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Experimental occlusion of the retinal vein

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Abstract. We used a pars plana approach to experimentally induce retinal vein occlusions (RVO) in cats by the application of electric energy near the veins at the optic nerve head. This experimental model was utilized to study the natural evolution of thrombosis in the cilioretinal veins, which are located near the lamina cribrosa in the cat. We observed that occlusion of the retinal veins occurs by the formation of a thrombus and that with time there is associated endothelial cell proliferation and recanalization in each instance.

Introduction

Central retinal vein occlusion (CRVO) was first described by Michel (1878), who demonstrated a cellular thrombus in the central retinal vein in the eye of a patient. There then followed a controversial series of papers by Coats (1904a, b, 1913) and Verhoeff (1906, 1907). Coats contended that most cases were caused by thrombosis, while Verhoeff was equally sure that the occlusion resulted from either an obliterating endophlebitis or endothelial cell proliferation.

Following Scheerer's 1923 publication and Klien's later reports (1944, 1953), enthusiasts for endothelial cell proliferation seemed to be in ascendancy. In addition, Klien believed that there was no occlusion in some cases of CRVO and that the vein lumen was narrowed by a process referred to as "phlebosclerosis."

In a previous report from our laboratory (Green et al. 1981), we performed a prospective study of 29 eyes with clinical histories or gross findings of CRVO and found that a fresh or recanalized thrombus was formed at or near the lamina cribrosa in each eye. We concluded that there is a natural evolution of an occlusion of the vein, and this includes: thrombosis, recanalization with endothelial cell proliferation, inflammation, organization, and phlebosclerosis.

Our present study was conducted to test the formation and evolution of a thrombus in the cilioretinal vein at the lamina cribrosa, using a modification of the method reported by Becker and Post (1951).

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Materials and methods

Adult cats of both sexes (weighing 3 to 4 kg), were anesthetized with ketamine and acepromazine. The pupil was dilated with 2.5% phenylephrine (Neosynephine) and 1% Cyclogyl. A bipolar coaxial diathermy probe was introduced into the eye through a 20-gauge incision at the pars plana. An indirect ophthalmoscope was then used to direct the tip of the probe through the vitreous until it was near the head of the optic nerve. The tip of the probe was next placed over (but not touching) a branch of the retinal veins near the nerve head. A current was applied which passed between the two elements at the tip of the probe. This current was adjusted to produce a constriction of the retinal vein branch and a whitening of the adjacent retina. A few gas bubbles were occasionally liberated. The probe was then removed from the eye and the incision site was closed by a single, interrupted 7-0 silk suture. Some eyes has a single branch of the retinal vein treated, while others had two or all three vessels treated. Cautery of any branch of the retinal arteries was avoided.

Each eye was examined by indirect ophthalmoscopy, and color fundus photography was taken prior to the vascular occlusion and thereafter for up to 1 month. The temporal histopathology of the eyes was studied at 15 h, 1–2 days, 1–2 weeks, and 1 month after the occlusion. The cilioretinal veins surrounding the optic nerve were traced by studying longitudinal or cross-serial sections, which were variously stained with hematoxylin and eosin, periodic-acid Schiff, Van de Grift, phosphotungstic-acid hematoxylin, and Prussion blue.

Results

Ophthalmoscopic observations

At the end of the procedure, no hemorrhages or exudates were visible in the treated eye. The retinal veins were engorged, and the arteries appeared to be normal or slightly narrow. At 12–14 h after treatment, there was venous engorgement and retinal edema in the peripapillary area. Within 15–24 h, retinal hemorrhages and exudated were noted, as well as markedly dilated and totuous retinal veins. These latter changes began at the disc and extended 1 to 2 disc diameters peripherally (Fig. 1). These features intensified with time, so that by 2–3 days of the occlusion, the fundus showed retinal edema, diffuse hemorrhages, and exudates in the distribution of the dilated veins. Capillary

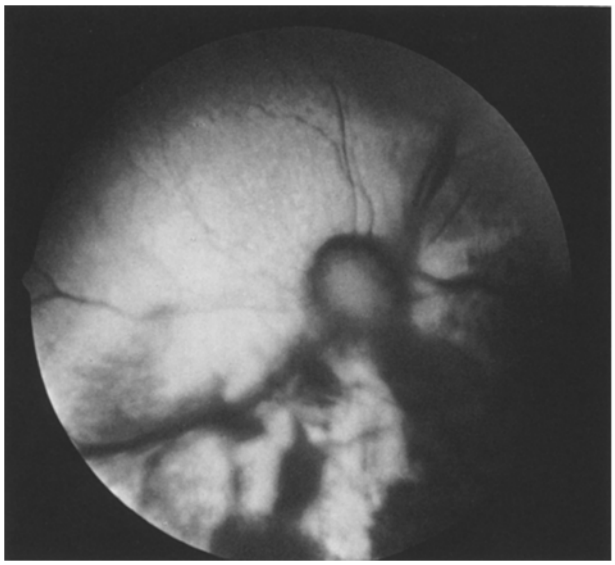

Fig. 1. Appearance of cilioretinal vein occlusion 24 h after treatment, showing retinal hemorrhages along the dilated and tortuous retinal veins

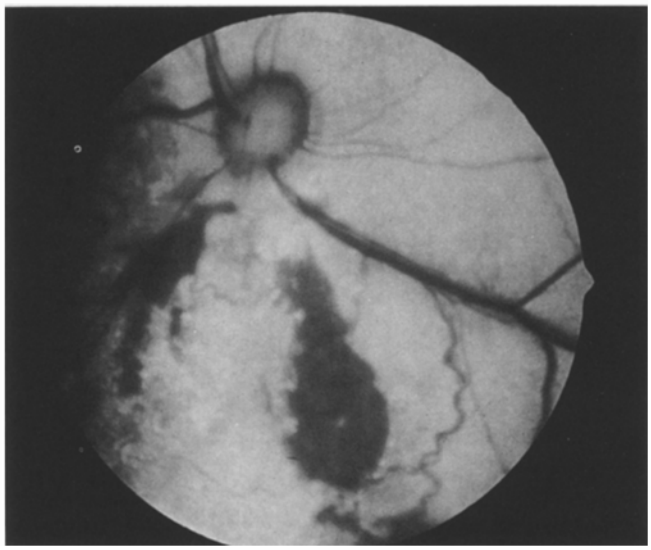

Fig. 3. Retinal hemorrhages and exudates become less intense at 2 weeks after treatment

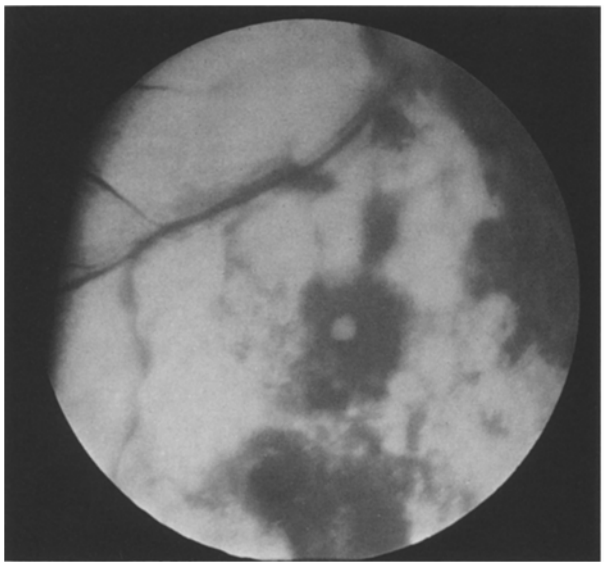

Fig. 2. Retinal hemorrhages and exudates become more marked at 2.5 days after treatment

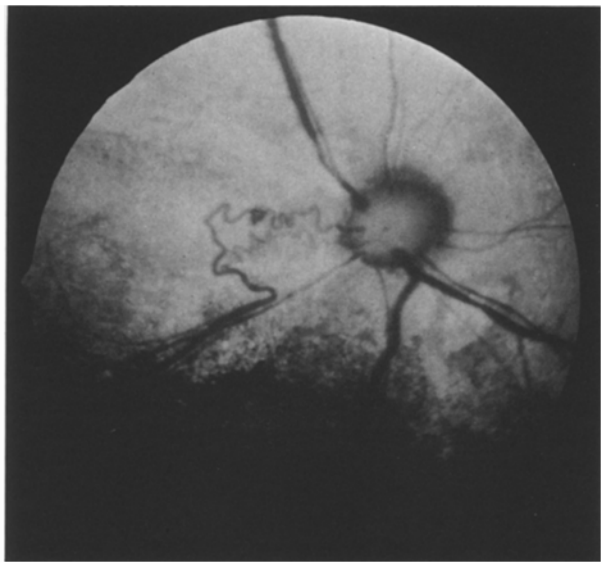

Fig. 4. One month after treatment, there is further clearing of retinal hemorrhages and exudates, and vein-to-vein collaterals can be identified

microaneurisms and occasional hemorrhages into the vitreous were also present (Fig. 2).

Collateral and shunting vessels were visible by 2–3 weeks, with the exudates and hemorrhages present gradually resolving (Fig. 3). One month later, all retinal exudates and hemorrhages had cleared, but with persistence of large collaterals resembling optociliary shunts (Fig. 4).

Histopathologic observations

Sequential histopathologic study of the treated eyes disclosed venous thrombi in various stages of evolution corresponding to the time following treatment.

Fifteen hours after occlusions the retinal veins were markedly engorged and tortuous. A fresh thrombus was located in the lumen of the cilioretinal vein, and was mainly composed of fibrin, with polymorphous neutrophils migrating to the venous wall. The accompanying artery was patent (Fig. 5).

One to two days after occlusion, there were numerous round and flame-shaped hemorrhages and exudates in the posterior pole of the retina. Microscopic examination revealed a fresh or early organized thrombus which was composed of fibrin, platelets, and blood cells in the cilioretinal vein at the intrascleral portion of the lamina cribrosa (Fig. 6). The endothelium was absent in most regions where the thrombus was directly adherent to the venous wall.

One to two weeks after occlusion, retinal hemorrhage became intensified. By the end of 3 weeks, the hemorrhages and exudates present started to resolve, and early retinal collaterals were present on gross examination. A recanalized thrombus with small channels, mild-to-moderate en-

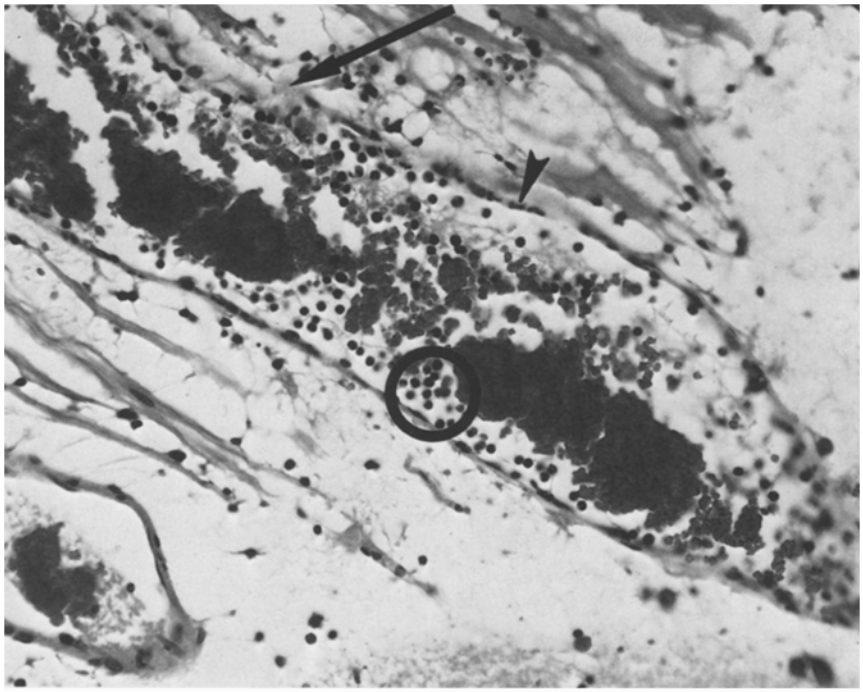

Fig. 5. A fresh thrombus containing platelets, fibrin, and neutrophils (*circle*) is present in a cilioretinal vein just anterior to the lamina cribrosa at 15 h after treatment. The endothelium is discontinuous in areas (*arrow*), occasional neutrophils are present in the wall of the vein (*arrowhead*), and the surrounding area is edematous. (Hematoxylin and eosin; ×275)

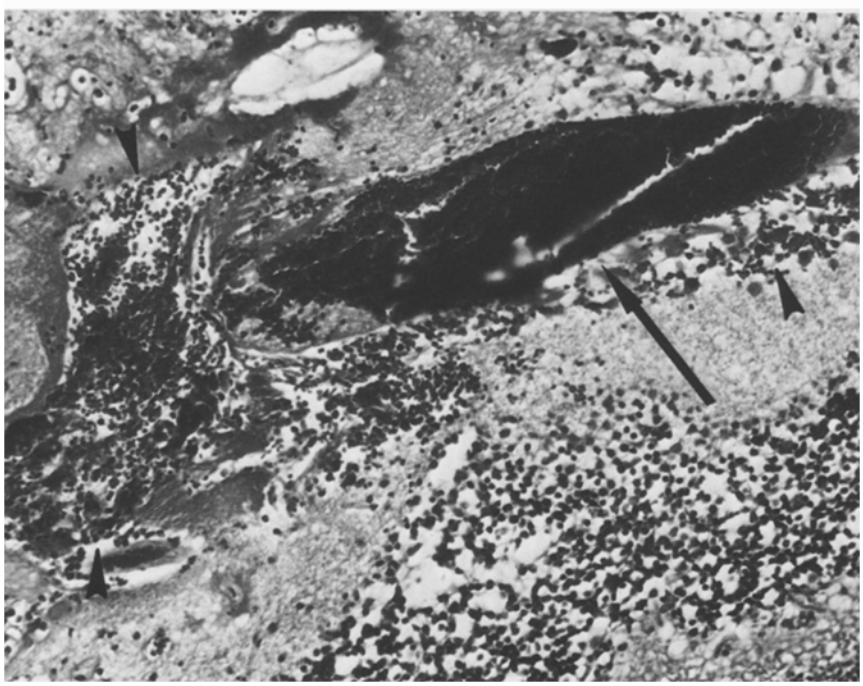

Fig. 6. Thrombus in the dilated prelaminar portion of a cilioretinal vein (*arrow*) at 24 h. Extravasation of blood (*arrowheads*) is present adjacent and proximal to the vein (Van de Grift stain; ×240)

dothelial cell proliferation, and minimal lymphocytic infiltration was demonstrated in the occluded cilioretinal vein (Fig. 7a and b).

One month after the occlusion, only large retinal collateral vessels were seen on gross examination, and all hemorrhages of exudates had resolved. Hemosiderin deposits were identified microscopically in the retina, as were markedly dilated retinal veins near the head of the optic nerve.

Discussion

There have been a number of experimental studies detailing central and branch retinal vein occlusion, but none of these have concentrated on the actual site of the vein's occlusion and the evolution of changes at the point.

Becker and Post (1951) produced retinal vein occlusion in cats by the use of electric cautery and demonstrated a recanalized thrombus in the CRV inside the optic nerve 10 days after occlusion.

Flynn (1966) injected serum thrombotc accelerator (STA) into the external jugular vein of a dog and produced thrombosis in retinal veins and arteries. This led to massive retinal hemorrhage, similar to the ophthalmoscopic picture of CRVO in humans. This experiment, however, also produced extensive thrombosis in many orbital vessels and did not selectively occur in one or more retinal veins.

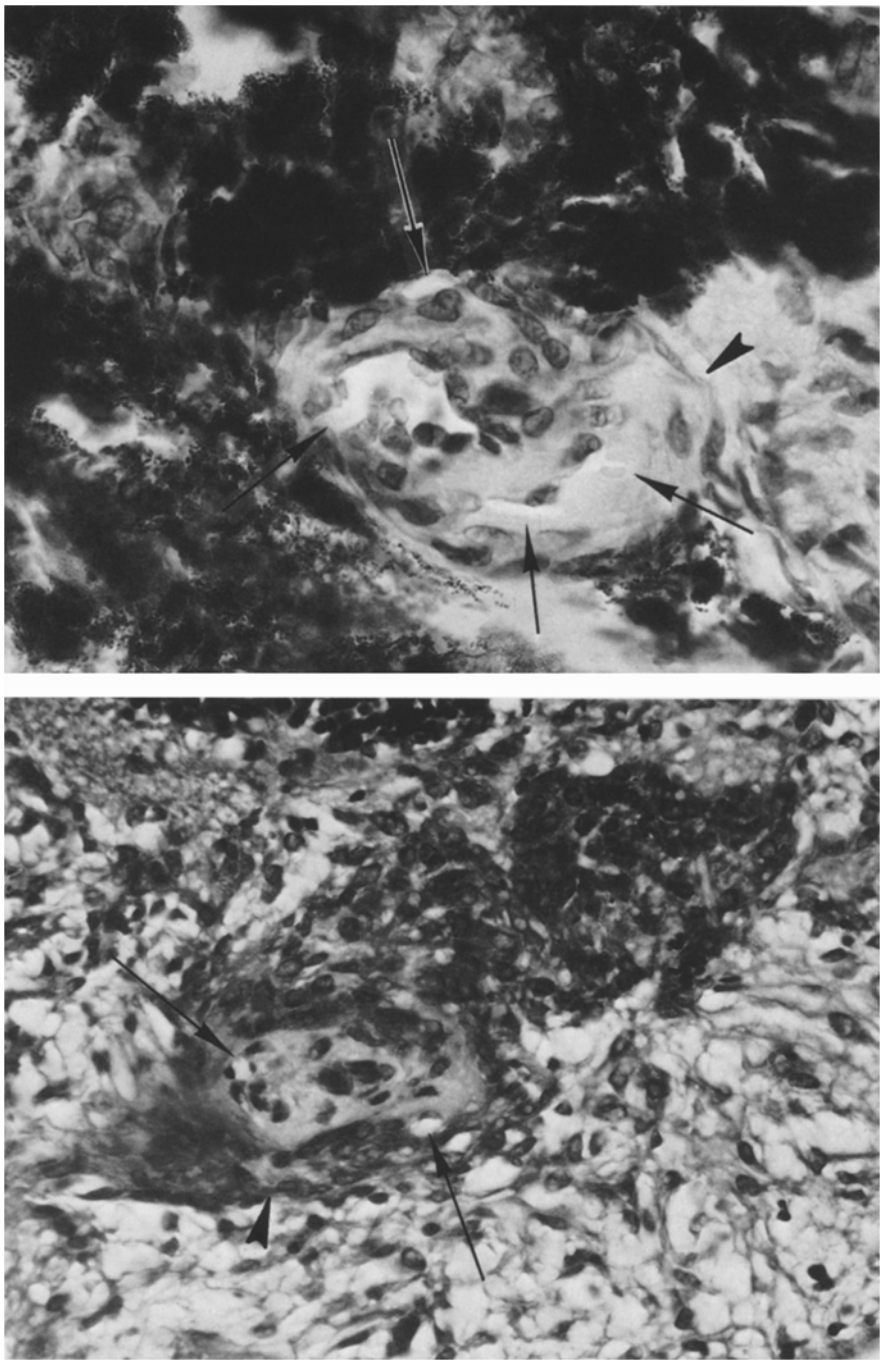

Fig. 7a and b. Two examples of thrombi in the cilioretinal vein (*arrowheads*) just anterior to the lamina cribrosa. There is marked endothelial cell proliferation and several channels of recanalization (*arrows*).
a One week after thrombosis (Hematoxylin and eosin; ×700)
b Two weeks after thrombosis (Phosphotungstic acid-hematoxylin; ×440)

Fujino et al. (1968) occluded the CRV in the monkey by injection of liquid latex into an orbital vein and consequently also occluded the branch retinal veins and the CRV on the optic disc. This caused venous congestion and prompt irreversible stagnation of flow in the central retinal artery to produce an overwhelming ischemic and hemorrhagic retinopathy. The CRA and CRV did not demonstrate pathological changes, although there were retinal hemorrhages and necrosis. However, the authors did note that this experimental model was not a suitable model to simulate the disease in man.

Hayreh (1964, 1965) produced experimental CRVO in the monkey by ligating both the CRV and CRA in the orbit and outside the optic nerve. No detailed histopathologic studies of the CRV and CRA were described in these experiments. Later, he and others acknowledged that the clinicopathologic findings were not entirely identical to those seen in humans with CRVO (McLeod 1975; Hayreh et al. 1978).

Experimental BRVO has been studied microscopically by many investigators (Linner 1961; Okun and Collins 1963; Voipio and Riotta 1964; Mutlu 1966; Kohner et al. 1970; Archer et al. 1976; Hamilton et al. 1979). Histopathological and electron microscopical studies of branch and hemispheric vein occlusion produced in rhesus monkeys by argon laser photocoagulation disclosed a sequence of changes leading to permanent capillary closure (Hockley et al. 1979). Thrombus formation in the capillaries occurred at

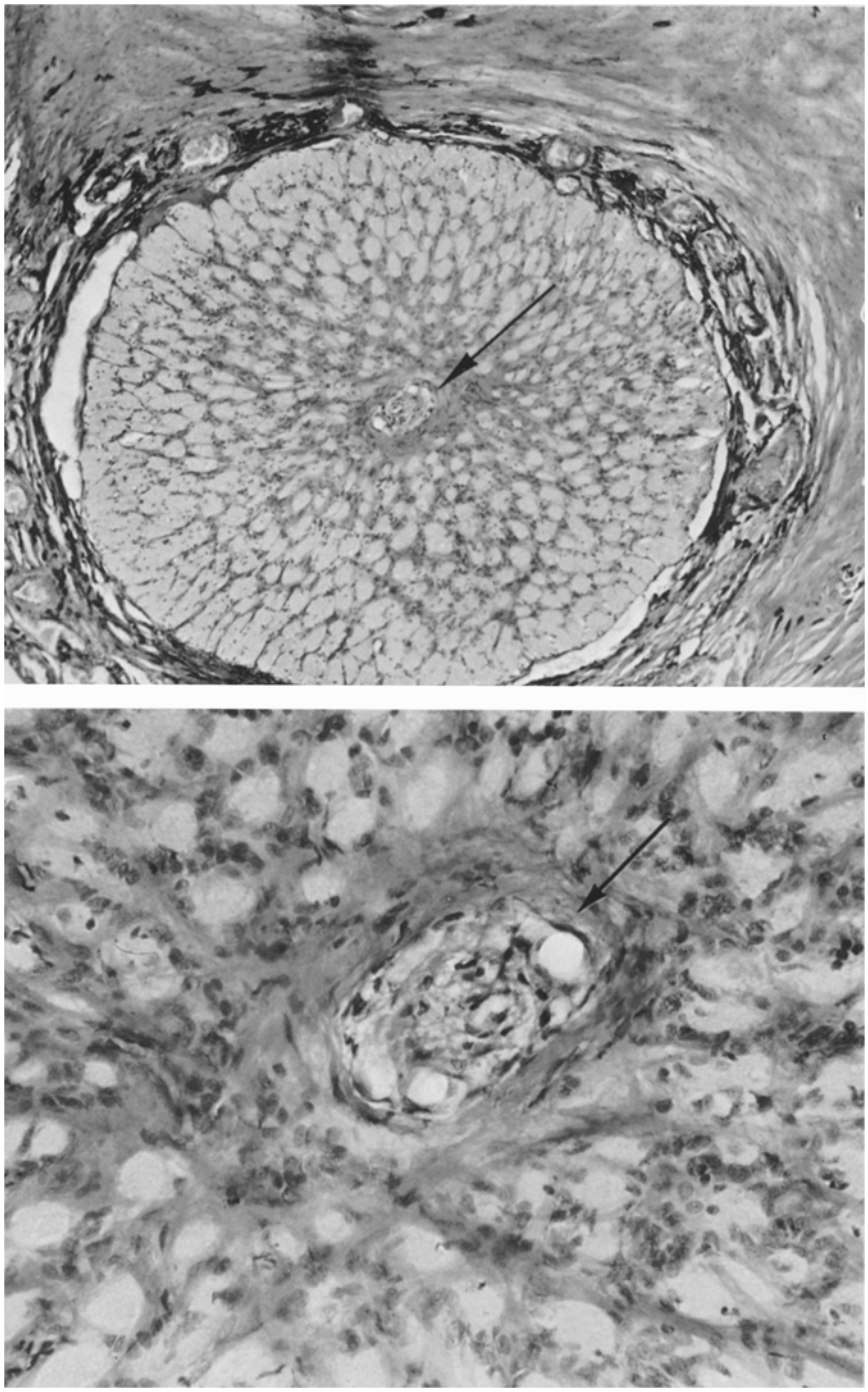

Fig. 8a and b. Cross-section of the retrolaminar portion of the optic nerve of the cat, showing a central fibrocapillary zone (*arrow*) that has a striking resemblance to a recanalized thrombus. (Periodic acid-Schiff stain; **a** ×60; **b** ×255)

about 6 h after laser occlusion of a branch retinal vein. In this latter study, particular attention was given to the changes occurring in the capillaries as a result of venous occlusion. These authors found the damaged vein to be occluded by a fresh thrombus, but this area was not studied temporally, as were the alterations in the affected capillary bed.

Our original intent was to produce CRVO in the cat as a model for further investigations. After preliminary studies (and a study of serial sections of the normal optic nerve head), we concluded that the cat does *not* have a central retinal vein. We also concluded that previous studies may have misinterpreted the central fibrocapillary zone in the retrolaminar portion of the optic nerve as a recanalized thrombus (Becker and Post 1951).

We have found that the internal carotid artery is a vestigial vessel in the cat and no ophthalmic artery or major central retinal artery is present. The blood supply to the eye is derived from several ciliary arteries that enter the eye around the optic nerve and originate from the internal maxillary artery as a major terminal branch of the external carotid artery. The retina is then supplied by the terminal posterior ciliary branches of a ciliary artery. The retinal veins drain into the ciliary system (Davis and Story 1943; Daniel et al. 1953). In other respects, however, the cat retina does resemble the human retina: that is, the entire inner

retina receives its blood supply directly from the retinal vessels. The normal fundus of the cat also shows 3–4 major venous trunks and 3–6 arrterial vessels at the optic disc (Duke-Elder 1958; Campbell 1961). The fibrocapillary zone in the central optic nerve of the cat, which represents a vestige of the CRA, has a striking resemblance to a recanalized thrombus (Fig. 8a and b).

As we have shown, organization and recanalization of a retinal thrombus can be demonstrated by temporal studies in our experimental model. This reproducible model substantiates the observations of the natural evolution of a thrombus in CRVO (Green et al. 1981) and branch retinal vein (Frangieh et al. 1982) in human eyes. This evolution includes a fresh thrombus, endothelial cell proliferation and – finally – recanalization.

References

Archer DE, Ernest JT, Maguire CJF (1976) Experimental branch vein obstruction. In: Cant JS (ed) Vision and circulation (Proceedings of the Third William Mackenzie Symposium 1974), Klimpton, London, pp 226–242

Becker B, Post LT Jr (1951) Retinal vein occlusion. Am J Ophthalmol 34:677–686

Campbell FP (1961) The eye of the cat in ophthalmic research. Arch Ophthalmol 65:11–15

Coats G (1904a) A case of thrombus of the central vein pathologically examined. Trans Ophthalmol Soc UK 24:161–173

Coats G (1904b) Thrombosis of the central vein of the retina. Roy London Ophthalmol Hosp Rep 16:62–122

Coats G (1913) Der Verschluss der Zentralvene der Retina. Eine Übersicht über pathologisch-anatomisch untersuchte Fälle. Graefe's Arch Clin Exp Ophthalmol 86:386–393

Daniel PM, Dawes DK, Prichard MML (1953) Studies of the carotid rete and its association arteries. R Soc London Philos Trans B 237:173–237

Davis D, Story HE (1943) Carotid circulation in the domestic cat. Field Mus Nat Hist Zool Serv 28:5–28

Duke-Elder S (1958) The eye in evolution. In: Duke-Elder S (ed) System of ophthalmology, vol I. Kimpton, London, pp 477 and 500

Flynn JT (1966) Experimental retinal thrombosis. Am J Opthalmol 62:944–952

Frangieh GT, Green WR, Barraquer-Somers E, Finkelstein D 619827 Histopathologic study of nine branch retinal cein occlusions. Arch Opthalmol 100:1132–1140

Fujino T, Curtin VT, Norton EWD (1969) Experimental central retinal vein occlusion. A comparison of intraocular and extraocular occlusion. Arch Ophthalmol 81:395–406

Green WR, Chan C, Hutchins GM, Terry JM (1981) Central retinal vein occlusions: A prospective histopathologic study of 29 eyes in 28 cases. Retina 1:27–55

Hamilton AM, Kohner EM, Rosen D, Bird AC, Dollery CT (1979) Experimental retinal branch vein occlusion in rhesus monkeys. I. Clinical appearance. Br J Ophthalmol 63:377–387

Hayreh SS (1964) An experimental study of central retinal vein occlusion. Trans Opthalmol Soc UK 84:586–593

Hayreh SS (1965) Occlusion of the central retinal vessels. Br J Ophthalmol 49:626–645

Hayreh SS, van Heuven WAJ, Hayreh MS (1978) Experimental retinal vascular occlusion. Arch Ophthalmol 96:311–323

Hockley DJ, Tripathi RC, Ashton N (1979) Experimental retinal branch vein occlusion in rhesus monkeys. III. Histopathological and electron microscopical studies. Br J Opthalmol 63:393–411

Klien BA (1944) Obstruction of the central retinal vein: a clinical-histopathological analysis. Am J Opthalmol 27:1339–1354

Klien BA (1953) Occlusion of the central retinal vein: clinical importance of certain histopathologic observations. Am J Ophthalmol 36:316–324

Kohner EM, Dollery CT, Shakib M, Henkind P, Paterson JW, de Oliveira LNF, Bulpit CJ (1970) Experimental retinal branch vein occlusion. Am J Ophthalmol 69:778–825

Linner E (1961) Occlusion of the retinal veins in rabbits induced by light coagulation. Acta Ophthalmol (Copenh) 62:282–286

McLeod D (1975) Cilio-retinal arterial circulation in central retinal vein occlusion. Br J Ophthalmol 59:486–492

Michel J (1878) Die spontane Thrombose der Vene Centralis des Opticus. Graefe's Arch Clin Exp Ophthalmol 24:37–70

Mutlu F (1966) Experimental retinal vein occlusion and treatment with fibrinolysin. Am J Ophthalmol 80:591–601

Okun E, Collins EM (1963) Histology of experimental photocoagulation in the dog eye, part III. Microaneurysm formation following branch vein occlusion. Am J Ophthalmol 56:40–45

Scheerer R (1923) Zur pathologischen Anatomie der Netzhautzentralgefäße bei der sog: Thrombose der Zentralvene und Embolie der Zentralarterie mit besonderer Berücksichtigung ihrer Beziehungen zu anderweitigen Veränderungen am Sehnervenkopf bei Glaukom und verwandten Zuständen. Graefe's Arch Clin Exp Opthalmol 112:206–233

Verhoeff FH (1906) Obstruction of the central retinal vein. Ophthalmol Rev 25:353–357

Verhoeff FH (1907) Obstruction of the central retinal vein. Arch Ophthalmol 36:1–36

Voipio H, Riotta C (1964) Branch vein occlusion by photocoagulation in the rabbit eye. Acta Ophthalmol (Copenh) 42:544–549

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