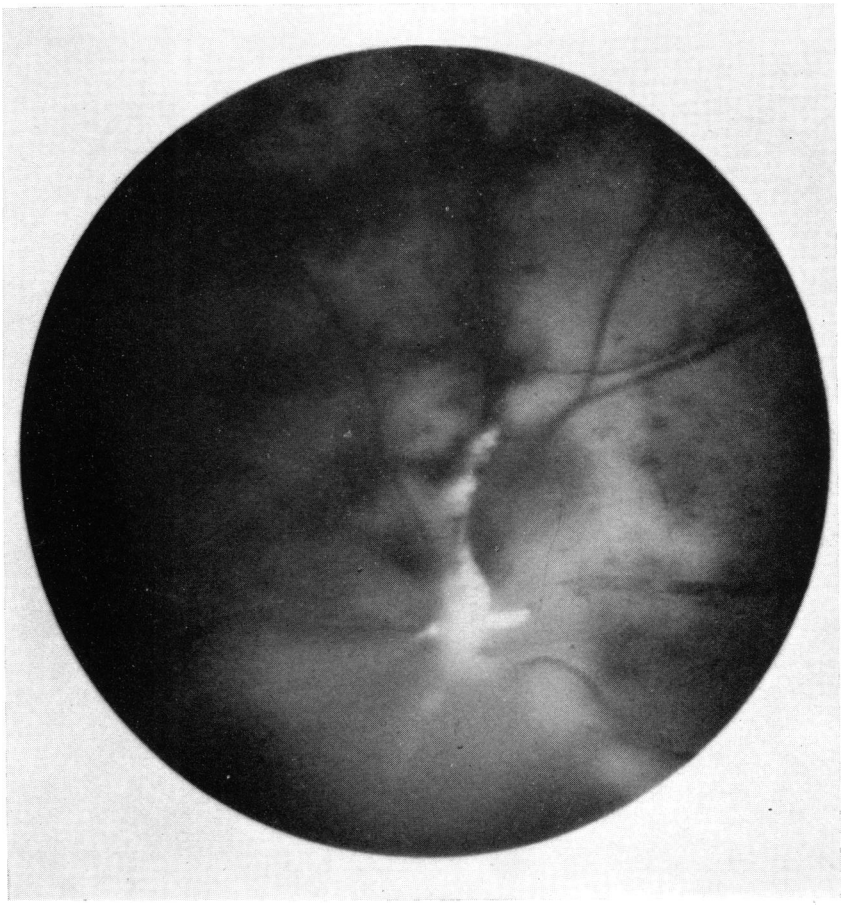

FIGURE 9
(Monkey 23 R) Same eye as Figure 6 three days later.

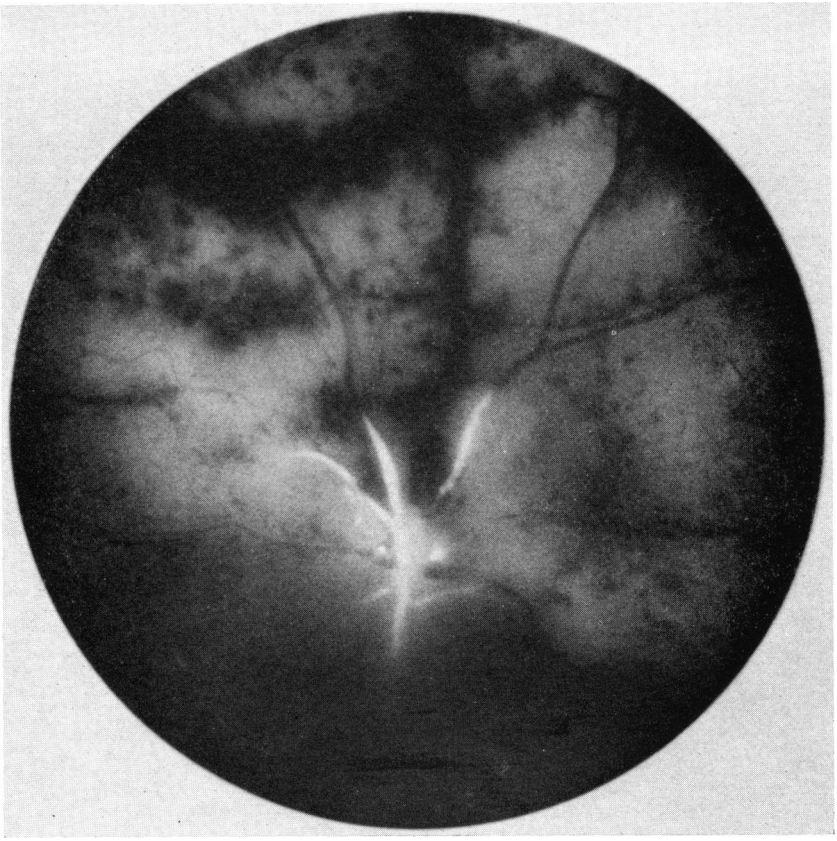

FIGURE 10

(Monkey 23 R) Three days after neoprene injection. Beginning of arterial phase.

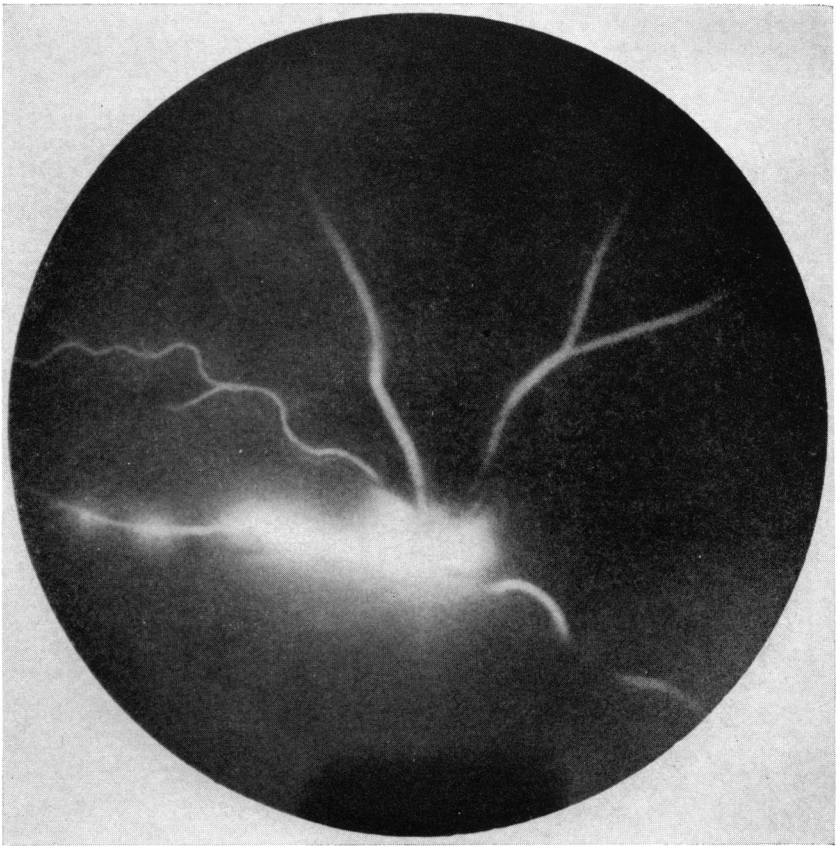

FIGURE 11

(Monkey 23 R) Seventy seconds after Figure 10. Incomplete arteriolar filling and no venous filling.

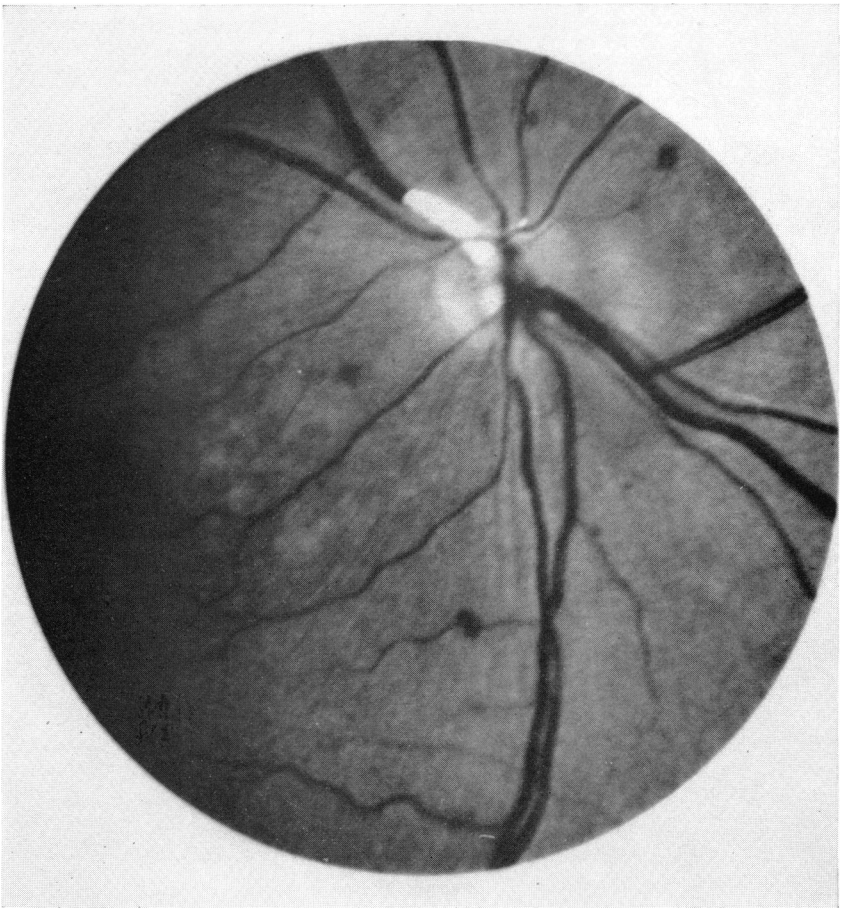

FIGURE 12

(Monkey 20 L) One day after injection of neoprene into central retinal vein. Veins are dilated and a few round retinal hemorrhages are present.

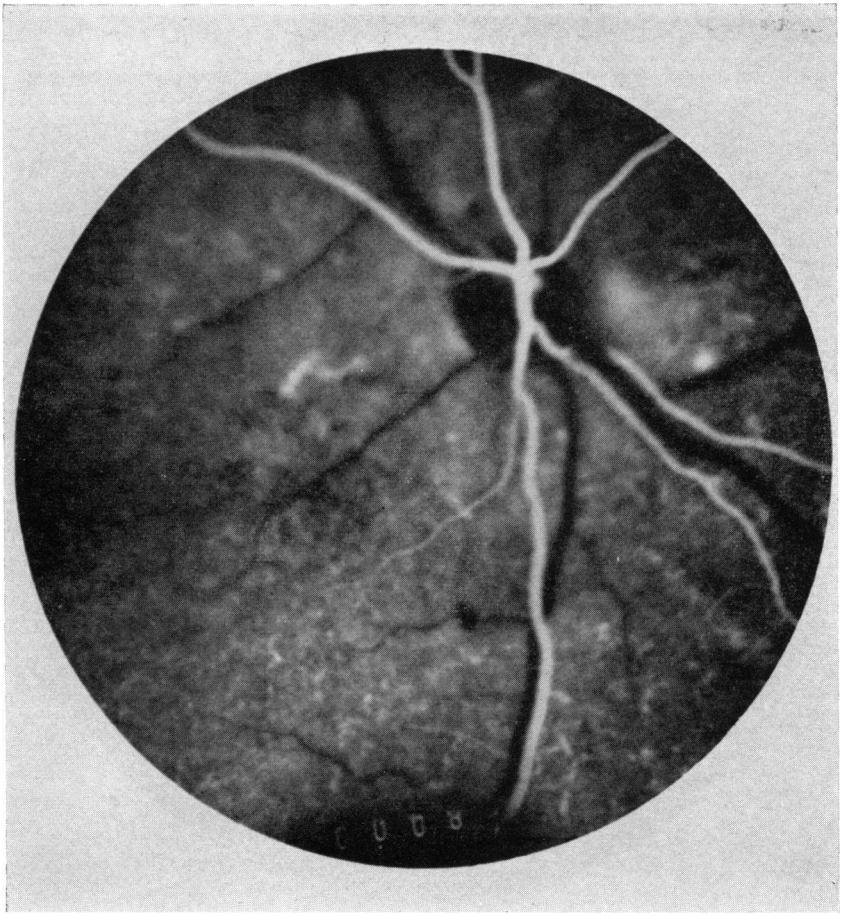

FIGURE 13

(Monkey 20 L) One day after neoprene injection. Arterial phase 8.5 seconds after injection.

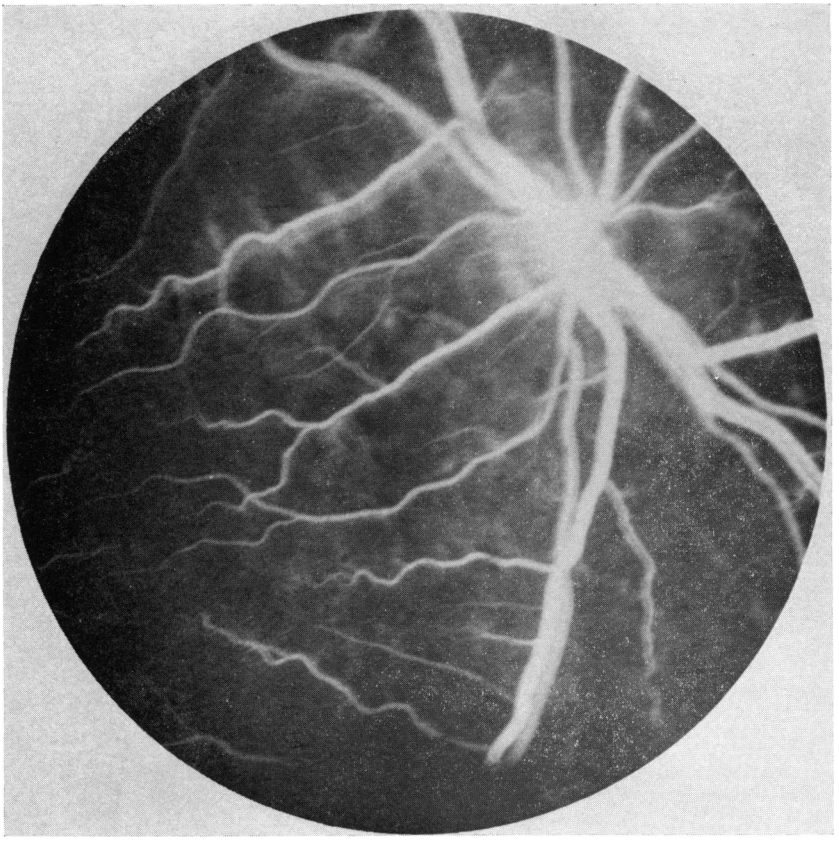

FIGURE 14
(Monkey 20 L) Complete venous filling twelve seconds after Figure 13.

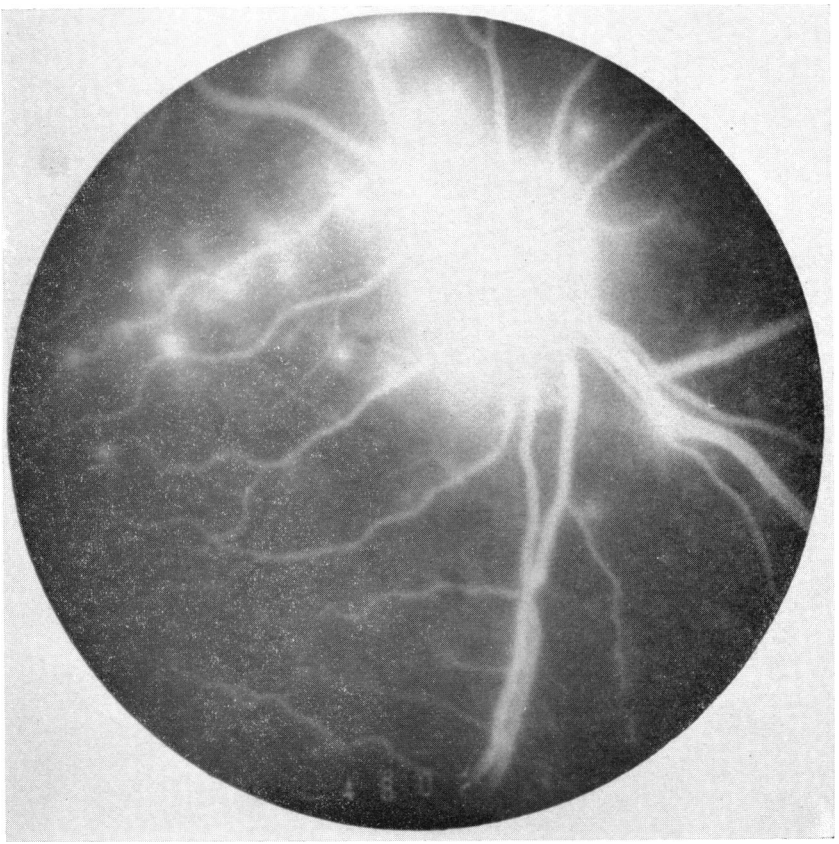

FIGURE 15

(Monkey 20 L) Eight minutes after injection of fluorescein. Considerable extravascular dye about disk and veins.

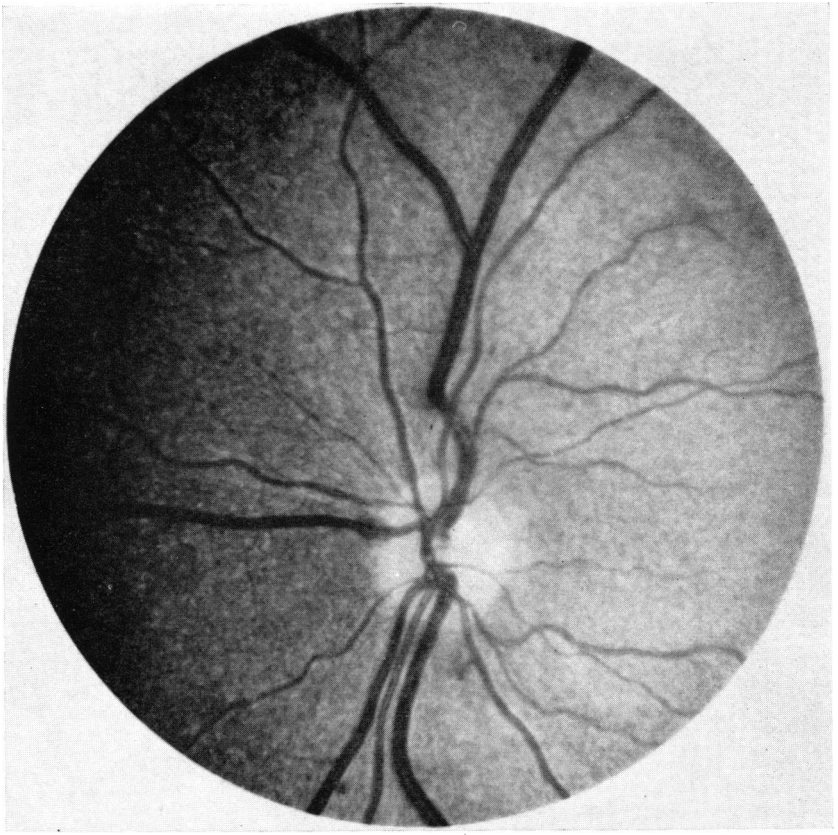

FIGURE 16

(Monkey 31 R) Two hours after ligation of central retinal vein. Retinal veins are dilated.

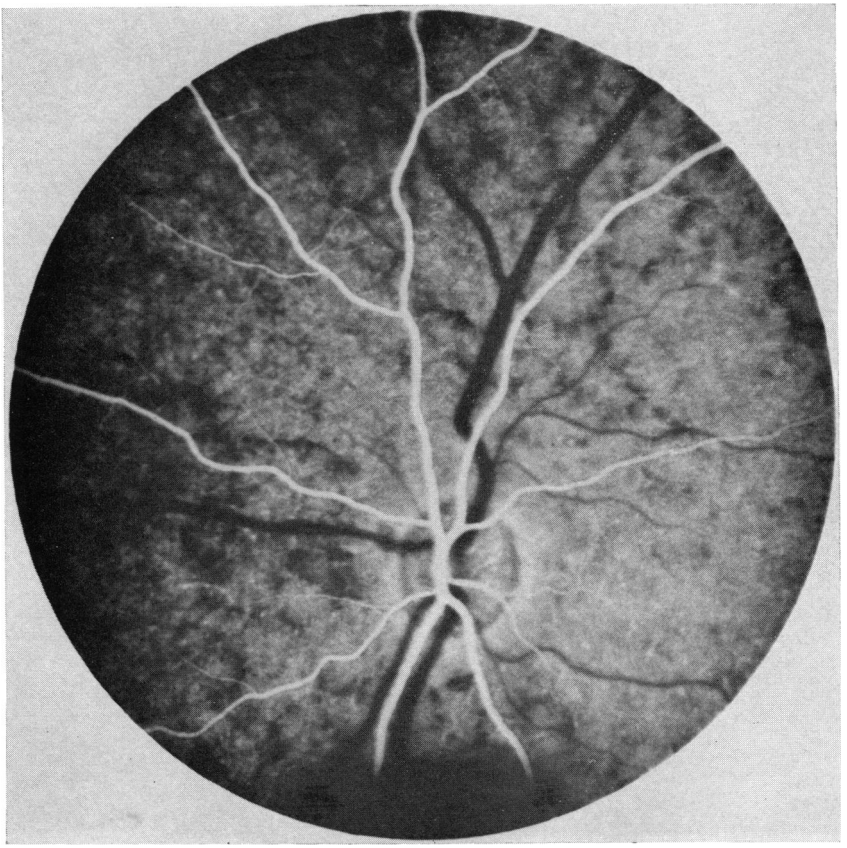

FIGURE 17
(Monkey 31 R) Two hours after ligation of central retinal vein. Arterial phase.

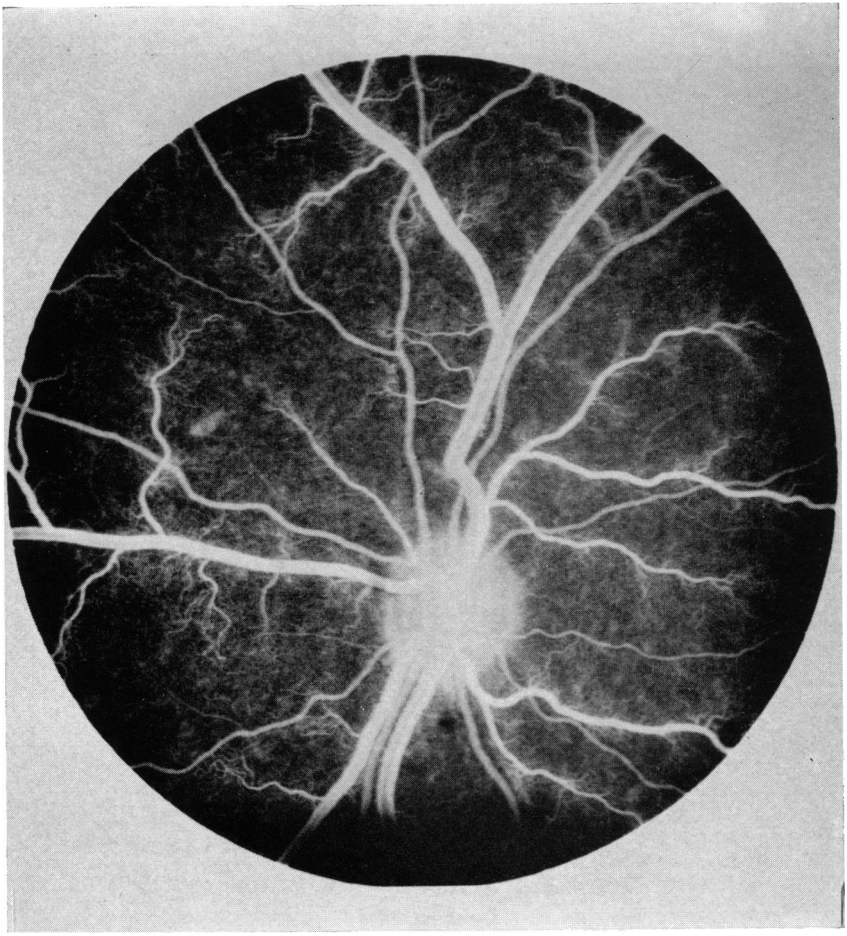

FIGURE 18

(Monkey 31 R) Venous filling not quite complete eight seconds after Figure 17.

19), the dye remains primarily intravascular, although there may be slight seepage at the disk. Another eye in Group II (Figure 20) has venous distention and a small hemorrhage of the disk four days after operation. Fluorescein study reveals rapid arterial filling (Figure 21) and venous filling four seconds later (Figure 22). In the same eye, eighteen days later (Figure 23), the fundus photograph demonstrates retinal veins of normal caliber and pallor of the disk. In another eye four weeks after ligation of the central retinal vein, the retinal vessels appear normal. Arterial and venous filling studied by fluorescein angiography are unimpeded, as in the preceding case.

One eye in Group II did not fall into this pattern of change. Thirty minutes after operation, the veins are distended (Figure 24). Slight retinal edema temporal to the disk obscures the choroidal pattern when compared to the nasal side. A progression of retinal damage occurred and, at five days (Figure 25), retinal hemorrhages, exudates, edema, and a localized retinal detachment depict the fundus. Fluorescein angiography performed one hour postoperatively do not reveal any significant alteration of flow, but dye leaks readily from many vessels. At one day, complete venous filling requires nine seconds after dye appears in the arteries whose filling was slightly delayed. At three and five days postoperatively, the photographs missed the first arterial phase of the study so the sequence could not be timed. The striking feature of these photographs is the rapid and extensive leakage of dye from the vessels.

Pathologically, the two groups segregate just as distinctly. In Group I at six hours, light microscopy does not reveal significant change. In Figure 26, retinal architecture is well preserved. The distended central retinal vein in the optic nerve flanks the artery which contains blood (Figure 27). No reaction occurs about the vessels. The vein is empty as processing removes the neoprene occluding its lumen. In the trypsin digestion mount pattern (Figure 28), the endothelial cells do not stain robustly. By one day, the tenor of irreversible damage predominates throughout the microscopic examination. Retinal hemorrhages extending from the internal limiting membrane to the external limiting membrane distort the retinal architecture (Figure 29). Hemorrhage extends into the optic nerve through the incompetent wall of the central retinal vein (Figure 30). Myriads of retinal hemorrhages extend primarily along the venous tree in the flat retinal preparation (Figure 31). Endothelial cells degenerate and stain poorly whereas mural cells retain their identity better (Figure 31). On the third day, there is further distortion of the retina by hemorrhage and necrosis

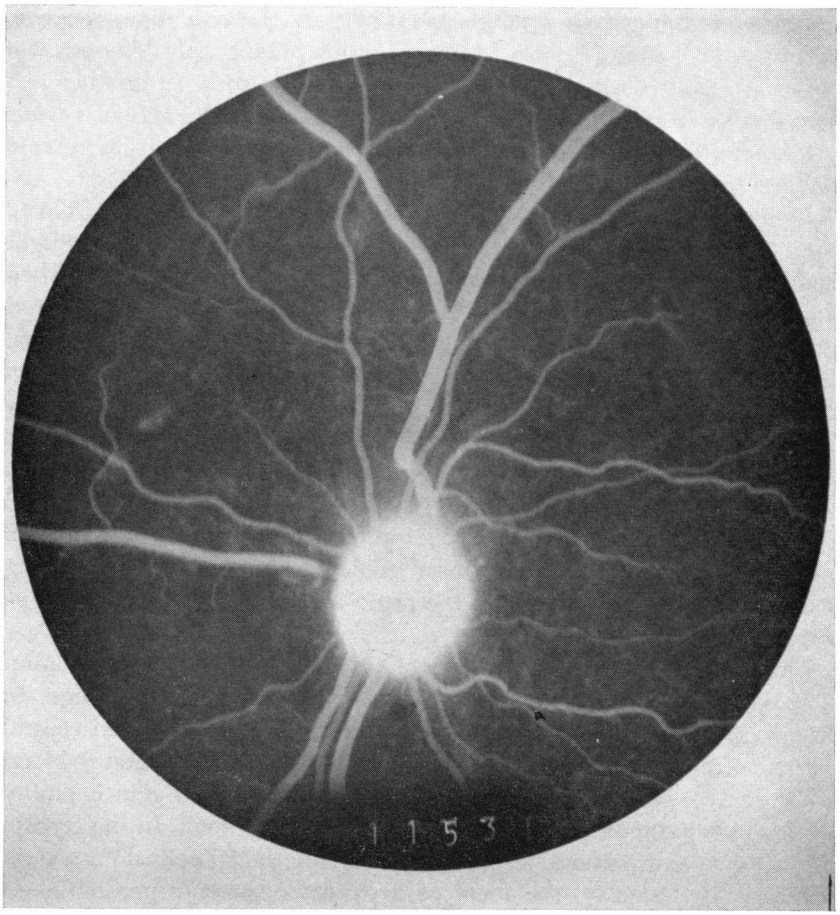

FIGURE 19
(Monkey 31 R) Twenty minutes after injection of fluorescein. Minimal leakage of dye.

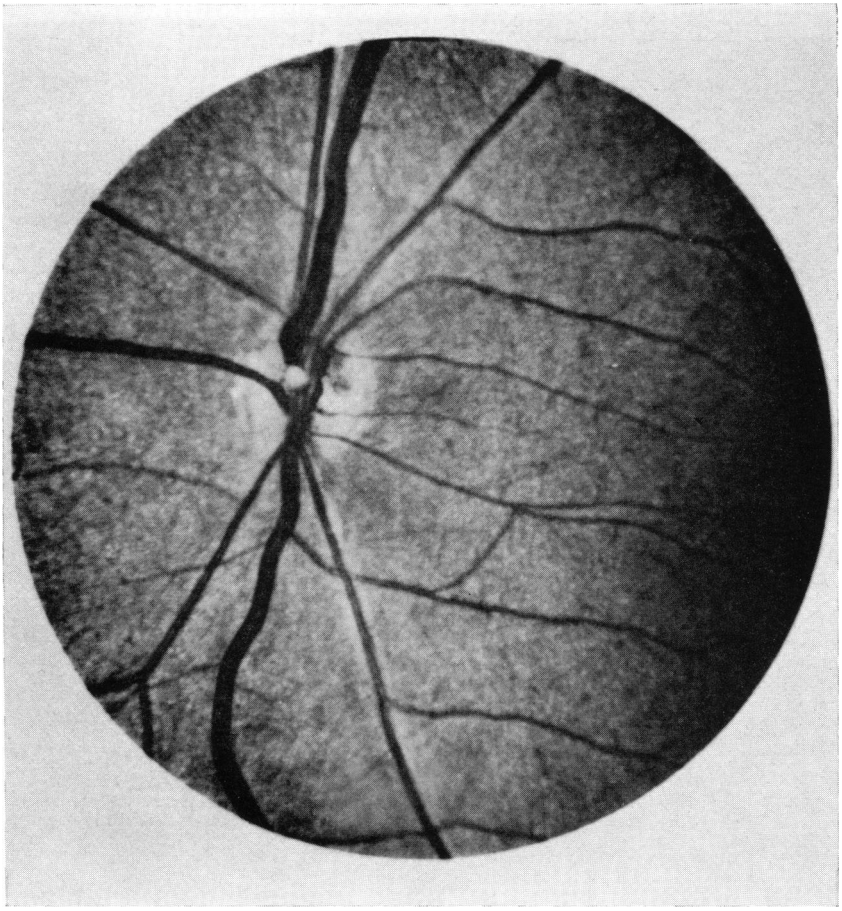

FIGURE 20

(Monkey 4 R) Four days after ligation of central retinal vein. Veins are dilated.

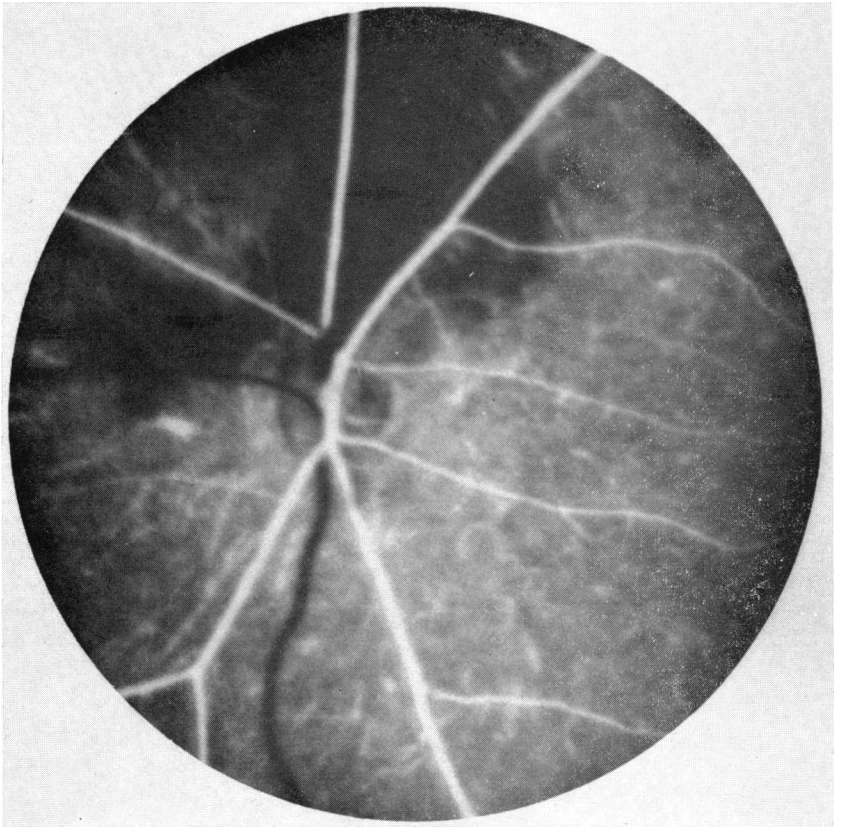

FIGURE 21

(Monkey 4 R) Four days after ligation of central retinal vein. Rapid arteriolar filling.

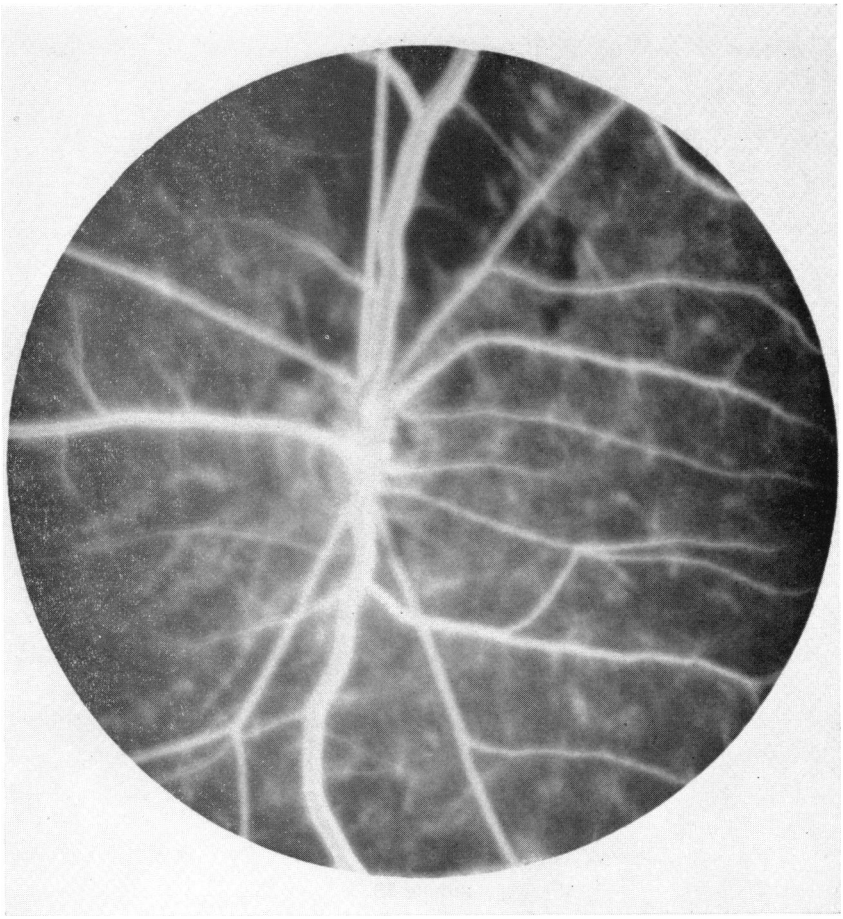

FIGURE 22
(Monkey 4 R) Four seconds after Figure 21. Veins are nearly full.

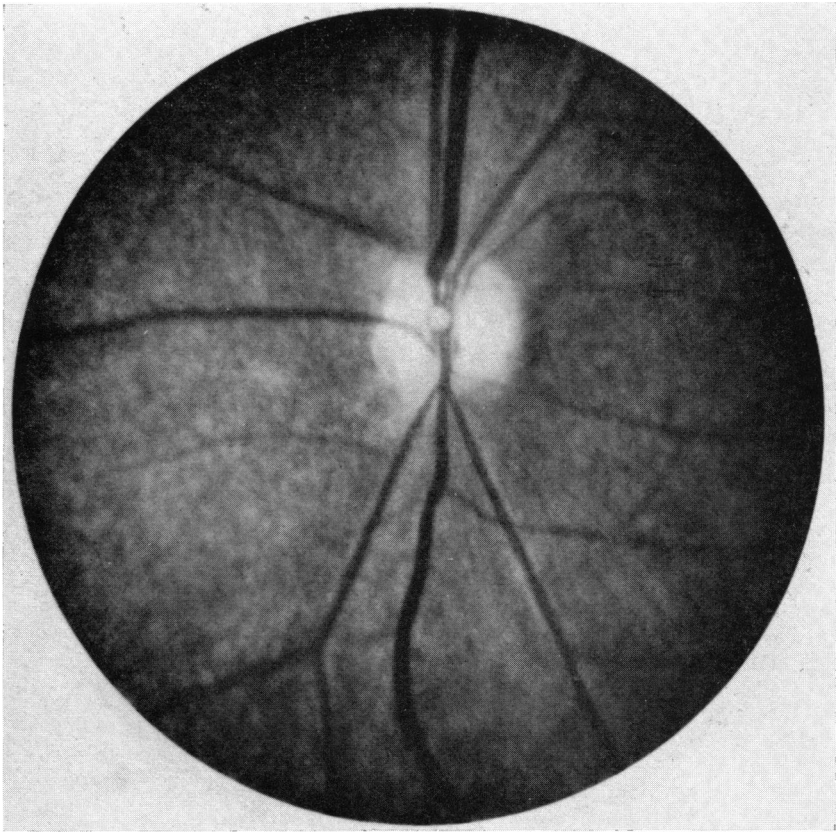

FIGURE 23

(Monkey 4 R) Same eye as Figure 20, eighteen days later. Retinal veins are of normal size.

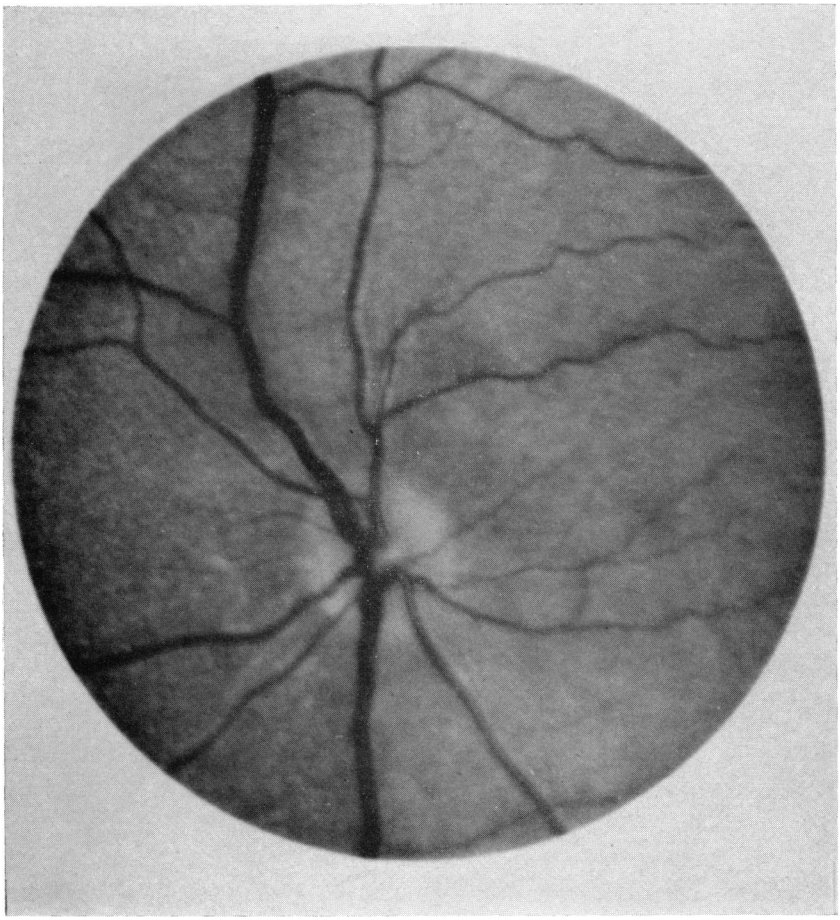

FIGURE 24

(Monkey 25 L) Thirty minutes after ligation of central retinal vein. Veins are dilated. Slightly retinal edema temporal to disk.

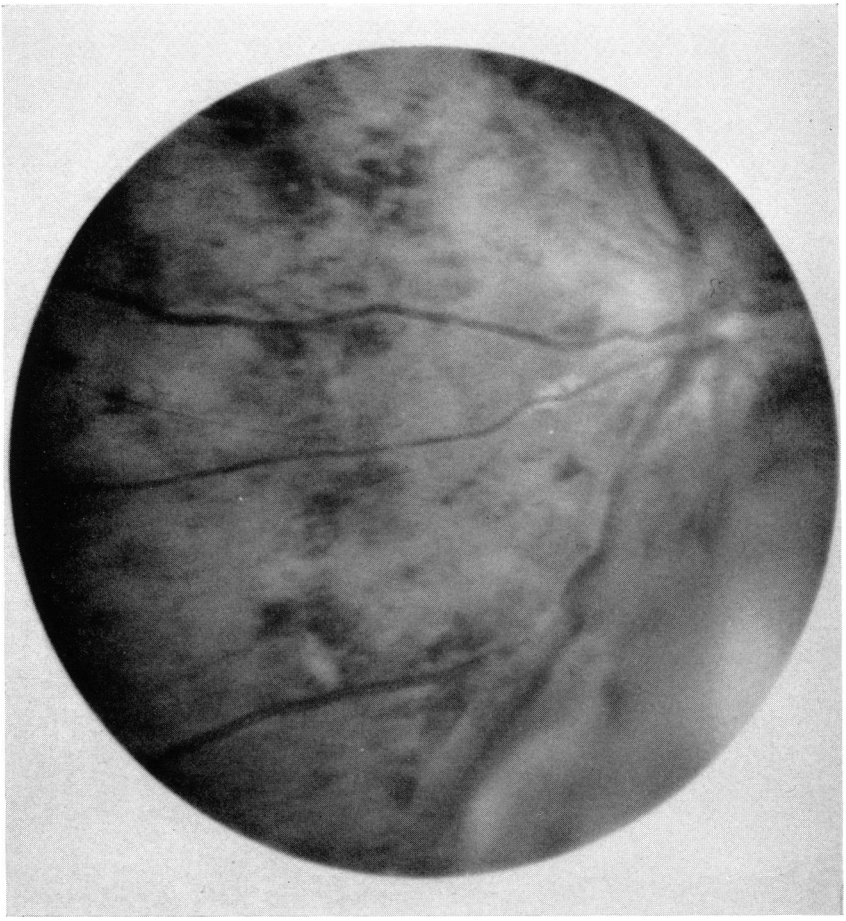

FIGURE 25

(Monkey 25 L) Five days after Figure 24. Retinal hemorrhages and edema and below the disc a localized detachment.

(Figure 32). The flat mount of the retina reveals a brittle capillary bed with extensive loss of both endothelial and mural cells (Figure 33). In one week, there is further necrosis of the inner half of the retina (Figure 34) and further degeneration of the capillary cells (Figure 35). Six weeks postoperatively, inner retinal necrosis is more extensive (Figure 36) as is the capillary degeneration (Figure 37). In the eye with incomplete occlusion by neoprene, pathologic sections of the retina (Figure 38) and the optic nerve (Figure 39) show normal cytology as does the flat preparation (Figure 40).

In 4 of the 6 eyes of Group I, no India ink entered the retinal circulation of the animals injected with this material, although it circulated throughout the other ocular tissues. In the other two eyes, India ink reached only the circumpapillary blood vessels, and, in the eye with partial venous occlusion, India ink readily flowed through the retinal circulation (Figures 39 and 40).

In Group II, the eyes followed a different course. At one day, no alterations occur in the retina (Figure 41), in the optic nerve and its vessels (Figure 42), or in the retinal capillaries (Figure 43). At four weeks (Figures 44, 45, and 46), there is no pathologic change in these structures. In the one eye in which there was a clinically progressive vascular and retinal degeneration (Figures 24 and 25), microscopic examination on the fifth day revealed severe hemorrhagic and necrotic retinal degeneration (Figure 47). No obvious change is present in the blood vessels of the optic nerve and disk (Figure 48). The cell population of the capillaries in the whole mount (Figure 49) seems close to normal, but the endothelial cells stain faintly.

In Group II, India ink circulated throughout the retinal vessels of the eyes (Figures 42 and 43) of the three monkeys injected, including the eye with progressive retinopathy (Figures 48 and 49).

DISCUSSION

These results leave little doubt that there is a vast difference between the eyes of Group I and those of Group II. When neoprene completely occludes the venous circulation at the disk, the circulatory dynamics of the retina are promptly and irreversibly affected. The increased intravascular pressure is transferred across the capillary bed to the arterial side. The latter's flow falters rapidly and stops within a day. A course of ischemic and hemorrhagic retinopathy paints a colorful but destructive fundus appearance. The insult so severely damages

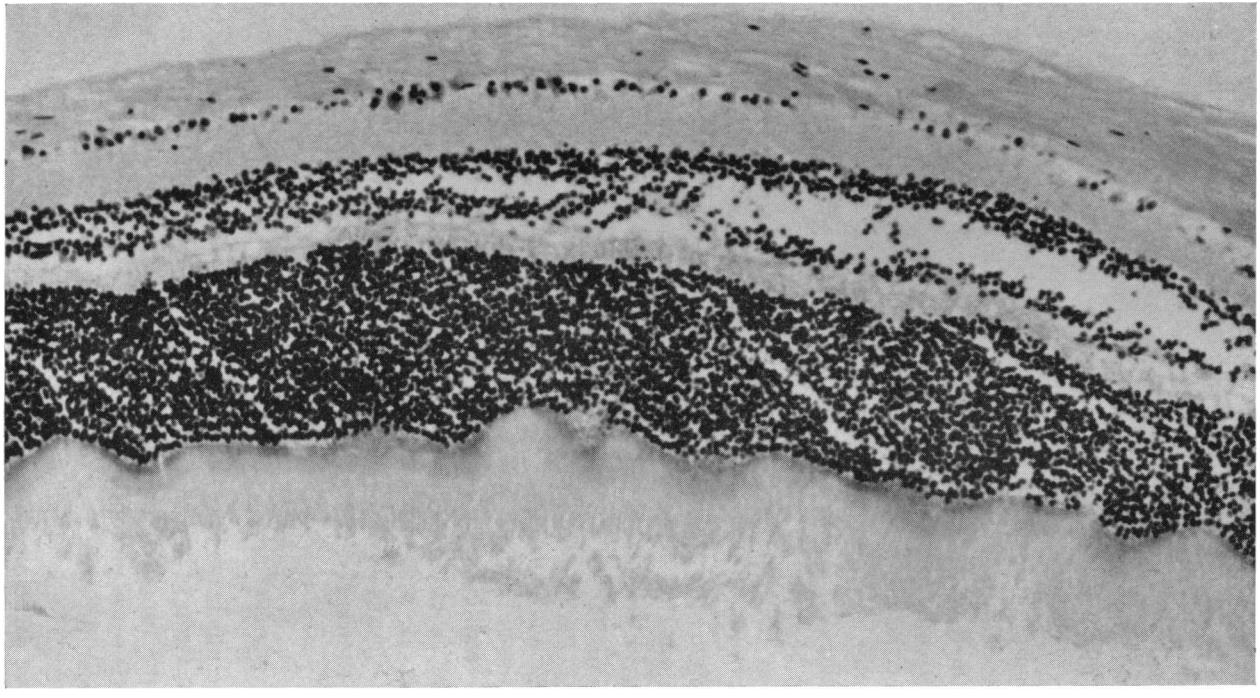

FIGURE 26

(Monkey 16 L) Six hours after neoprene injected into the central retinal vein. No significant retinal change. (H & E; × 175)

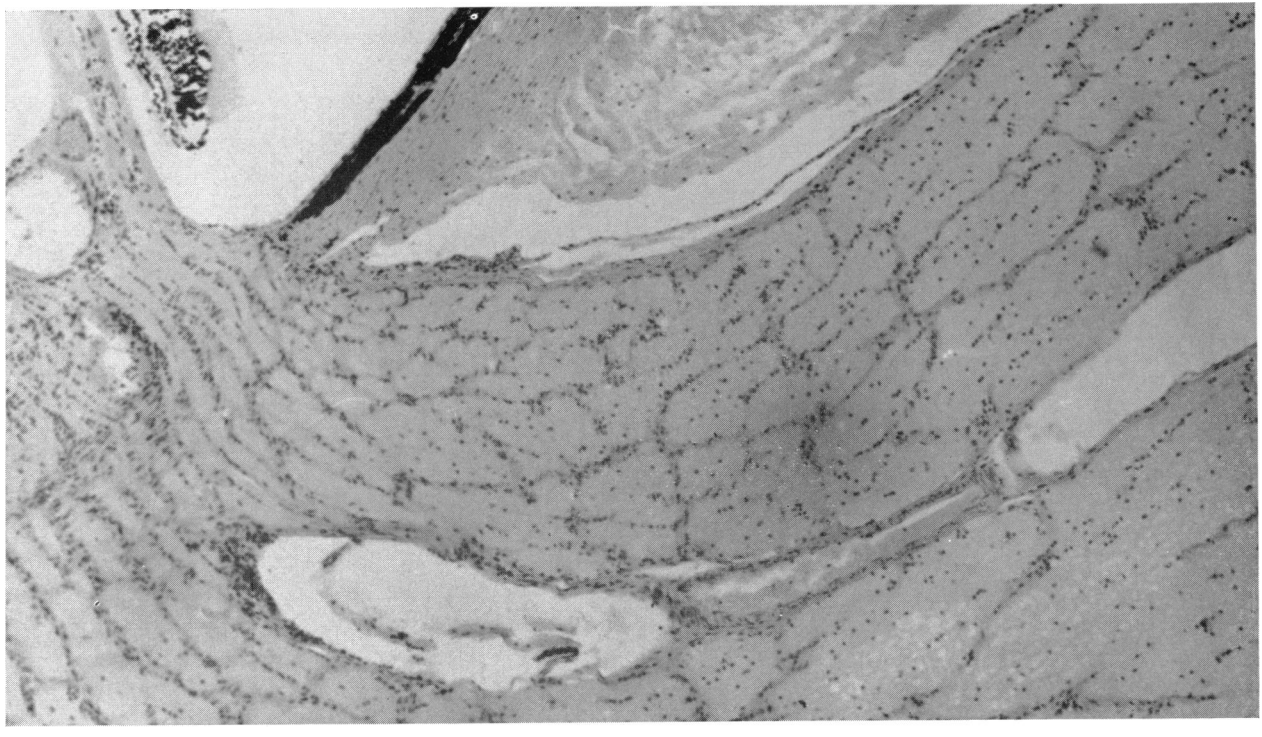

FIGURE 27

(Monkey 16 L) Six hours after neoprene injection. Retinal vein flanks artery which contains blood. No reaction about vessels. (H & E; × 70)

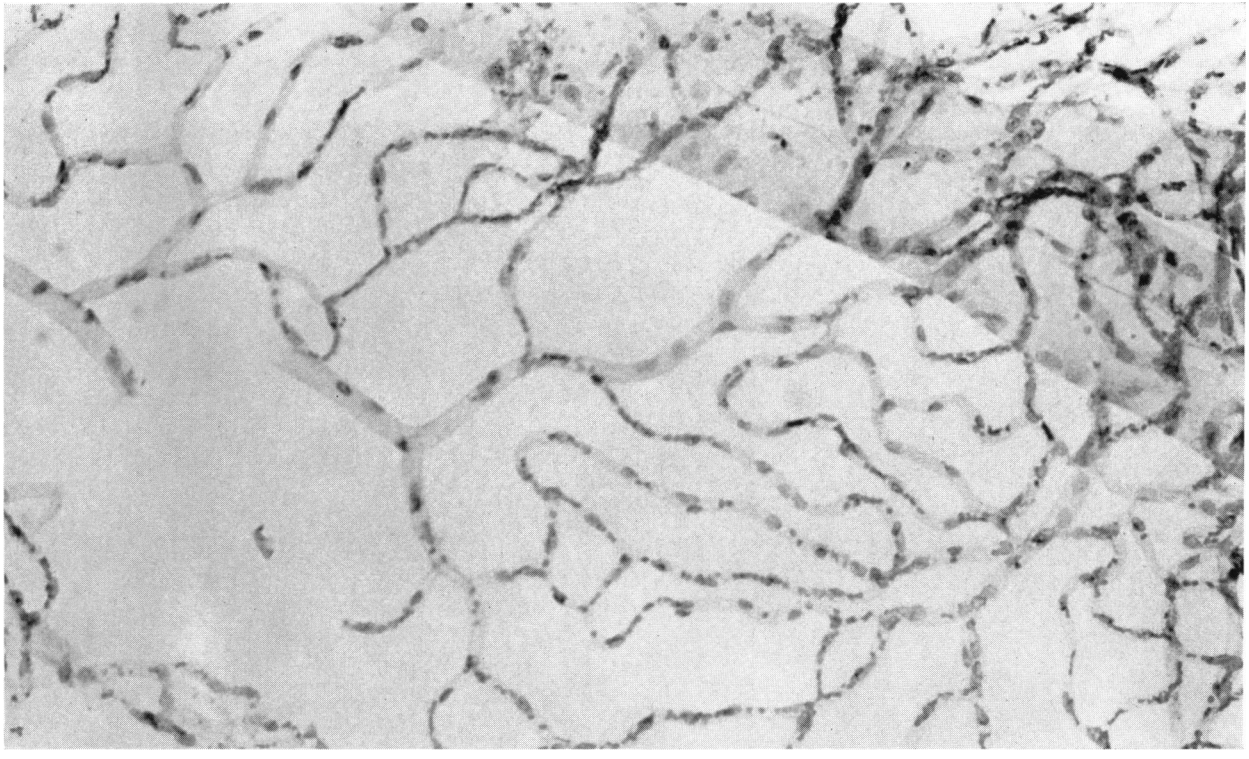

FIGURE 28

(Monkey 16 L) Six hours after neoprene injection. Trypsin digest preparation of retinal vessels with little change. Endothelial cells stain poorly. (PAS; × 175)

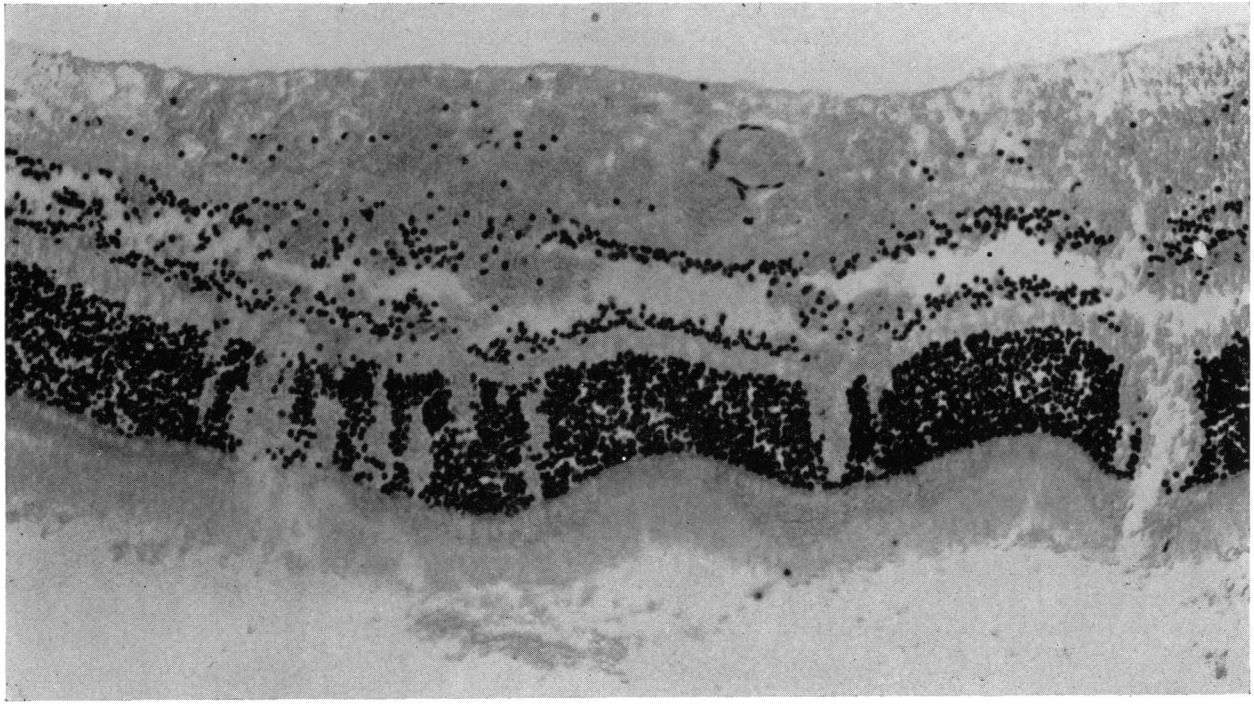

FIGURE 29

(Monkey 22 L) One day after neoprene injection. Extensive retinal hemorrhages in all layers. (H & E; × 175)

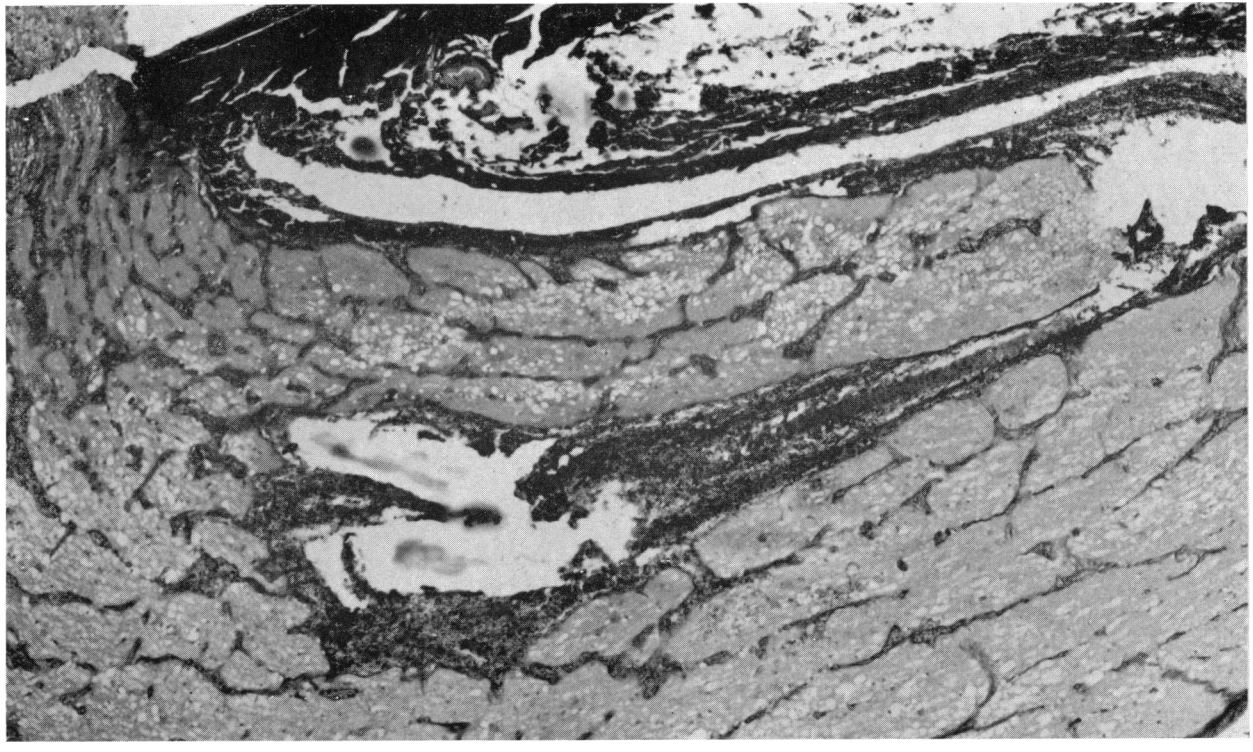

FIGURE 30

(Monkey 22 L) One day after neoprene injection. Hemorrhage extends into optic nerve about the wall of the vein. (Verhoeff's elastic stain; × 70)

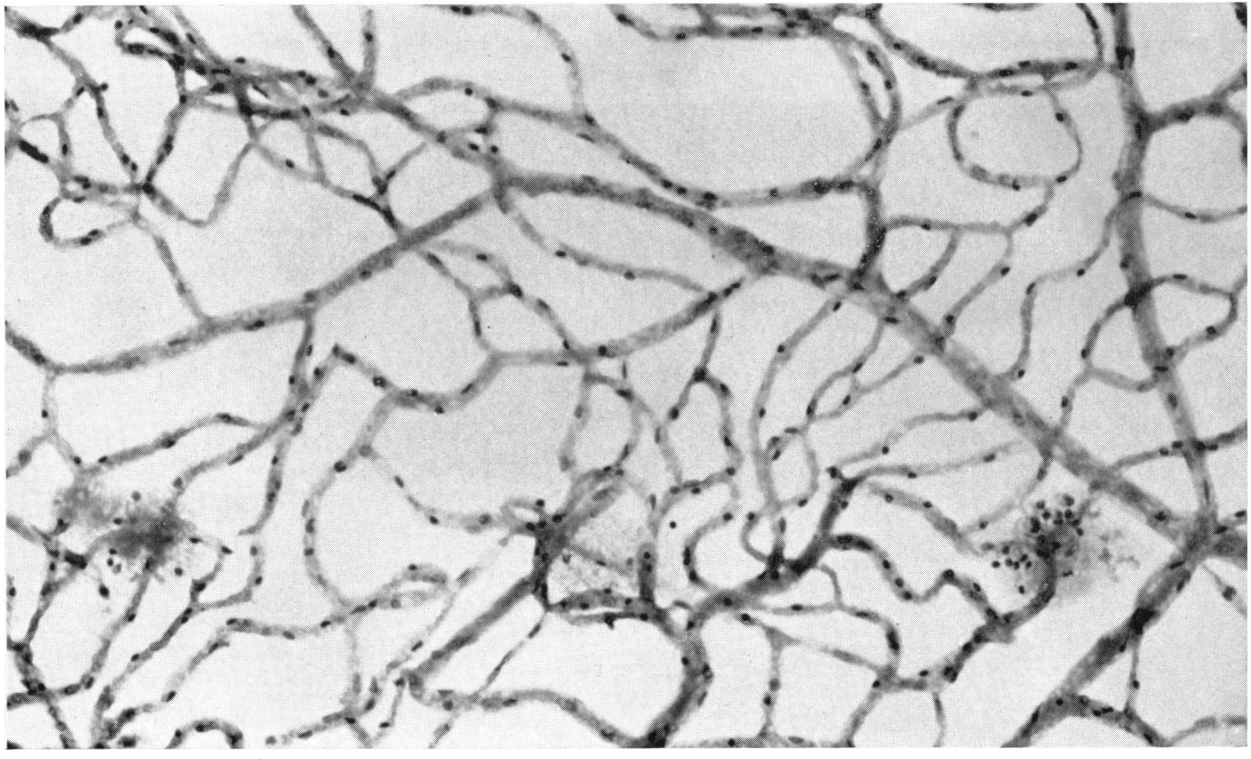

FIGURE 31

(Monkey 22 L) One day after neoprene injection. Decrease in endothelial cells. (PAS; × 175)

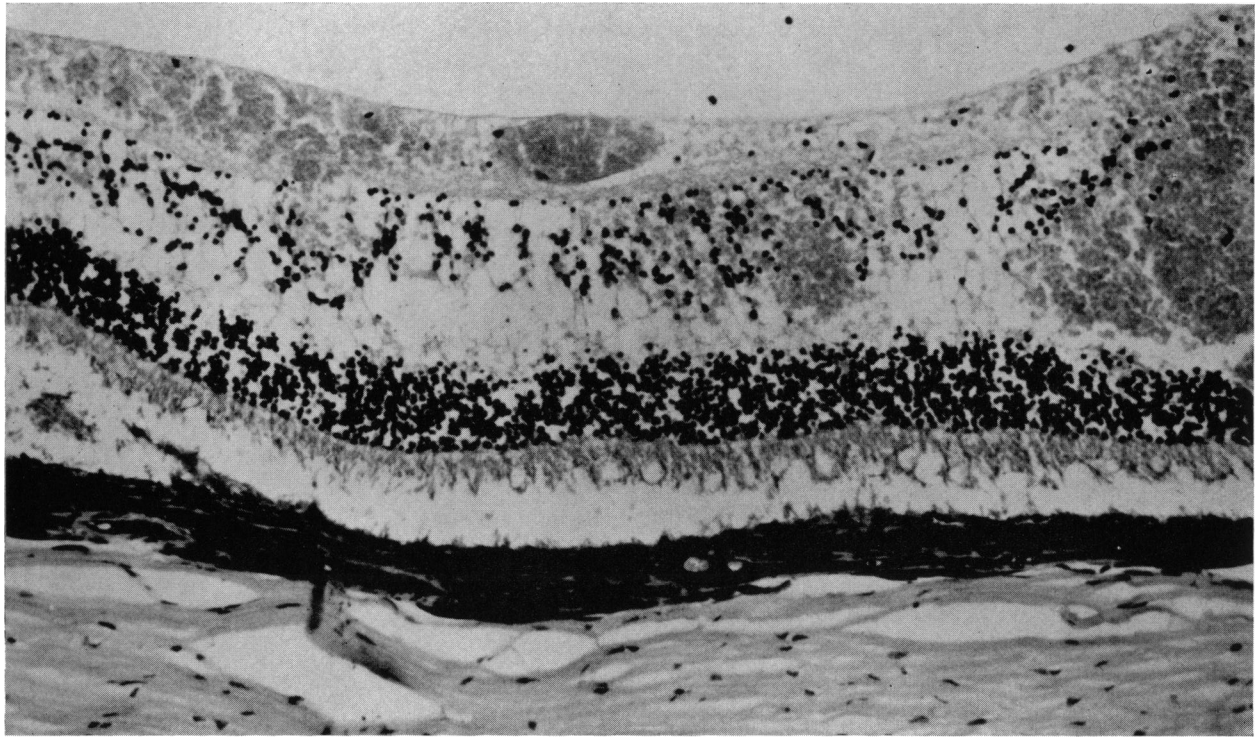

FIGURE 32

(Monkey 26 L) See Figure 3. Three days after neoprene injection. Extensive retinal hemorrhage and necrosis of inner half of retina. (H & E; × 175)

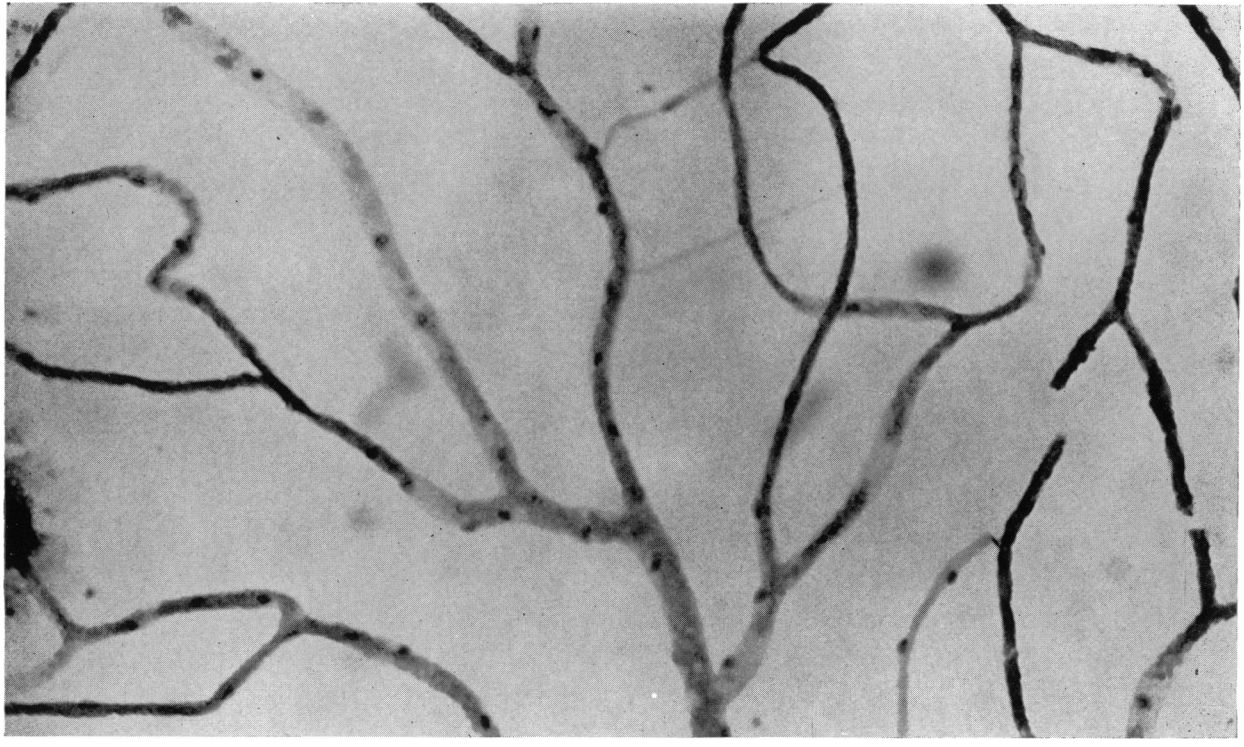

FIGURE 33

(Monkey 26 L) Three days after neoprene. Extensive degeneration of endothelium and to a lesser degree of the mural cells. (PAS; × 175)

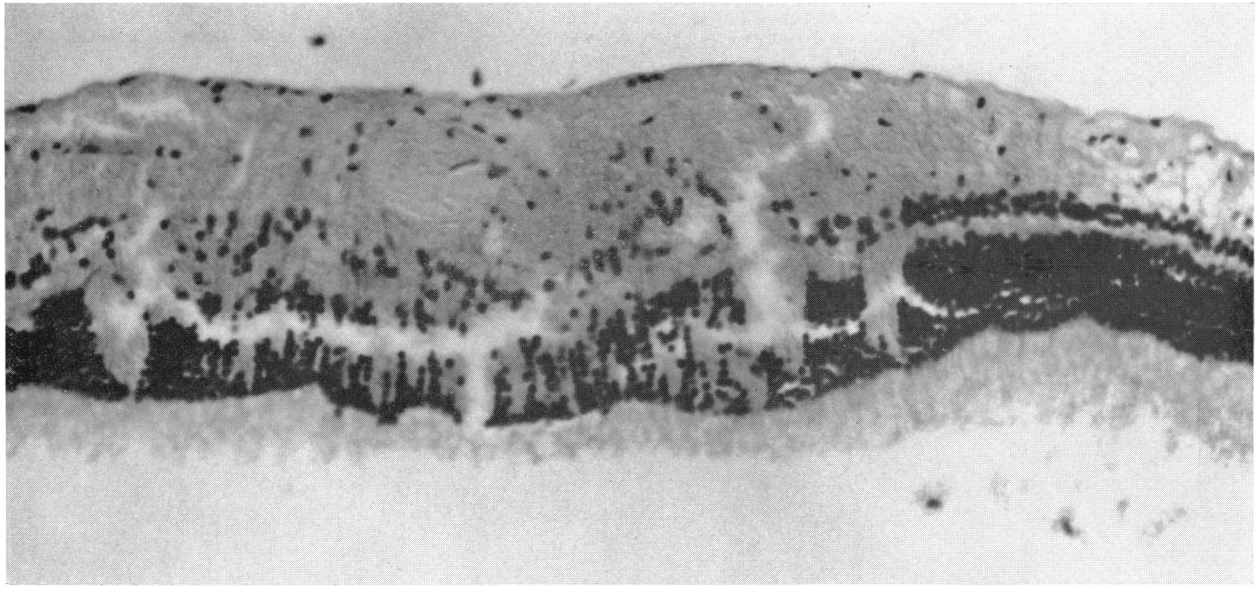

FIGURE 34

(Monkey 20 R) One week after neoprene injection. Pronounced degeneration in a hemorrhagic retina. (H & E; × 175)

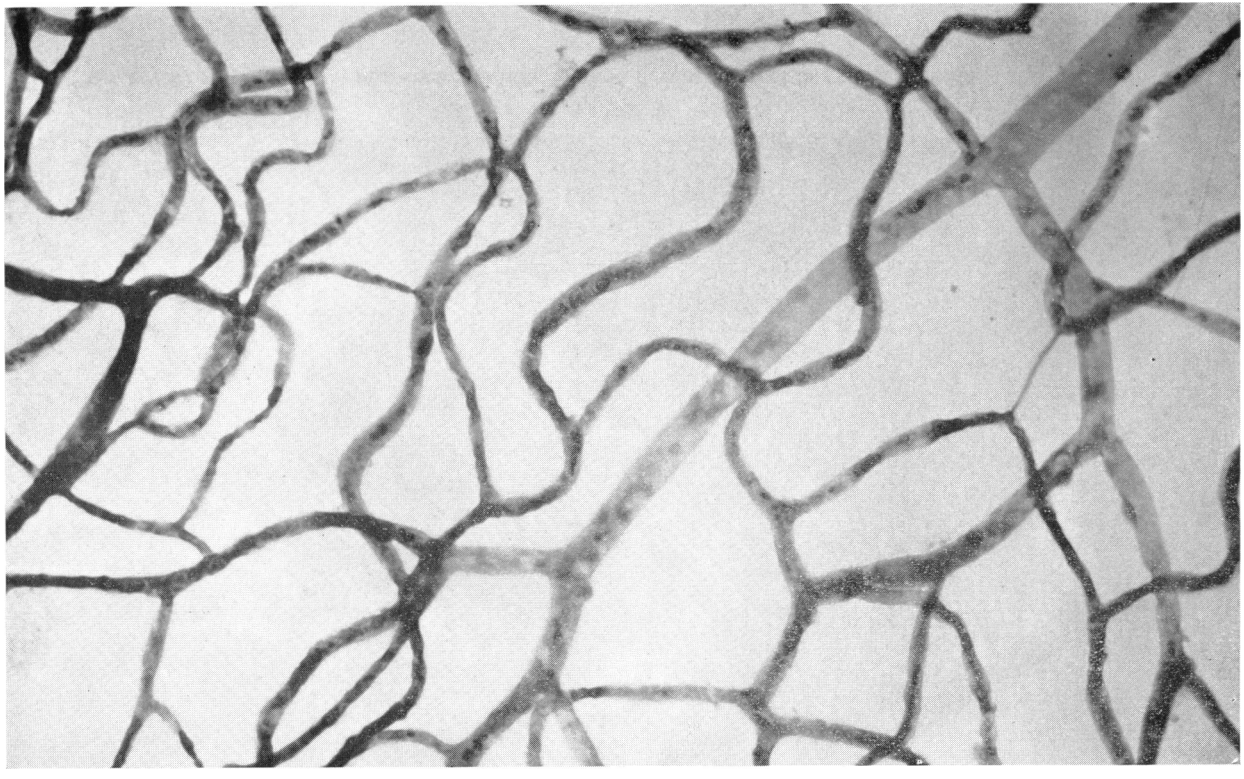

FIGURE 35

(Monkey 20 R) One week after inejction of neoprene. Marked loss of endothelial and mural cells. (PAS; × 175)

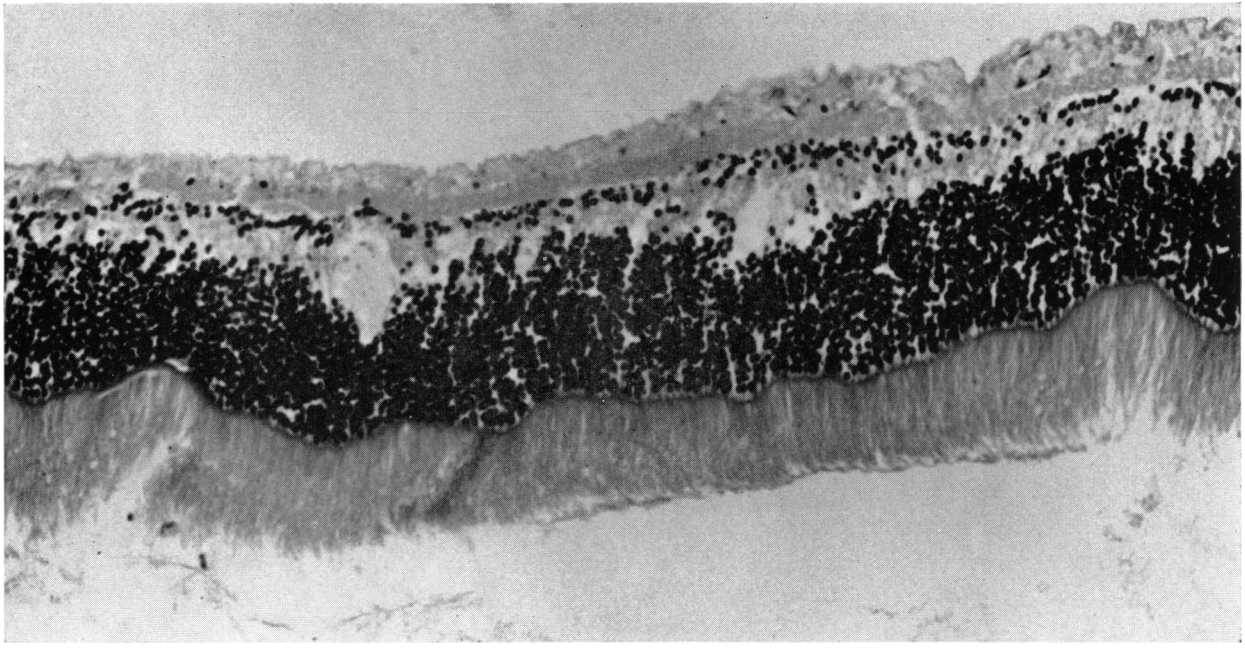

FIGURE 36

(Monkey 5) Six weeks after neoprene injection. Marked degeneration of inner half of retina. (H & E; × 175)

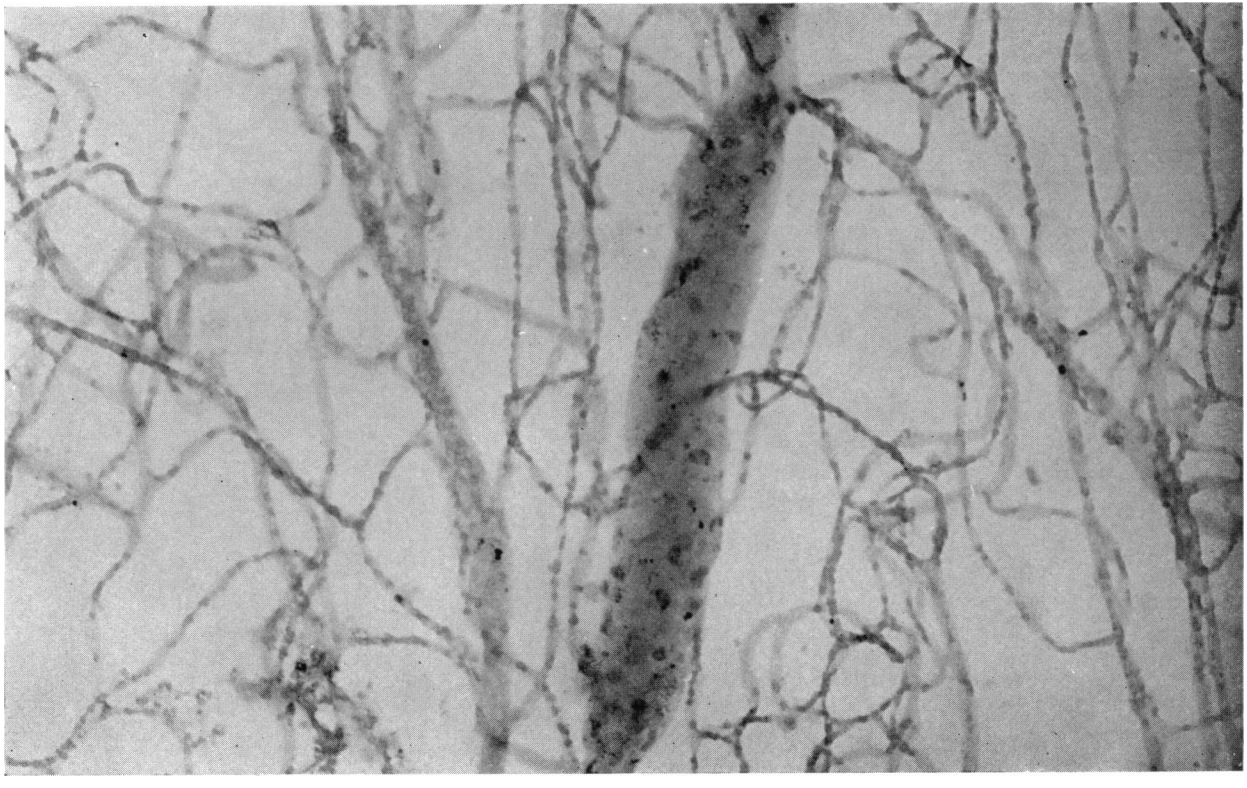

FIGURE 37

(Monkey 5) Six weeks after neoprene injection. Nearly acellular capillary bed. (PAS; × 175)

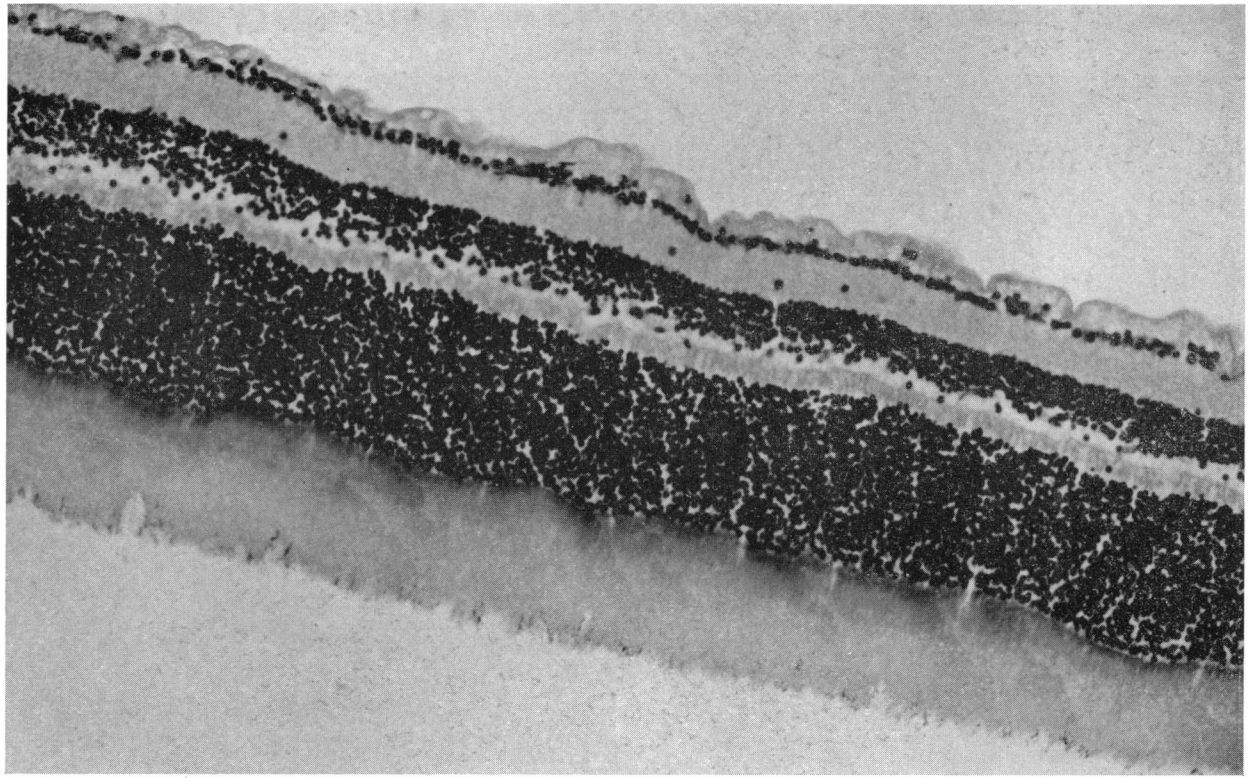

FIGURE 38

(Monkey 20 L) One day after neoprene injection. Normal retinal architecture. (H & E; × 175)

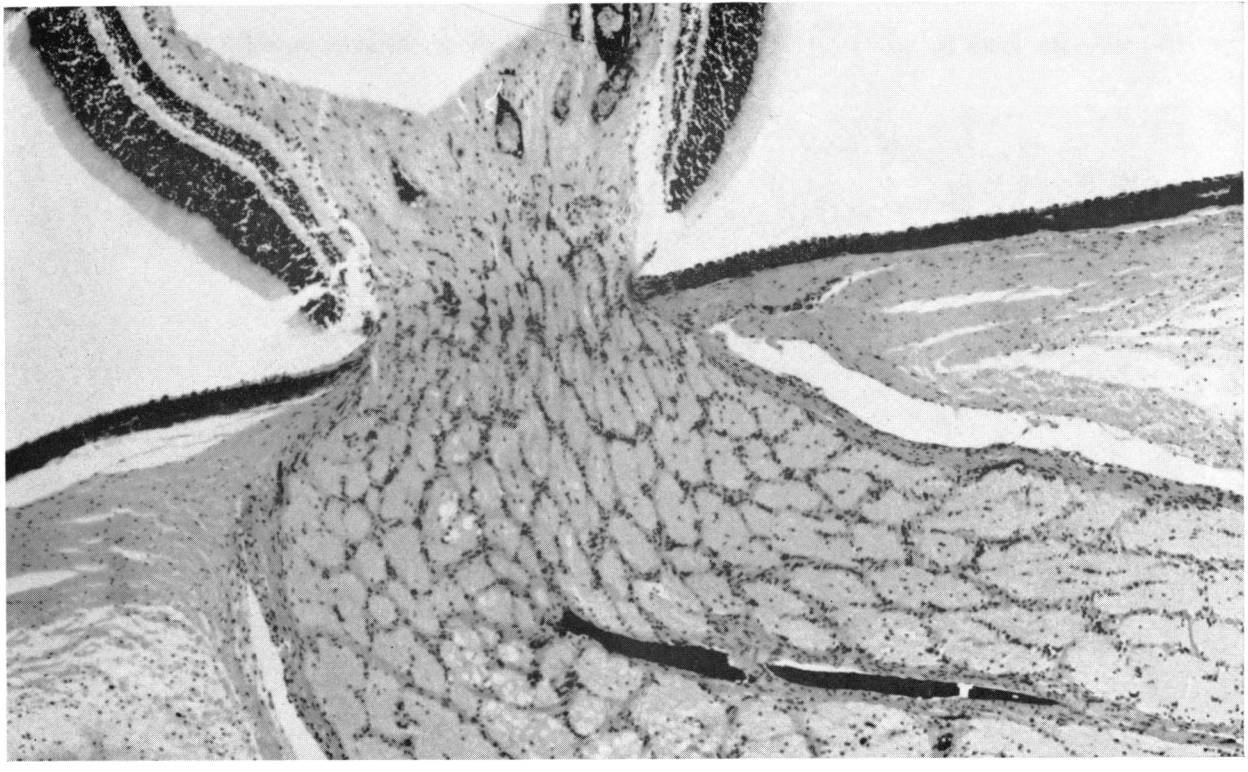

FIGURE 39

(Monkey 20 L) One day after neoprene injection. Vessels in retina and optic nerve contain India ink. (H & E; × 70)

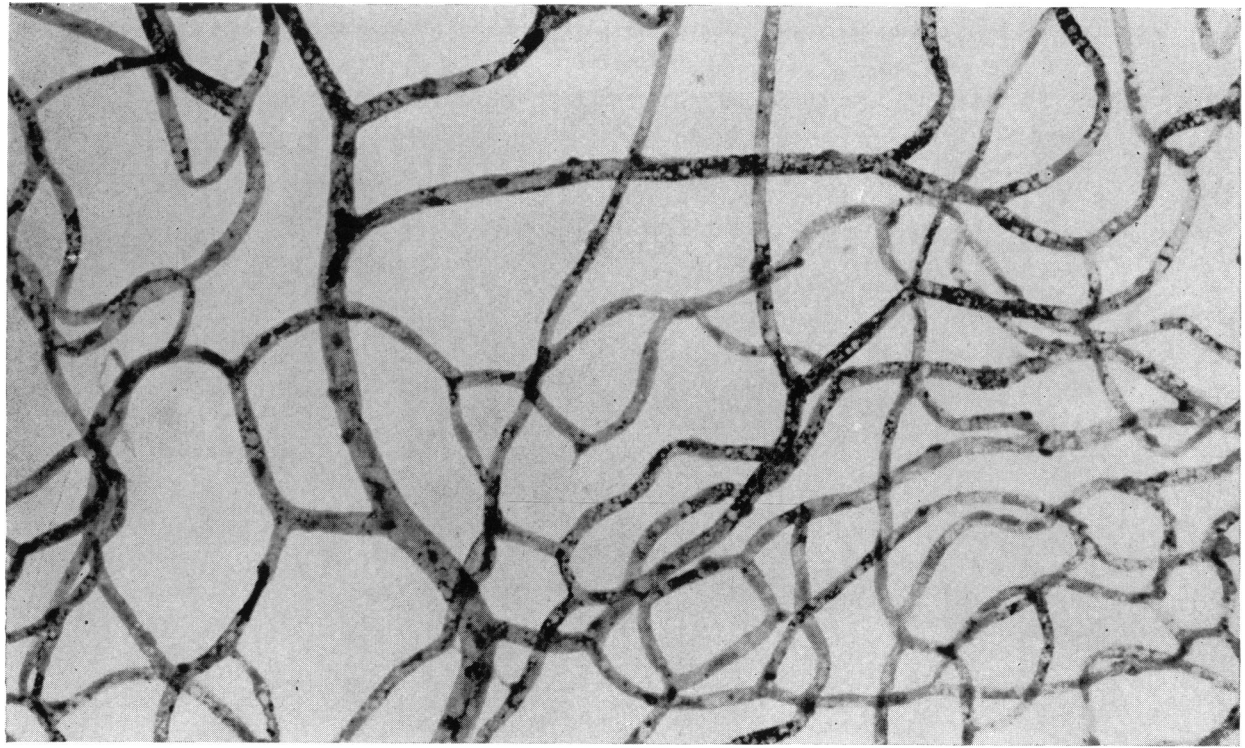

FIGURE 40

(Monkey 20 L) One day after neoprene injection. Normal capillary structure. Black material within vessels is India ink. (PAS; × 175)

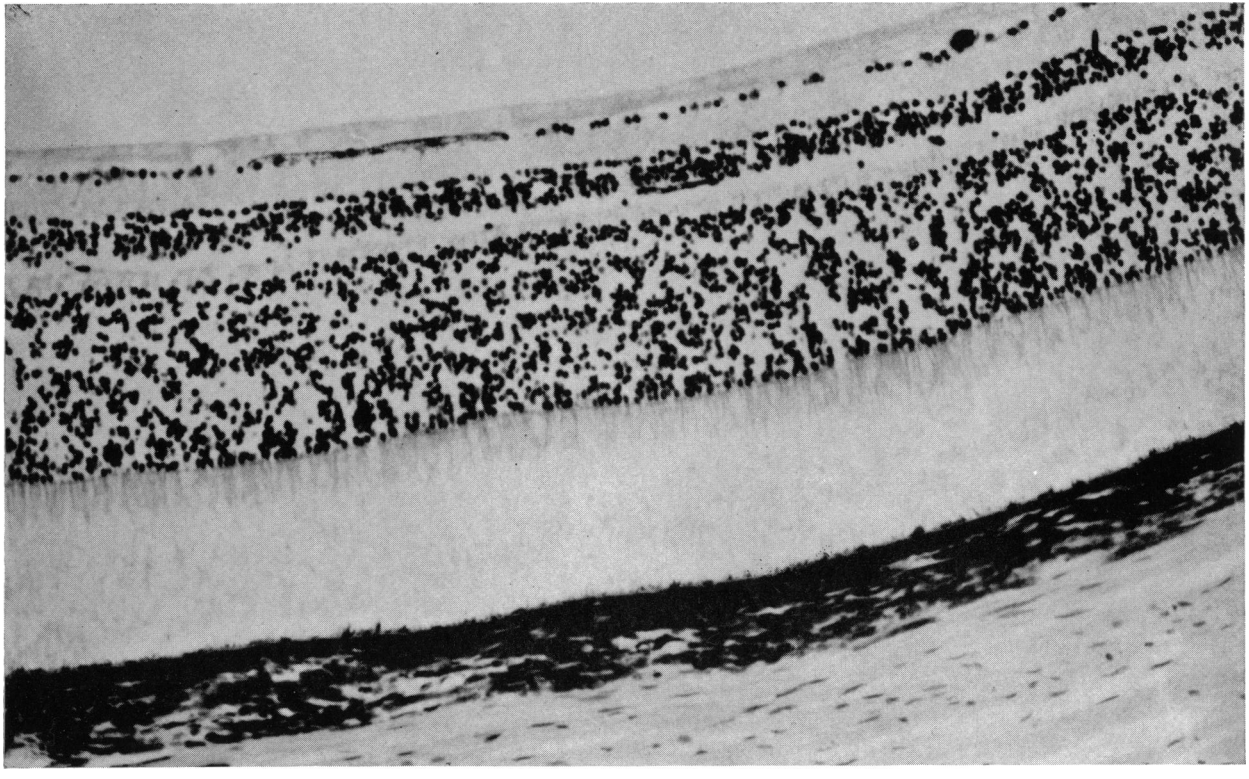

FIGURE 41

(Monkey 31 R) One day after ligation of central retinal vein. Normal retinal architecture. India ink in small retinal vessel. (H & E; × 175)

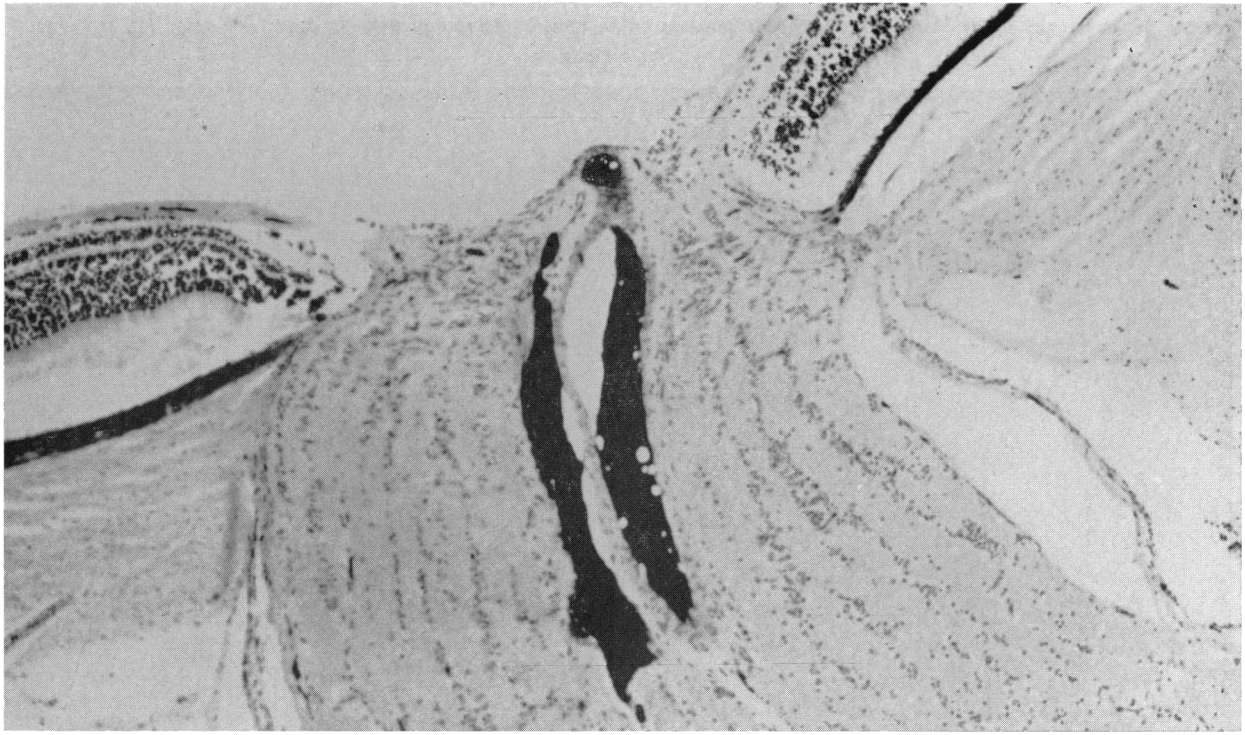

FIGURE 42

(Monkey 31 R) One day after ligation of central retinal vein. Normal central retinal artery and vein containing India ink. (H & E; × 70)

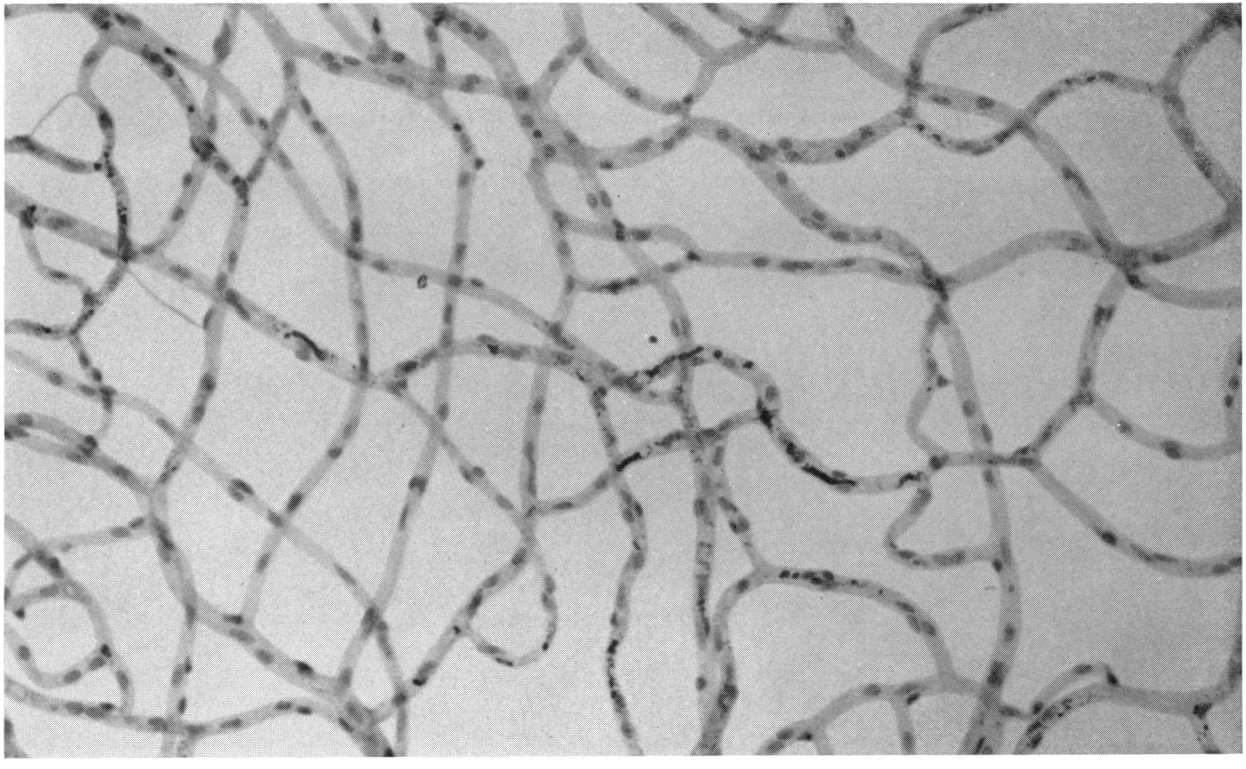

FIGURE 43

(Monkey 31 R) One day after ligation of central retinal vein. Normal capillary pattern containing India ink within the vessels. (PAS; × 175)

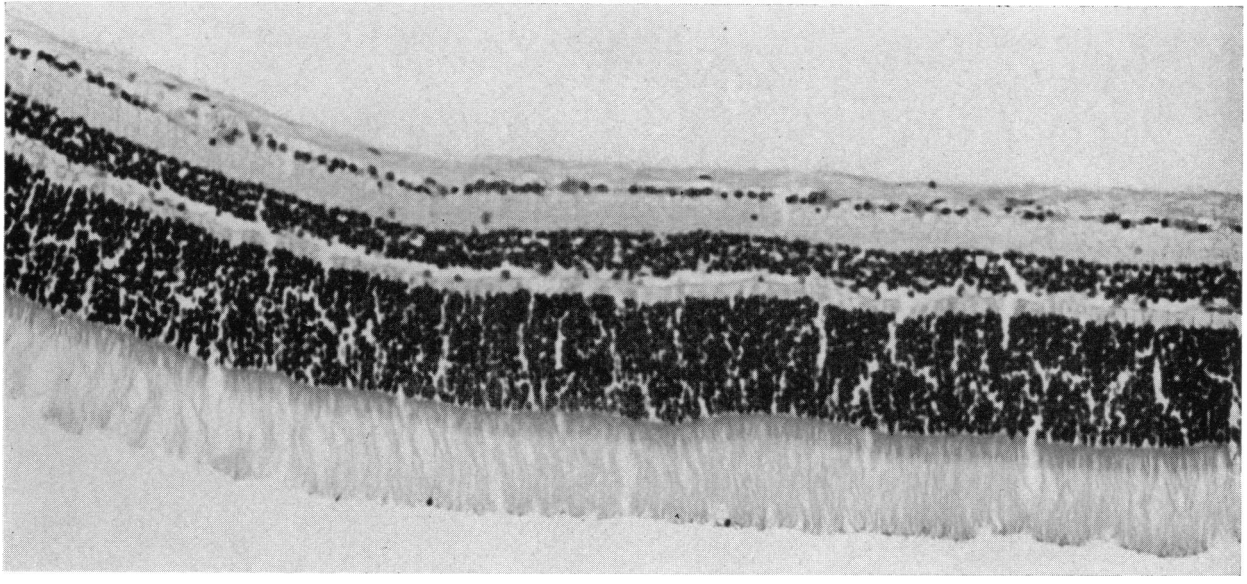

FIGURE 44

(Monkey 6 R) Four weeks after ligation of central retinal vein. Normal retina. (H & E; × 175)

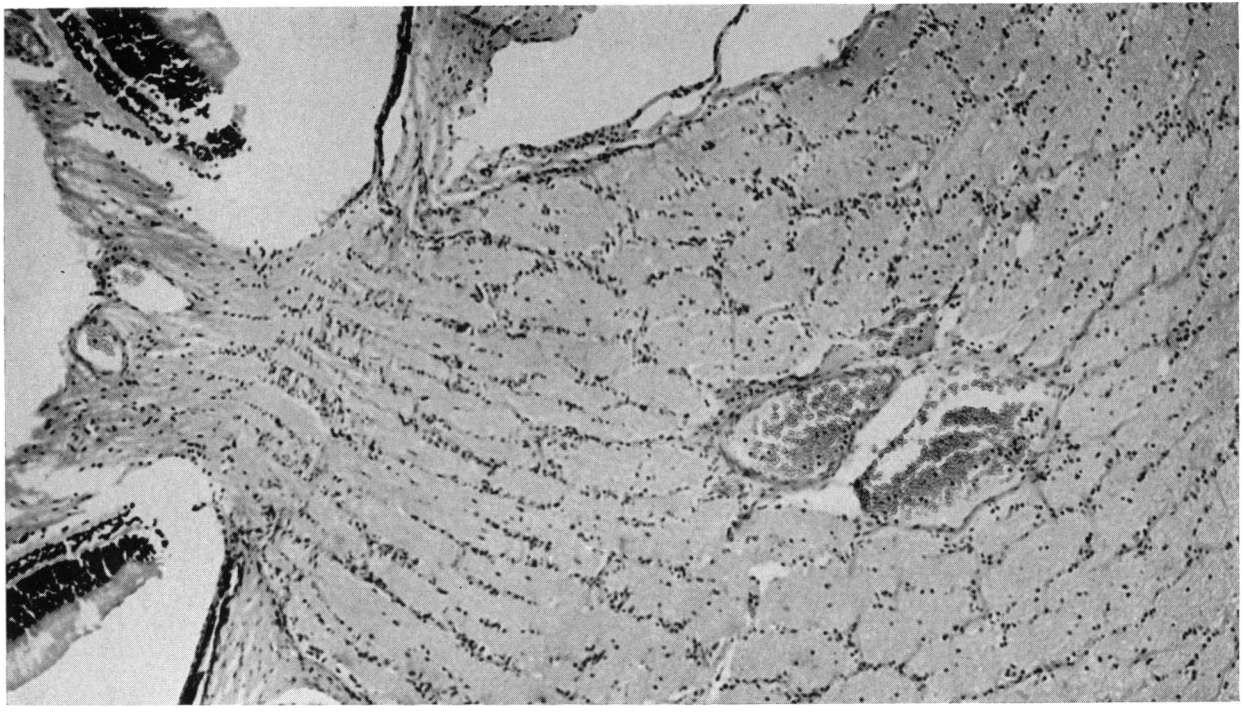

FIGURE 45

(Monkey 6 R) Four weeks after ligation of central retinal vein. Normal central retinal artery and vein in optic nerve. (H & E; × 70)

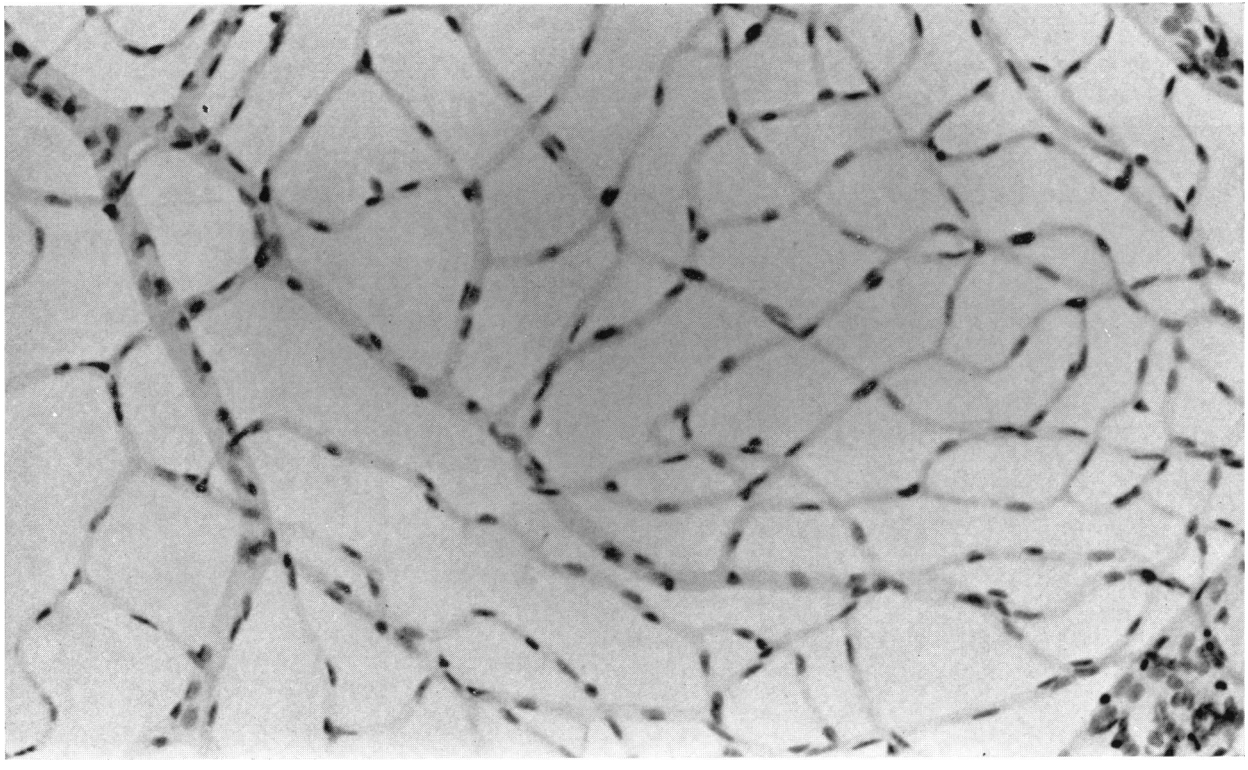

FIGURE 46

(Monkey 6 R) Four weeks after ligation of central retinal vein. Normal capillary bed. (PAS; × 175)

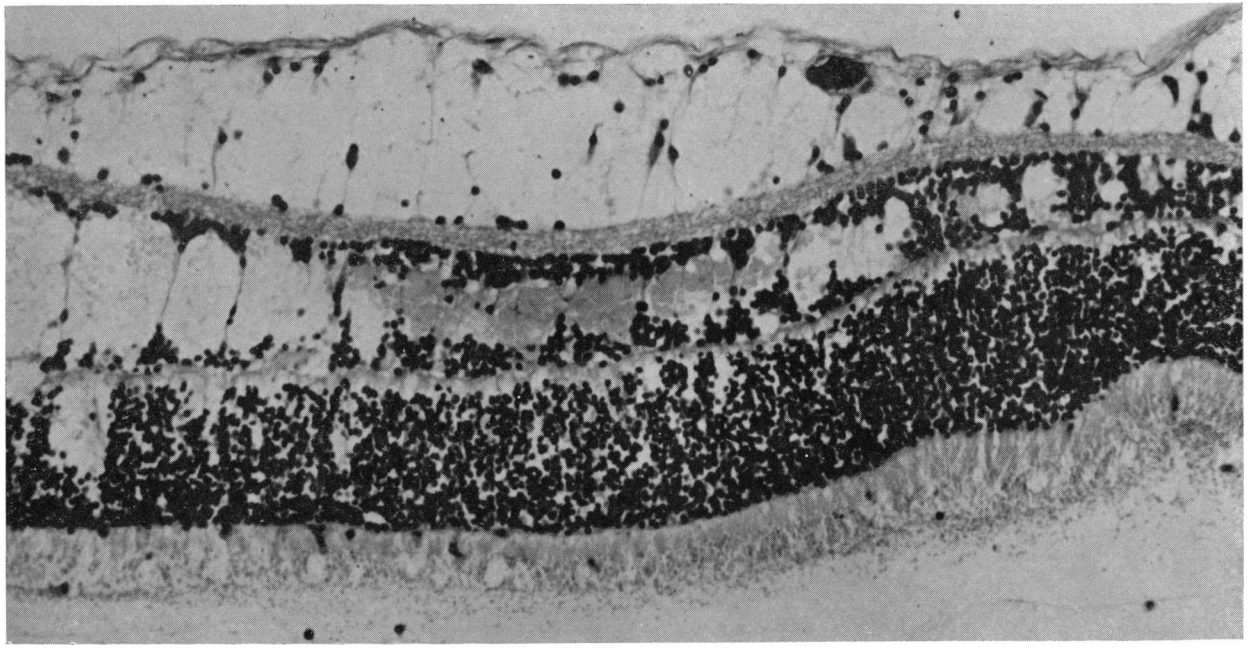

FIGURE 47

(Monkey 25 L) Five days after ligation of central retinal vein. Extensive retinal necrosis with hemorrhage in bipolar cell layer. India ink is present in the small vessel. (H & E; × 175)

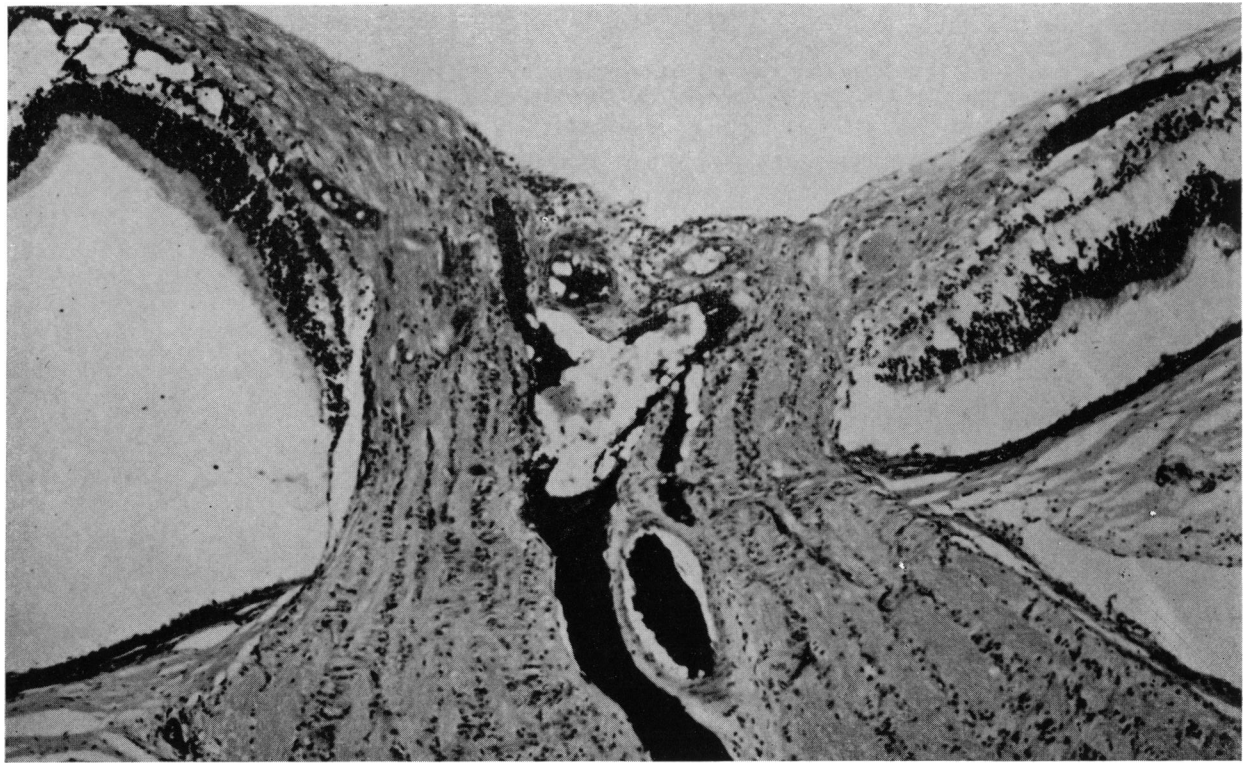

FIGURE 48

(Monkey 25 L) Five days after ligation of central retinal vein. Central retinal artery and vein appear unaltered and contain India ink. (H & E; × 70)

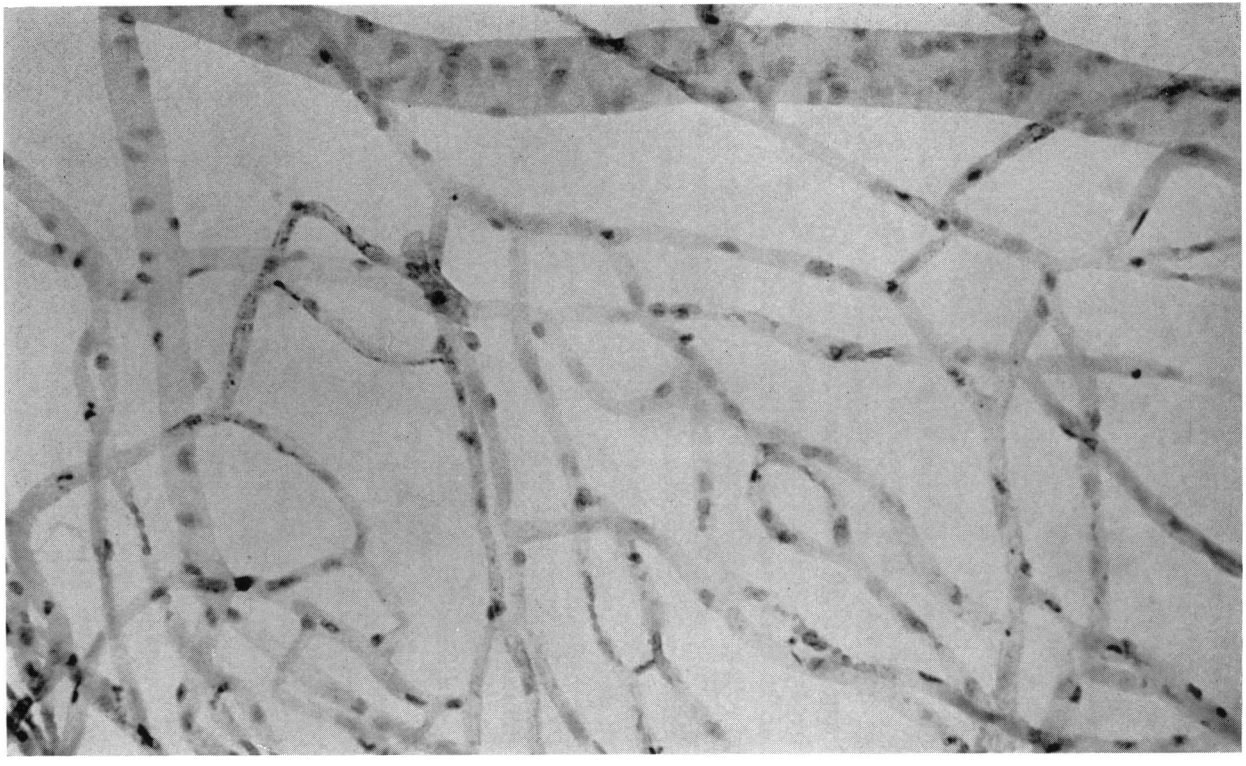

FIGURE 49

(Monkey 25 L) Five days after ligation of central retinal vein. Cells of capillaries about normal but endothelium stains less intensely. India ink is present in some of the capillaries. (PAS; × 175)

the retina that it never recovers. There is no evidence in the photomicrographs (Figures 27, 30, and 39) to attribute arterial blockage to intravenous neoprene by a secondary effect upon the artery in the optic nerve. These vessels and the optic nerve show no inflammatory reaction, which would be expected if the neoprene were toxic to the vessels or the tissue. The primary event is venous occlusion with secondary arterial insufficiency.

When occlusion of the central retinal vein occurs after the vein emerges from the optic nerve, venous outflow is temporarily impaired, but not enough to affect arterial inflow. The eye adapts quickly to the altered state and, within four days, retinal circulation is nearly normal (Figures 21 and 22). This form of venous occlusion does not damage the retina. Collateral circulation explains best the difference between Group I and Group II. When alternate routes of drainage allow blood flow to bypass the occluded vessel, no permanent damage is done.

None of the experimental models reproduced the actual appearance of central retinal vein occlusion in man. The damage in the eyes with complete venous obstruction in Group I is much more severe than central retinal vein occlusion in man. The eye in which neoprene partially occluded the venous outflow more closely simulated central vein occlusion in man. This incomplete occlusion produced a few scattered retinal hemorrhages without ischemic retinopathy by the first day (Figure 12). Angiograms (Figures 13, 14, and 15) demonstrated unimpaired arterial flow, venous filling prolonged to twelve seconds, and later extravasation of the dye. Angiography readily explains the different sequence of events in this eye as compared with the others in Group I. This eye still has a means of venous drainage either by collateral channels or an incompletely occluded vein while the other eyes had no means of return. One eye (Figure 25) after venous ligation (Group II) produced a fundus picture of hemorrhagic and ischemic infarction similar to that described by Hayreh in the animals in which he diathermized the central retinal artery and vein. To explain this event, we postulate that the artery was injured or occluded at some time during the operative procedure. This damaged the retinal vascular bed. When blood flow was re-established, blood entered damaged retinal vessels with an impaired venous drainage. This substrate set the stage for ischemic hemorrhagic infarction of the retina similar to that seen in Group I. This similarity is understandable since an ischemic process is superimposed on a partially obstructed venous system. This overwhelming insult to the retina does not correlate closely to that of central retinal vein occlusion in man where

initial loss of visual function is related to the retinal and vitreous hemorrhages and not to ischemia.

CONCLUSIONS

1. Complete central retinal occlusion in the optic disk in the owl monkey causes venous congestion and prompt, irreversible stagnation of flow in the central retinal artery and produces an overwhelming ischemic and hemorrhagic retinopathy.
2. Ligation of the central retinal vein of the owl monkey as it emerges from the optic nerve causes temporary, reversible venous congestion without any demonstrable effect upon arterial flow.
3. Collateral circulation between the disk and the emergence of the central retinal vein from the optic nerve best explains the difference in the two groups.
4. Changes in arterial flow in Group I were secondary to venous obstruction and no changes in arterial flow were demonstrated in Group II.
5. Neither experimental model reproduced the exact appearance of central retinal vein occlusion in man. The closest approximation was in the eye in which fluorescein angiography demonstrated a partial, but not total, occlusion of venous outflow.

SUMMARY

The circulatory dynamics and pathology of occlusion of the central retinal vein was compared at two sites in the owl monkey eye. In 17 eyes, neoprene occluded the central retinal vein at the disk, and, in 10 eyes, the central retinal vein was tied and cut as it emerged from the optic nerve. The first group of animals demonstrated rapid ischemic and hemorrhagic infarction of the retina with obstruction of the arterial flow on fluorescein. The second group demonstrated a temporary and reversible increase in venous congestion without secondary damage to the eye. Collateral circulation in the region of the disk and posterior to it explains best the difference in the two groups. Partial obstruction of the central retinal vein by neoprene approximated the central vein occlusion in man, but neither model exactly reproduced it.

ACKNOWLEDGMENT

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DISCUSSION

DR. GEORGE N. WISE. I should like to thank the authors for permitting me to see their paper prior to the meeting, and to congratulate them on a technically difficult, but well done, project. It is from such correlative clinical, hemodynamic, and microscopic studies that reliable new knowledge applicable to human disease is best gained.

Neither of the experimental models of the authors produced the clinical or microscopic picture usually found in human central retinal vein obstruction. There are at least two major factors making difficult the production of an animal model of this human disease:

(1) the speed of collateral formation in animals as compared with that in man. Collaterals may be clinically visible within several days in the cat or pig and only slightly later in the rhesus monkey, while they are seldom seen in man before two or three months. Thus, the effect of venous outflow impedance in the animal is quite transient as compared with that in humans.

(2) the frequency of attendant arterial disease in microscopic studies of human central retinal vein obstruction. Coats and Verhoeff called attention to the rarity of finding a normal central retinal artery in microscopic specimens of occluded central retinal veins. Hayreh's production of a picture comparable to human central retinal vein obstruction by occluding both central artery and vein is in keeping with this concept. The benign quality of central vein occlusion in the young, where attendant arterial disease would not be expected, as compared with its malignancy in the elderly, where associated arterial disease would be anticipated, is also compatible with this idea.

I note with some dismay that the authors have used longitudinal sections to demonstrate the pathology of the central retinal vessel obstructions. This has been a common occurrence in the recent literature on this subject. It

seems an appropriate time to call attention again to Coats' and Parsons' emphasis that central retinal vein occlusion in the human can be reliably diagnosed only by serial cross section from the lamina to the exit of the vein from the nerve.

Hayreh worked with the rhesus monkey whose vascular anatomy in this area is very similar to that of the human. Our own limited study of the owl monkey, whose fluid vitreous, vascular fovea, absence of radial peripapillary capillaries, and wider retinal capillary mesh, suggest that there may be other vascular differences in this animal and man. Knowledge of the normal owl monkey's retinal and optic nerve blood supply is essential before definitive conclusions may be drawn.

I would like to take issue with the authors where they state in the written report: "This overwhelming insult to the retina does not correlate closely to that of the central retinal vein occlusion in man where loss of visual function is related to the retinal and vitreous hemorrhages and not to ischemia." Excluding ensuing glaucoma, vitreous hemorrhage is a rarer cause of temporary loss of vision in this disease and retinal hemorrhages play little or no part in the visual loss. It is macular edema, cystic macula, rupture of a central macular cyst, macular pigment disturbance, or macular fibrosis, roughly in that sequence, that produce the central scotoma accounting for the major visual loss. The relative depression of the remainder of the visual field as compared with the macular destruction is of less visual consequence.

DR. THOMAS P. KEARNS. It is obvious from this excellent study that something about vein occlusion in experimental animals is different from the typical vein closures that we see in human patients.

Dr. Michaelson from Israel dropped a bombshell on this subject at the recent meeting of the Ophthalmological Society of the United Kingdom in Cardiff. On histologic examination of three autopsy specimens of branch vein closure, Dr. Michaelson and his co-workers found that there was no pathologic change in the vein, but there was pathologic change in the artery. Therefore, they now believe that what we have called a "vein closure" or "vein obstruction" is really arterial, and that the changes we are seeing are due to ischemia.

I would like to ask the authors if they have given this theory any thought. Perhaps they are aware of Dr. Michaelson's work.

I still have not prepared myself to accept this theory entirely. However, there is a strong resemblance to another condition that both Dr. Hedges and I reported independently about five years ago, which we call "venostasis retinopathy." This condition is a capillary retinopathy produced by ischemia due to carotid disease. These retinopathies closely resemble the appearance of an incomplete central vein closure. Whether all vein closures are ischemic, I do not know; but I do know it is extremely important for the ophthalmologist to recognize that what may look like an impending central vein

closure may, in truth, be an ischemic phenomenon from carotid disease. There is one simple way to differentiate them, and that is to check the retinal artery pressure on every patient who has what appears to be an impending central vein closure. It is of major importance to the patient that the ophthalmologist be able to distinguish between the venous stasis retinopathy of carotid occlusive disease and the idiopathic impending occlusion of the central vein.

Dr. Albert M. Potts. I think the authors are to be congratulated for the definitive way in which they have demonstrated the collateral circulation at the periphery, at the entrance of the central retinal vein into the optic nerve. The question is how well one can extrapolate from the owl monkey to the human.

In our laboratory we have approached this sort of problem from a slightly different point of view. We have been injecting eyes from the eye-bank, through the short posterior ciliary arteries and retrograde through the vortex veins. We then clear the eyes by a technique which was recently published in the *American Journal of Ophthalmology*.

In these specimens we have been able to demonstrate an inconsistent kind of collateral circulation both at the arteriolar level and at the venous level. These connections are close to the disk, between the choroidal circulation *via* its supply to the optic disk and the central retinal circulation. The inconstancy of this in the human as compared with the few rhesus monkeys we have seen suggests that there is a real difference between species.

It is our particular concern to know whether the high-pressure retinal arterial circulation could supply a failing disk circulation. If so, this might be the reason why some patients are able to sustain high intraocular pressures in glaucoma. Our suggestion is that this might be inconstant simply because of the inconstant anatomical feature.

There is obviously no way to do the authors' experiment in human beings. The ever-present difficulty of extrapolating from anatomy to physiology in the human presents a problem we still have to face.

Dr. David Shoch. I was in Israel just before Dr. Michaelson left for England and I saw the slides that Dr. Kearns talked about, and I can corroborate the fact that they do show ischemia.

There are two points to be made. One is that the ophthalmoscopic picture we call venous occlusion is certainly not one disease. The common entity in this picture is probably blood sludging and diminished blood flow. This can be due to three different factors. First, an interruption in the outflow, that is, some obstruction in the venous system; second, interruption in the blood inflow, that is, an obstruction in the arterial supply which would in turn slow down the venous return; and third, an intravascular disease such as

sickle-cell anemia or macroglobulinemia which would also cause blood sludging. It is certainly possible that two of these factors may be present at the same time. Leber pointed out in 1915 that the common factor in many venous diseases is slowing of the rate of blood flow through the eye.

The second point is why does the ophthalmoscopic picture of arterial occlusion vary? I think one can postulate that the variations are due to the acuteness of the arterial occlusion. If one gets a sudden closure of the central retinal artery, then the typical picture of edema of the retina, cherry-red spot and collapsed arterioles, results. However, if the arterial occlusion is a very slow and gradual one persisting over some period of time, it is perfectly possible that the initial ophthalmoscopic signs will be those on the venous side giving the picture of venous stasis retinopathy.

DR. THOMAS R. HEDGES, JR. We seem to have come to a realization that our anatomy of the venous outflow of the eye has never been clearly understood. We have always assumed that the central retinal vein carried the blood out. The arterial supply has always been well outlined. What we need is a greater appreciation not only of the species difference in our experimental animals but how much collateralization there is between the prelaminar area and the retrolaminar areas through other channels than the central vein.

DR. VICTOR T. CURTIN. I wish to thank the discussers for their comments.

Dr. Wise has had more opportunity to study the paper and think about it than I have had to answer some of his questions. I guess when we do an experiment we solve some problems and perhaps create more.

In the paper I did not mean to indicate that there was no component of arterial insufficiency in the human central retinal vein occlusion. My main point is that even if there is arterial insufficiency—and there probably is because most of these patients are older and have vascular changes in their vessels—still the precipitating event is partial or total obstruction on the venous side.

I agree with Dr. Wise about longitudinal sections *versus* cross sections of the optic nerve, but in this experiment we did not do cross sections through the optic nerve.

The owl monkey's eye circulation is comparable to that of the rhesus monkey. Although they may not be exactly the same, our experimental results closely simulate those of Hayreh. The interpretation is different. In clinical cases of central retinal vein occlusion when there are no macular hemorrhages or vitreous hemorrhage, vision is good. This is contrary to the profound visual loss which occurs with ischemic damage to the retina secondary to arterial occlusion. So I think there is a significant difference between human venous occlusion and what Hayreh produced. His model was more similar to what I produced in the first group with the injection of

neoprene and is a much more severe insult than that seen in human patients with central venous occlusion.

I agree with all that Dr. Kearns said. I think that vein occlusion and carotid artery disease can be difficult to differentiate, but fluorescein angiography and ophthalmodynamometry help. Not having seen Dr. Michaelson's work I do not wish to comment further.

This controversy has been going on for at least eighty years in the literature. Michel in 1878 was the first to correlate the fundus picture with venous disease in the eye and there are still many unresolved questions.

I believe in my excitement that I missed Dr. Hedges' question.

DR. HEDGES. I would like to ask whether you are going to pursue the studies of the anatomy of the venous circulation and what your thoughts are in this regard.

DR. CURTIN. I hope to learn more about the venous circulation as well as the arterial circulation of the eye. Fluorescein angiography is a most helpful adjunct in this study.