International Ophthalmology **13**: 269–279, 1989.

Diabetic choroidal and iris vasculature scanning electron microscopy findings

Andrzej W. Fryczkowski[1], Barton L. Hodes[2] & Jonathan Walker[1]
[1] *Department of Ophthalmology, The Ohio State University, Columbus, Ohio; and:* [2] *Department of Ophthalmology, The University of Arizona, Tucson, Arizona, USA*

Accepted 10 May 1989

Key words: choroid, diabetic mellitus, vasculopathy

Abstract

Scanning Electron Microscopy (SEM) was used to study vascular casts of twenty-four autopsy eyes taken from patients with long-standing insulin-dependent Diabetes Mellitus. These casts were compared to casts of ten 'normal' autopsy eyes from patients without a history of diabetes or other vascular disease. The SEM findings in the choroidal vessels of the diabetic eyes included: increased tortuosity, focal vascular dilations and narrowings, hypercellularity, vascular loops and microaneurysm formation, 'drop-out' of choriocapillaries, and sinus-like structure formation between choroidal lobules in the equatorial area. In the iris, neovascularization was evident in the vascular casts in cases with clinically recognized rubeosis iridis. These findings indicate that there is significant involvement of the uveal tract in diabetic eyes. The present study strongly supports the Hidayat and Fine light microscopic observation that the diabetic choroid demonstrates significant vascular changes (e.g. narrowed vessels with possible 'drop-out' of capillaries and neovascularization). Changes in the diabetic choroid, especially in the choriocapillaris, may be a contributing factor in diabetic retinopathy, resulting in decreased oxygenation of the outer layer of the retina. Short reviews and updated information of diabetic eye disease provide some additional insights into the vascular problems in the eye.

Introduction

So far only a few authors have presented studies on the choroidal changes in long-standing Type I diabetes mellitus [3, 12, 14–16, 19, 20, 28, 37, 46]. However, this neglected topic could be important in understanding the development of diabetic retinopathy. The present study focused on the changes in the choroidal vasculature and its relationship to changes in the retina in diabetes.

Materials and methods

Twenty-four autopsy eyes from patients with long-standing Type I diabetes (8–35 years duration) were examined and compared with ten autopsy eyes from control subjects who had neither a history of diabetes nor any clinically evident vascular disease. All tissue was relatively fresh, having been obtained from 2 to 12 hours post-mortem. Cannulation and injection of the ophthalmic artery was performed using Batson's mixture with Sevriton, and the vascular casts were then prepared according to a previously described modified technique [15, 16]. The casts of the choroidal and iris vasculature were then studied using an Autoscan model S-570 Scanning Electron Microscope. After general observation under SEM, the specimens were frozen and dissected. Carefully labeled pieces of

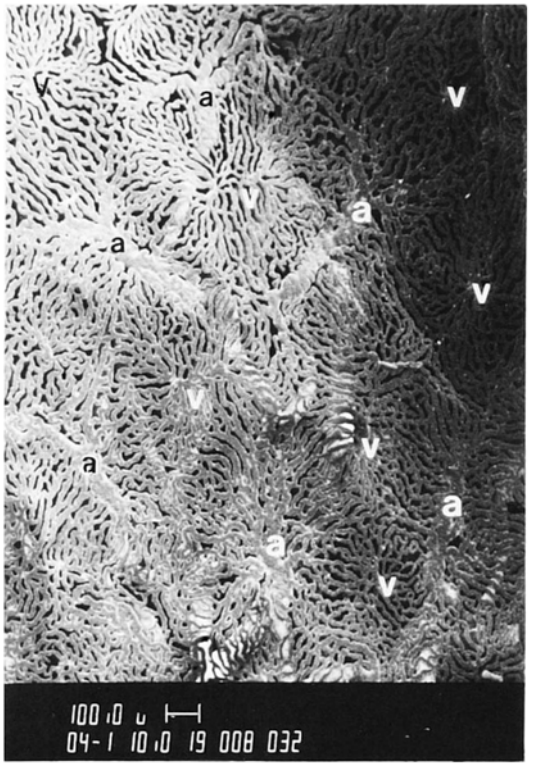

Fig. 1. SEM Photomicrograph. A 55-year old female. Anterior (retinal view). Regular lobular pattern in the choriocapillaris of the posterior pole. Metarteriole (a). Venule (v). SEM × 91.

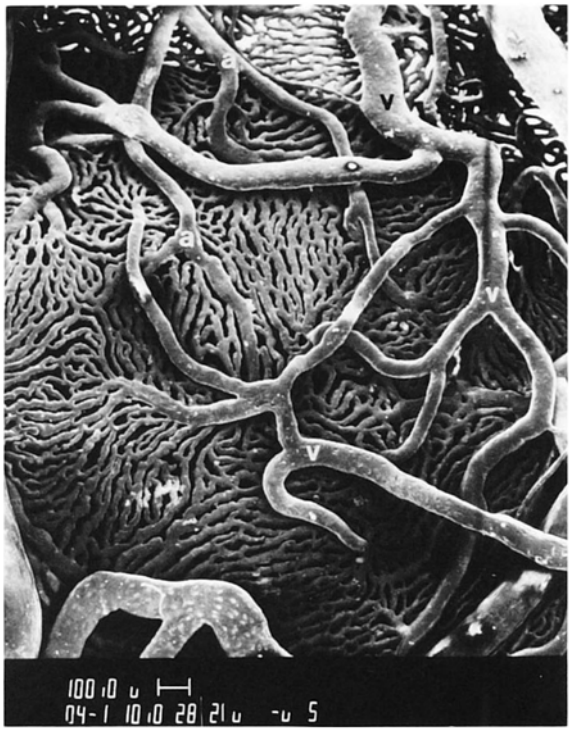

Fig. 2. Same case as in Fig. 1. Choriocapillaris. Posterior (scleral) view. Posterior pole. Distribution of the venules (v) and arterioles (a) is clearly seen. SEM × 98.

the choroid and retina were separately mounted on the scanning stub and recoated with gold and palladium: All areas were examined with SEM from anterior (retinal) and posterior (scleral) views. Photomicrographs were taken of significant areas of the choroidal and iris vasculature. The photomicrographs were then extensively studied and compared to detect any anatomic differences between the diabetic and control eyes. Efforts were taken to localize choroidal changes and compare them to those which were seen 'in vivo' in the retina and iris.

Results

Part I. The normal choroid

The normal SEM images of vascular casts of the human choroid were recently brought to the attention of ophthalmologists (Yoneya et al.) [49, 50]. In this monograph, we shall provide several SEM photomicrographs to show the normal appearance of the architecture of the choriocapillaris and iris. Figures 1 through 4 and 13 of the normal choroid and iris are from the controls; the details of these are reported in the legends. Of particular importance in interpreting the casts is the fact that one can differentiate the arterial from venous channels by proper identification of endothelial cell impressions in the casts. In addition, when viewing the choroid from the anterior (retinal) side of the choriocapillaris, it is possible to recognize and localize the feeding arterioles and collecting venules.

The findings in the SEM vascular cast studies of the normal choroid have demonstrated several significant points.

1. In the submacular area of the choroid, there is a dense vascular network having a large number of interconnections with the choriocapillaris. In

Fig. 3. A 20-year old male. Choriocapillaris. Anterior view. Note the round, smooth vascular dilations located between the peripheral portion of two lobules (asterix). Note juxtaposed double annular filling defects (constrictions?) which suggest the possibility of sphincters (open arrow). SEM × 154.

this area, the feeding arterioles and the collecting venules are found outside the choriocapillaris monolayer when viewed from scleral side. In addition, there are more arteriolar openings than venular openings in this area.

2. In the posterior pole outside of the submacular zone extending to the equatorial area, a lobular appearance of the choriocapillaris can be seen. The number of the choriocapillaris interconnections markedly decreases giving them a less reticulated appearance and allows some of the feeding arterioles and collecting venules to be found in the plane of the choriocapillaris. The balance of the feeding arterioles and collecting venules in the plane of the choriocapillaris have a branching type of appearance and this combined with the focal type of openings 90° to the choriocapillaris gives this area its lobular structure. Unlike the submacular area, the actual number of venular openings increases and outnumber the arteriolar openings.
3. Between the lobuli of the equatorial choriocapillaris of the choroid, we found dilated vascular structures with annular constrictions on their border which could be sphincters. We refer to these as 'interlobular vascular dilatations'.
4. The peripheral choriocapillaris assumes a more simple and elongated pattern which allows easier identification of the arteriolar and venular sides.

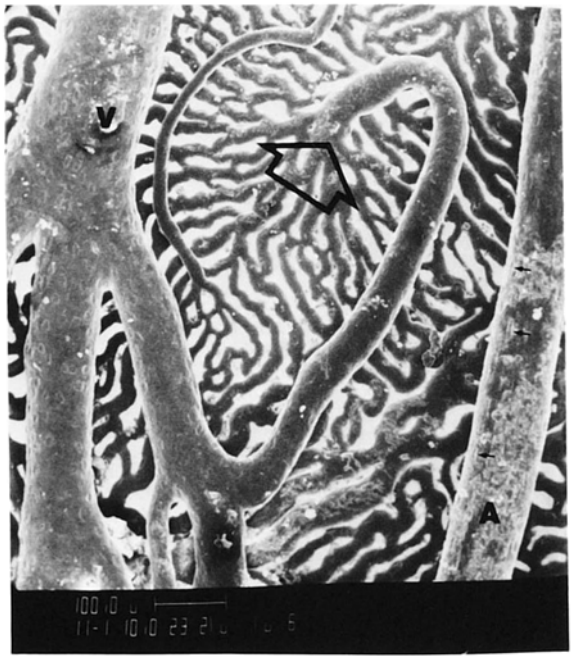

Fig. 4. A 60-year old male. Posterior view of the choroid. Equatorial area. Vortex vein (V). Venular openings in the plane of the choriocapillaris (open arrow). Artery (A) have spindle shape endothelial cell nuclear indentations (small arrows) which differ from round or oval shape veins indentations. SEM × 273.

Part II. The diabetic choroid

The diabetic choroid in all cases showed characteristic changes. The degree of the vascular involvement correlated very closely with the duration and severity of the disease. Early changes in the peripheral choriocapillaris were seen in patients with Type I diabetes of only 8 to 9 years duration. These

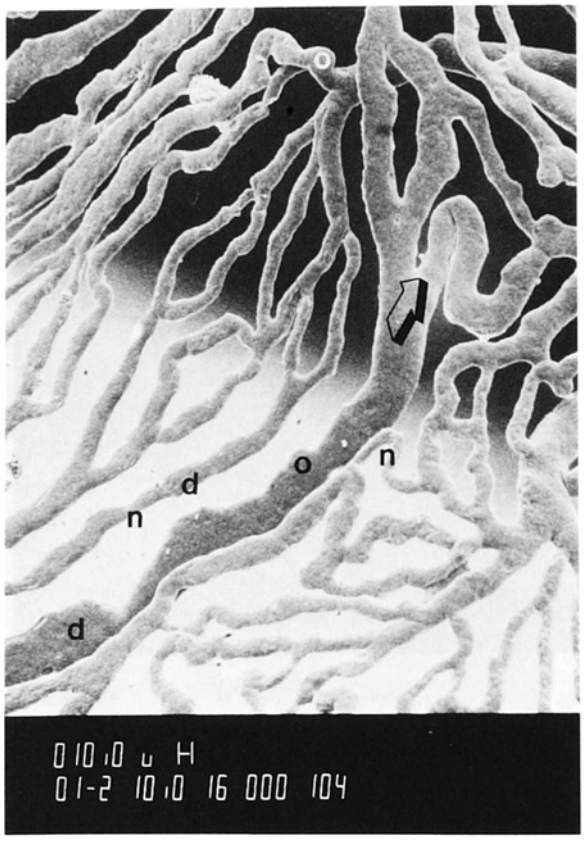

Fig. 5. A 67-year old female. Diabetic Type I of 15 years' duration. Choriocapillaris, midperipheral area. Anterior view. Dilations (d), narrowing (n), outpouching (o) of the vessels. Vascular loop (arrow). SEM × 221.

include: tortuosity of the choriocapillaries, dilatations and narrowings of the vascular lumens and deformation of the normal interlobular vascular structures.

These changes were most marked in the area between the equator and ora serrata in the temporal aspect of the choroid.

A significant increase of the tortuosity in the vessels with simultaneous appearance of dilation in one vessel and narrowing in another in the equatorial and peripheral choriocapillaris occurred as the duration of diabetes increased. In the late stages of the disease, frequent formations of vascular loops and microaneurysms in the midperipheral choriocapillaris can be observed along with an increased number of endothelial cell nucleus indentations on the venous side of the choroidal circulation. The normal appearance of the vessels and number of endothelial cell indentations has been discussed elsewhere [17] (Fig. 5–10).

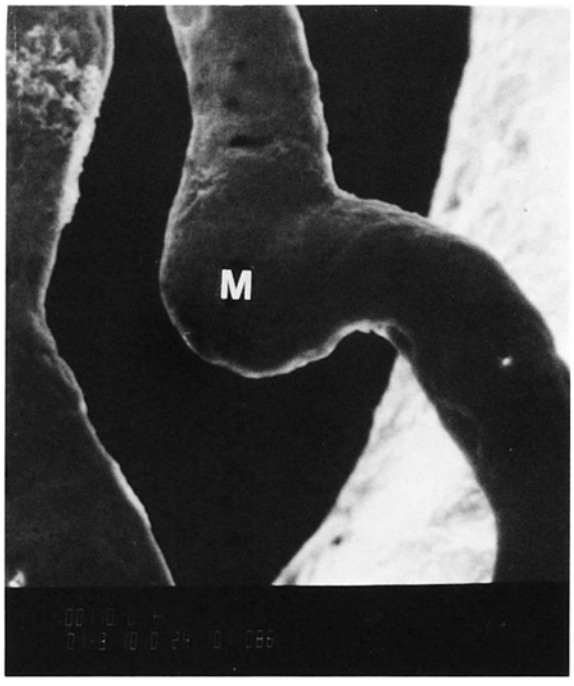

Fig. 6. Same case as in Fig. 5. Choroidal microaneurysm (M). SEM × 429.

Significant changes occurred in the interlobular vascular dilatations which are located in the equatorial area. The normal biannular constrictions which are suggestive of sphincter-like regulatory structures are lost and the formation of marked dilatations up to 150 × 90 μm in size were noted (Fig. 11).

When viewing from the scleral side, one can observe marked dilatation of one vessel and narrowing of others beside it in the second layer of the choroid. Increased tortuosity, vascular outpouchings, and microaneurysm formation can be also observed in the choriocapillaris in the equatorial area, particularly when viewed from the scleral side.

In the peripapillary area, 'drop-out' of choriocapillaris along with choroidal venule and collector vein changes (dilatation and narrowing), tortuosity, outpouching, and hypercellularity significantly increased. One of our cases presented an unusual

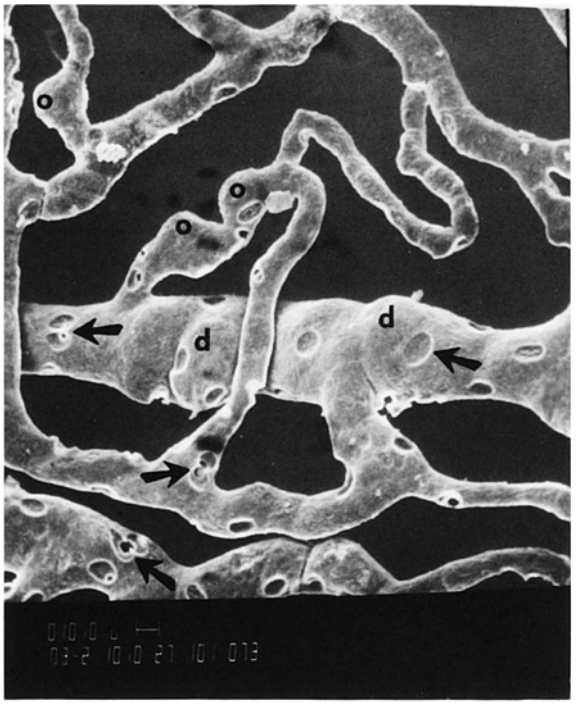

Fig. 7. A 67-year old female. Diabetes Type I of 18 years' duration. Choriocapillaris from the midperiphery. View from the retinal side shows an increased number of venous endothelial cell indentations (arrow). Dilations (d). Outpouchings (o). SEM × 286.

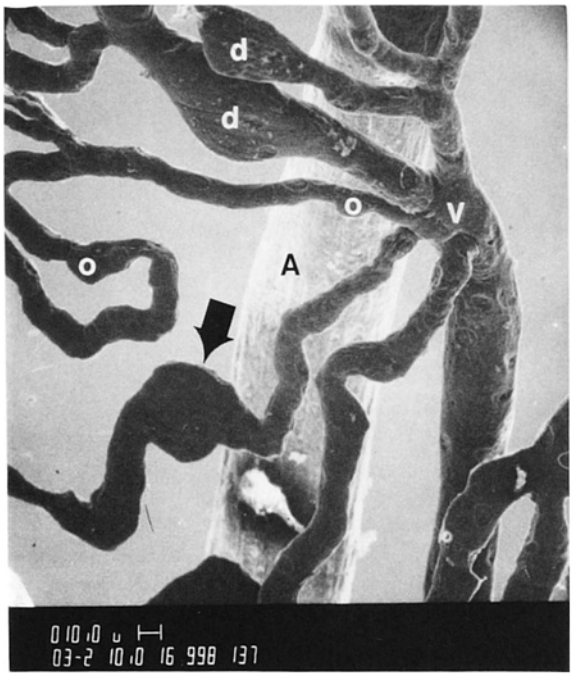

Fig. 8. Same case as in Fig. 7. Choriocapillaris, midperiphery. Anterior views show dilations (d), outpouchings (o), and microaneurysm (arrow). Vein (V). Artery (A). SEM × 429.

course of the retinal capillaries in the peripheral area which is shown on Fig. 12. We are unable to tell if this is a retinochoroidal vascular anomaly or whether this represents a pathological change due to diabetes.

Changes in the iris include significant focal dilatations and narrowings of the venous vasculature and neovascularization (Fig. 14).

The major localization of these changes in the iris vasculature were seen in the superficial and the peripheral iris. These were the areas with clinically observed rubeosis iridis.

Discussion

In the past quarter of a century, enormous effort has been made to clarify the pathogenesis of diabetic retinopathy [1, 5, 8, 9, 11, 13, 21, 25, 40, 46, 47]. Studies of the choroidal changes in diabetes, however, have been few in number during this time period [3, 14, 19, 31, 37, 46]. Based upon our observations and observations of others, it is our feeling that the changes in the diabetic choroid may be as significant in the pathogenesis of diabetic eye disease as the much more familiar retinal vascular changes. The proper functioning of the choriocapillaries is crucial for the metabolism of the photoreceptor – retinal pigment epithelium – Bruch's membrane interface, and it seems possible that any deterioration of choroidal function will adversely affect this important anatomic complex.

Despite all the known objections to injection studies, coated vascular casts are the only presently known technique that allows three-dimensional studies of vascular integration and continuity. Vascular casts allow an overall view of large areas and can also demonstrate fine details and focal vascular changes on high magnification. Vascular casts represent replicas of blood flow and the endothelial cells of vessel walls are seen as filling defects (indentations) when the vascular wall itself is digested. There are significant differences between arte-

Fig. 9. A 62-year old female. Diabetes Type I of 25 years' duration. Choroid, equatorial area. Posterior view. Tortuosity, outpouchings (o), dilations (d), and narrowings (n) of the choriocapillaris located below the vortex vein (V). Drop-out of capillaris is marked. Artifacts (X). SEM × 288.

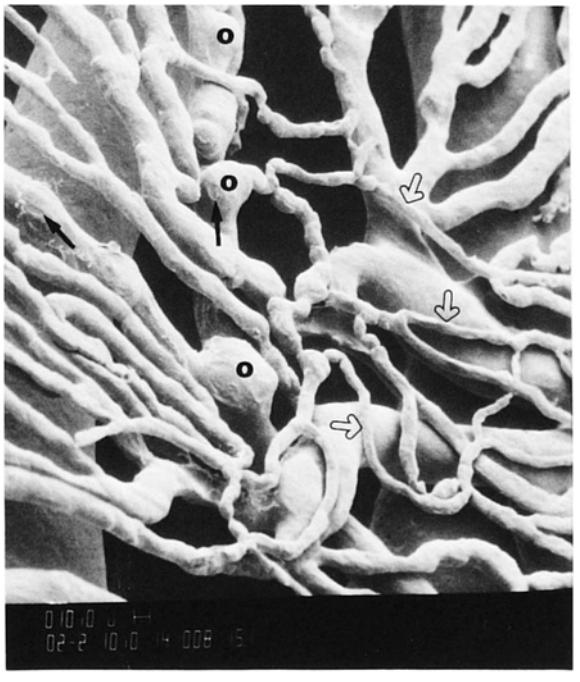

Fig. 10. A 68-year old female. Diabetes Type I of 25 years' duration. Choroid, mid-periphery. Anterior view. Significant narrowing of the choriocapillaris (open arrows) and outpouchings (o) of the larger vessels. The venous character of this vessel is indicated by endothelial cell indentations (solid arrows). SEM × 312.

rial (spindle-shaped) and venous (oval or round) endothelial nuclear cells indentations. This differentiation is essential to recognize vessels down to the capillary level. This also is important in discussing any focal involvement of the ocular vasculature in disease states. Also, occluded vessels which 'in vivo' were eliminated from the blood flow because of vascular constrictions will be filled postmortem by plastic. Injection pressure variations can cause artifacts; with Batson's mixture, this occurs only infrequently.

The objections and disadvantages of the injection study are understandable, so only positive findings from the SEM three-dimensional images are considered significant.

The vascular changes in long-standing diabetes are most interesting. These changes include: increased vascular tortuosity, focal vascular dilatations and narrowings, vascular outpouchings, vascular loop and microaneurysm formation, capillary drop-out, and sinus-like structure formation. These were found in the choroid of all diabetics studied and were not observed in any of the 'normal' control group. In addition to the choroidal findings, in three of our cases a neovascular net was observed in the retinal vessels. Significant focal narrowing of some vessels seen in the present study supports the findings of Hidayat and Fine [20] and others [3, 31, 37]. All recorded choroidal vascular changes in diabetes were found at the equatorial and midperipheral areas, and were localized more peripheral to those changes which were found in the retinal vessels. In cases of long-standing diabetes, significant dilation of one vessel and narrowing of another adjacent vessel was found in the equatorial and midperipheral areas. The regular, spindle-shaped interlobular vascular dilations of

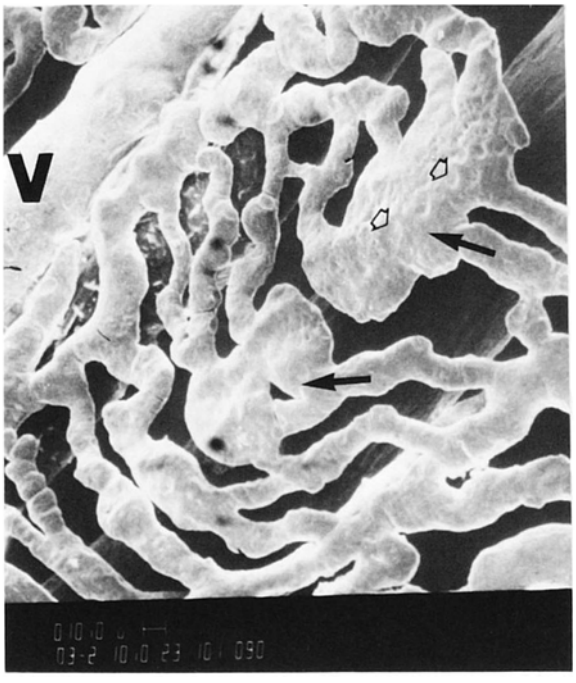

Fig. 11. Same case as in Fig. 10. Number of endothelial cell nuclear indentation (open arrows). Vein (V). SEM × 910.

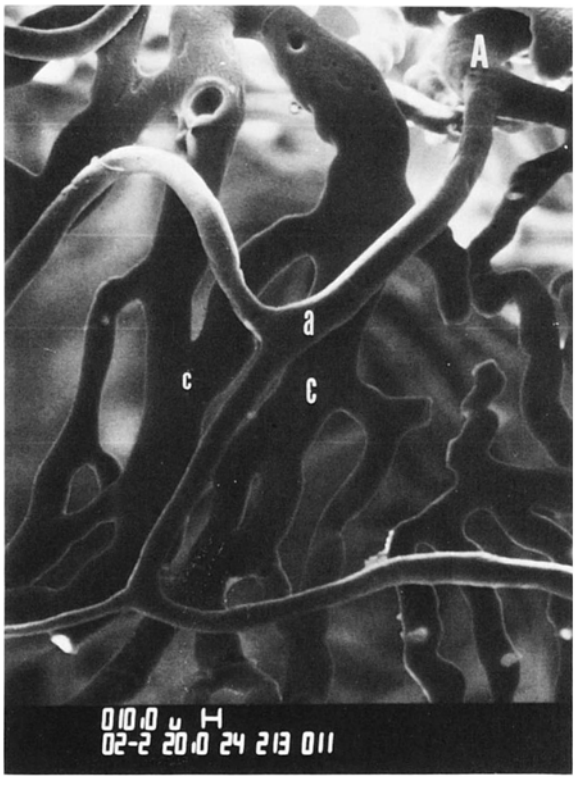

Fig. 12. A 70-year old female. Diabetes Type I of 33 years' duration. Midperipheral area. Anterior view. Retinal capillaris (a) originate from the arteriole (A), which is located behind the choriocapillaris (c). SEM × 288.

the equatorial area, which were observed in normal 'control groups', were seen as sinus-like structures in the diabetic choroid. The role that these sinus-like structures play in the choroidal circulation warrants further investigation.

Several hypotheses have been offered in attempts to understand the etiology and pathogenesis of the diabetic changes in the eye [31]. The vascular stress oxygenation-vasodilatation [11, 40, 47], biochemical, rheological changes [13, 25–27], and finally the angiogenic hypothesis [1, 9, 11, 29] all have been implicated in the pathogenesis of diabetic retinopathy. The consistently identified alterations in the choroid of diabetics suggests that the choroid may have a significant role in the development of diabetic eye disease [3, 14–16, 20, 31, 37]. The vascular changes which have been demonstrated include microaneurysms formation, changes in the course and caliber of larger choroidal vessels, and even choroidal neovascularization. The similarity of these changes to those seen in diabetic retinopathy would seem to be more than coincidental.

These similarities, however, are not surprising given the pervasiveness of the metabolic derangements felt to affect blood vessels in diabetes. On such derangement involves the enzymes aldose reductase which is responsible for the reduction of glucose to sorbitol. Normally, this metabolic pathway is minimal because of the low affinity that this enzyme has for glucose. However, when the glucose concentration is elevated, the production of sorbitol is increased. Because the cell membrane is not as permeable to sorbitol as it is to glucose, the high concentration of sorbitol within the cell creates an osmotic force drawing fluid into the cells thereby interfering with cell function. Although this has been well demonstrated in lens fibers, it has not directly been shown to be the case in endothelial cells [22]. Nevertheless, the fact that aldose reductase inhibitors can prevent the thickening of the retinal capillary basement membrane in diabet-

Fig. 13. A 46-year old male. Without known vascular disease. Ciliary processes (C.P.) and iris. Posterior view. Iris margin (arrows). SEM × 29.25.

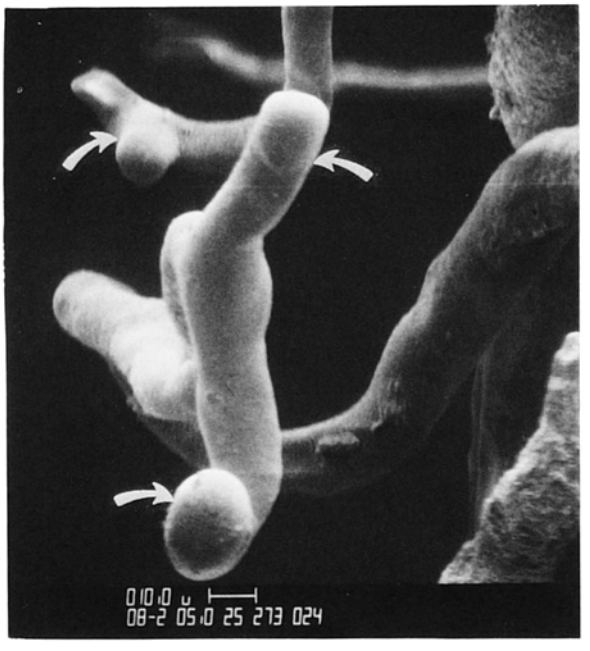

Fig. 14. Same case as in Fig. 9. Peripheral area of the iris. Neovascular fronds (arrows) are seen. SEM × 572.

ic animals implies that this enzyme system does have some effect on endothelial function [34, 35]. It is interesting that the retinal capillary pericytes seem particularly sensitive to this, perhaps resulting in loss of capillary wall support, microaneurysm formation, and possibly even loss of control over endothelial proliferation [7]. It is possible that such a process can also occur in the choroid, although pericytes are ordinarily less common in the choriocapillaris than elsewhere in the retinal circulation [27].

Another factor affecting vessel function is the thickening of the capillary basement membrane mentioned above. This is one of the earliest changes seen in diabetes [39, 47, 48]. Some of this may be due to weakening and incompetence of the endothelial tight junctions with subsequent leakage of plasma proteins into the basement membrane [24]. Other proposed mechanisms include increased basement membrane production from injured and regenerating cells [44] and abnormal regulation of basement production [24]. Direct glycosylation of basement membrane proteins may also be involved, perhaps by altering the biochemical characteristics of the basement membrane [23]. In any event, it seems clear that whatever the cause, such a grossly visible ultrastructural change must indicate aberrant basement membrane function in terms of diffusion and transport of metabolites. This is particularly significant in the choroid where the thickening is seen not only along vessels but within Bruch's membrane, implying a potential disruption of the very important metabolic exchanges going on across this structure [31].

Both hematologic and clotting abnormalities have been reported in diabetes, and these may also play a role in vessel damage. Diabetics have increased platelet adhesiveness [36], increased platelet aggregation [18, 33], increased fibrinogen turnover [6], and abnormalities of prostanglandin metabolism that may predispose toward clotting [2, 30, 32, 43]. Although it is not clear whether these changes are primary or secondary, it does seem likely that the potential to exacerbate endothelial damage would be high in any vascular bed. This is further compounded by various red blood cell changes seen in diabetes that can potentially pro-

duce vascular insult and injury. This includes alterations in erythrocyte physiology such as a decreased ability to release oxygen [10], poor deformability [27, 38], and an increased tendency to aggregate [43].

Systemic hypertension is a well known factor that contributes to microaneurysms development. It is possible that the vascular changes in diabetes (vessel dilation, endothelial injury and different rheological factors) may in turn create local areas of elevated blood pressure that predispose to microaneurysm formation [16].

Another factor that may affect the choroid in particular is the well known diabetic autonomic neuropathy. The choroid is richly innervated by both the sympathetic and parasympathetic system. Animal studies suggest that this choroidal innervation can be affected by diabetes [12], and if such a mechanism is active in humans, it may well imply a loss of vascular tone resulting in dilation and misdirection of blood flow.

Matusaka [28] has shown that a large number of the autonomic nerves to the choroid synapse on perivascular melanocytes and suggested that the choroidal melanocytes may be involved in mass control of the choroidal microcirculation. It would be interesting to investigate whether the autonomic neuropathy in diabetes affects this mechanism as well.

In spite of the fact that no single factor has been shown to be the direct cause of diabetic vasculopathy, it is clear that all of these mechanisms can act to further impair both the anatomy and physiology of the choroid. Even if none of these factors are the primary cause, they would all serve to further compromise choriocapillaris function once damage has begun. This becomes very significant, given the recent evidence that the RPE-photoreceptor region functions is in a milieu with barely sufficient oxygenation in the normal state [41]. The fact that these changes do occur has been well documented both in pathologic studies such as ours and also in clinical studies using fluorescein angiography [14], and even indocyanine green angiography [3]. These have shown definite choroidal changes such as poor filling, dilated vessels, aneurysms and even neovascularization. It is interesting that the regional differences in choriocapillaris structure may make certain areas more vulnerable to these changes than in others. In our study, most of the vascular changes were observed in the peripheral and equatorial regions where the choriocapillaris runs more directly between the arterioles and venules [49, 50]. The lobular pattern seen in the posterior pole was affected less, but the changes that were seen may reflect the involvement of the feeding metarterioles which would then explain the frequent segmental nature of posterior pole choroidal disease [42]. The peripapillary choroid is particularly unique with its end-arterial angioarchitecture. It is possible that this characteristic makes the region especially vulnerable to the vasculopathic factors seen in diabetes, and therefore more likely to develop ischemia. Is this the reason why the disc neovascularization is seen so frequently in proliferative diabetic retinopathy?

In addition to affecting the overall function of the retina in diabetes, the choroidal changes we have seen may be particularly significant when considering the current treatment for proliferative disease. The technique of panretinal photocoagulation is well accepted and is often dramatically effective in causing regression of neovascularization. However, there is still a significant number of cases where it is not effective with neovascularization, hemorrhage and scarring progressing unchecked in these eyes. It may well be that choroidal changes hidden beneath the retina are major factors in such situations. Perhaps what is needed is selective identification and treatment of areas of choroidal hypoperfusion, in addition to the traditional panretinal approach [41]. Alternatively, perhaps overly intense laser damage to a relatively healthy choriocapillaris may shut down vessels, thereby decreasing oxygenation in treated areas and defeating the whole purpose of the procedure.

Such thinking is highly speculative, but it does seem possible that the choroidal changes seen in diabetes are worthy of much more attention than they have traditionally been given. This is particularly true considering the choroid's role as the only support for the most important part of the retina: the photoreceptor – RPE complex. We hope that this work will create a new awareness of

the importance of the choroid in diabetes and encourage further research regarding the physiologic effects of the changes that have been shown.

Future complex investigations including regular histological sections, transmission electron microscopy and SEM vascular casts should be focused on the choroidal vasculature, which may be important in answering unanswered questions in the pathogenesis of diabetic retinopathy. Knowing that the outer retinal layers (up to 130 μm) are oxygenated and nourished from the choriocapillaris [29], it seems reasonable that changes in the choroid and decreased oxygenation to the outer retina and RPE can induce hypoxia, with resultant injury to the pericytes and retinal capillary closure. Thickening of the basement membrane, associated with biochemical and rheological factors, can also contribute to the observed changes in the microvasculature. All of these changes can often be stopped by photocoagulation which increases oxygen tension in the retina by shifting oxygen back from the choroid, and by destroying portions of the photoreceptors/RPE complex (especially mitochondria), thereby decreasing retinal tissue oxygen demands [4, 45]. As long as the balance between retinal tissue oxygen demand and supply are appropriate, the retinal vasculature will not be involved; if this balance fails, recurrence of the vascular pathology can be expected. These speculations will obviously require further study and evaluation.

References

1. Ashton N. Injection of the retinal vascular system in the enucleated eyes in diabetic retinopathy. Br J Ophthal 1950; 34: 38–41.
2. Betteridge CJ, El Tahir KEH, Reckless JPD et al. Platelets from diabetic subjects show diminished sensitivity to prostacyclin. Eur J Clin Invest 1982; 12: 395–8.
3. Bishoff PM, Flower RW. Ten years experience with choroidal angiography using indocyanine green dye: a new routine examination or epilogue? Doc Ophthal 1985; 60: 235–91.
4. Blankenship GW. A Clinical Comparison of Central and Peripheral Argon Laser Panretinal Photocoagulation for Proliferative Diabetic Retinopathy. Ophthalmology 1988; 95: 170–7.
5. Bresnick GH, Davis MD, Myers FL, Venecia G. Clinicopathological correlations in diabetic retinopathy. II. Clinical and histological appearance of retinal capillary microaneurysm. Arch Ophthal 1977; 95: 1215–23.
6. Borrows AW. Beta-thromboglobulin in diabetes: relationship with blood glucose and fibrinopeptide. A Horm Metab Res 1981; 11: 22–5.
7. Buzney SM, MacDonald SG, Gervino NH. Experimental retinal capillary wall: Interaction of endothelial cells and pericytes in vitro. Invest Ophthal Vis Sci (Supplement) 1984; 25: 159.
8. Cogan DG, Touissant D, Kuwabara T. Retinal vascular patterns. IV. Diabetic Retinopathy. Arch Ophthal 1961; 66: 366–78.
9. Cunha-Vaz JA. Pathophysiology of diabetic retinopathy. Br J Ophthal 1978; 62: 351–335.
10. Ditzel J. Affinity hypoxia as a pathogenetic factor of microangiopathy with particular references to diabetic retinopathy. Acta Endocrinol 1980; 238: 39–55.
11. L'Esperance FA Jr, James WA. Diabetic retinopathy. Clinical evaluation and management. St. Louis Toronto London: CV Mosby Co, 1981.
12. Fisher F. Disturbed vascular innervation of the diabetic choroid? International Symposium on the choroid (Procc.) May 11–14. Ittingen 1986; pp. 118–25.
13. Frank RN. On the pathogenesis of diabetic retinopathy. Ophthalmology 1984; 91: 626–34.
14. Freyler H, Prskavec F, Stelzer N. Diabetische choroidopatheine retrospective floureszenzangiographische studie. Klin Mbl Augenheilk 1986; 189: 144–7.
15. Fryczkowski AW, Sato SE. Scanning electron microscopy of the ocular vasculature in diabetic retinopathy. Ophthalmic Forum 1986; 4: 39–50.
16. Fryczkowski AW. Vascular casting and scanning electron microscopy in diabetes. Scanning Microscopy 1987; 1: 811–6.
17. Fryczkowski AW, Sherman MD. Angioarchitecture of the human submacular choroid. Acta Anatomica 1988; 132: 165–9.
18. Heath H, Bridgen WD, Canever JV et al. Platelet adhesiveness and aggregation in relation to diabetic retinopathy. Diabetologica 1971; 7: 308–15.
19. Hidayat AA, Fine BS. Diabetic choroidopathy. Invest Ophth Vis Sci (suppl) 1983; 24: 247.
20. Hidayat AA, Fine BS. Diabetic choroidopathy. Light and electron microscopic observations of seven cases. Ophthalmology 1985; 92: 512–22.
21. Hogan MJ, Alvarado JA, Weddel JE. Histology of the human eye. WB Saunders, Co, Philadelhia, London, Toronto, 1971.
22. Kinoshita JH. Aldose reductase in the diabetic eye. XLIII Edward Jackson memorial lecture. Am J Ophthal 1986; 102: 685–92.
23. Kohn RR, Schnider SL. Glucosylation of human collagen. Diabetes 1982; 31: 47–51.
24. Landrum AC. The hypertension diabetic kidney as a model of so-called collagen disease. Can Med Assoc J 1964; 88: 442–52.

25. Little HL. Alterations in blood elements in the pathogenesis of diabetic retinopathy. Ophthalmology 1981; 88: 647–54.
26. Little HL, Pathogenesis. In: L'Esperance FA, James WA, eds. Diabetic retinopathy: Clinical evaluation and management. St. Louis: Mosby, 1981: 74–5.
27. Little HL. The role of abnormal blood rheology in the pathogenesis of diabetic retinopathy. Am Ophthal Diabetologia 1973; 9: 20–4.
28. Matusaka T. The role of melanocytes in the choroidal circulation. International symposium on the choroid (Proceed) Ittingen, May 11–14, 1986; pp. 36–9.
29. Michealson IC. The mode of development of the vascular system of the retina with some observations on its significance for certain retinal diseases. Tr Ophthal Soc UK 1948; 78: 137–80.
30. Morita I, Takahashi R, Ito H, et al. Increased arachidonic acid content in platelet phospholipids from diabetic patients. Prostaglandins. Leukotrienes Med 1983; 11: 33–41.
31. Nauman GOH, Uvea. In: Nauman GOH (ed). Pathologie des Auges. Berlin, Springer-Verlag 1980; pp. 408–500.
32. Onodera H, Hirata T, Sugawara H, et al. Platelet sensitivity to adenosine diphosphate and to prostacyclin in diabetic patients. Tohoku J Exp Med 1982; 137: 423–8.
33. Paulsen EP, McClung NM, Sabio H. Some characteristics of spontaneous platelet aggregation in young insulin-dependent subjects. Horm Metab Res (Suppl) 1981; 11: 15–21.
34. Robinson WG Jr, Kador PF and Kinoshita JH. Retinal capillaries. Basement membrane thickening by galactosemia prevented with aldose reductase inhibitor. Science 1983; 211: 1117–21.
35. Robinson WG Jr, Kador PF, Akagi Y, Kinoshita JH, Gonzalez R, Dvornik D. Prevention of basement membrane thickening in retinal capillaries by a novel inhibitor of aldose reductase, tolrestat. Diabetes 1986; 35: 295–9.
36. Rosove MH, Frank HJL, Harwig SSL. Plasma betathromboglobulin, platelet factor 4, fibrinopeptide 4, and other hemostatic functions during improved short-term glycemic control in diabetes mellitus. Diabetes Care 1984; 7: 174–9.
37. Saracco JB, Gastand P, Ridings B, Ubawd CA. La choroidopathie diabetique. J Fr Ophthal 1982; 5: 231–6.
38. Schmid-Schonbein H, Volger E. Red-cell aggregation and red-cell deformability in diabetes. Diabetes 1976; 25: 897–902.
39. Siperstein MD, Unger RH, Madison LL. Studies of muscle capillary basement membranes in normal subjects, diabetic and prediabetic patients. J Clin Invest 1968; 47: 1973–99.
40. Stefansson E, Landers MB, III, Wolbarsht ML. Oxygenation and vasodilation in relation to diabetic and other proliferative retinopathies. Ophthalmic Surg 1983; 14: 209–26.
41. Steinberg RH. Monitoring communications between photoreceptors and pigment. Epithelial cells: Effects of 'Mild' systemic hypoxia. Friedenwald lecture. Invest Ophthal Vis Sci 1987; 28: 1888–1904.
42. Torczynski E, Tso MOM. The architecture of the choriocapillaris at the posterior pole. Am J Ophthal 1976; 81: 428–40.
43. Van Haeringen NJ, Osterhuis JA, Terpstra J, et al. Erytrocyte aggregation in relation to diabetic retinopathy. Diabetologia 1973; 9: 20–4.
44. Vracko R, Bendett FP. Restricted replicative life span of diabetic fibroblasts in vitro: Its relation to microangiopathy. Fed Proc 1975; 34: 68.
45. Wolbarsht ML, Landers MB. The rationale of photocoagulation therapy for proliferative diabetic retinopathy. A review and model. Ophthal Surg 1980; 14: 235–45.
46. Yanoff M. Ocular pathology of diabetes mellitus. Am J Ophthal 1969; 67: 21–38.
47. Yasuda H, Harano Y, Kousupi K, et al. Development of early lesions of microangiopathy in chronically diabetic monkeys. Diabetes 1984; 33: 415–20.
48. Yodaiken RE, Seftel HC, Kew MC, et al. Ultrastructure of capillaries in South African diabetics. II. Muscle capillaries. Diabetes 1969; 18: 164–75.
49. Yoneya S,Tso MOM, Shimizu K. Patterns of the choriocapillaris. Intnl Ophthal 1983; 6: 95–109.
50. Yoneya S, Tso MOM. Angioarchitecture of the human choroid. Arch Ophthal 1987; 105: 681–7.

Address for offprints:
Andrzej W. Fryczkowski,
Department of Ophthalmology,
The Ohio State University,
456 West Tenth Avenue,
Columbus, OH 43210, USA.