Acta Neuropathol (Berl) (1985) 68:295–305

Acta Neuropathologica

Microangiopathy in Human Diabetic Neuropathy*

H. C. Powell**, J. Rosoff, and R. R. Myers

Depts. of Pathology, Anesthesiology, and Neurosciences, University of California, San Diego, La Jolla, CA 92093, USA

Summary. Morphological change of endoneurial and perineurial vessels accompanied severe loss of myelinated axons in peripheral nerves of each of 17 patients with diabetic neuropathy. Vascular mural thickening averaged $18.9 \pm 9.9\ \mu m^2$ in diabetic capillaries ($n = 11$) vs. $6.9 \pm 4.1\ \mu m^2$ in controls ($n = 7$). Electron microscopy revealed vigorous endothelial proliferation as well as thickening and reduplication of basal lamina in each instance. Particular attention was paid to vessels which penetrate the perineurium en route to the endoneurial interstitium, since they provide a major portion of the endoneurial blood supply. Luminal narrowing and mural thickening of these vessels was compounded by basal laminar thickening of the perineurium. Fenestrated endoneurial capillary endothelium was noted in one case. Both demyelination and axonal degeneration were observed with intra-axonal glycogen accumulation in some axons. Morphometric analysis revealed extensive myelinated nerve fiber loss in diabetic nerves. These morphological findings emphasize the impact of diabetic microangiopathy on specialized endothelium and suggest that local anatomic factors in the perineurial sheath render the nerve vulnerable to chronic ischemia.

Key words: Microangiopathy – Diabetic neuropathy – Endothelium – Chronic ischemia

* Supported in part by the National Institute for Communicative Disorders and Stroke NS-14162 and by the Veterans Administration Research Service

** *Present address and address for offprint requests to:* Dr. H. C. Powell, University of California, San Diego, School of Medicine, Dept. of Pathology, M-012, La Jolla, CA 92093, USA

Introduction

Efforts to understand the pathogenesis of diabetic neuropathy have concentrated mainly on lesions of the nerve fibers, without much emphasis on changes of the endoneurial blood vessels or their possible role in development of diffuse symmetrical polyneuropathy. An early report by Fagerberg [11] described thickening of endoneurial vessel walls with accumulation of periodic-acid-Schiff (PAS)-positive material in their thickened walls. He suggested a pathogenic mechanism whereby intramural vascular thickening resulted in ischemia with generalized injury throughout the peripheral nervous system (PNS). The proposed mechanism differs from the discrete arterial occlusions which cause local infarction or mononeuropathy [1, 2, 31]. Fagerberg's hypothesis was challenged after subsequent studies of human diabetic neuropathy, which confirmed the structural changes he described, but failed to reveal focal neural degeneration [8, 13]. However, these studies were performed on paraffin-embedded tissue which is less than satisfactory for visualizing nerve fiber pathology.

There are compelling reasons to reconsider the role of vascular disease in symmetrical polyneuropathy associated with diabetes. Systemic changes occur in the microcirculation in which capillaries are thickened both by duplication of their covering basal lamina [3] and by endothelial proliferation which tends to efface their lumina. The blood viscosity is altered by microangiopathy [22] and by glycosylation of hemoglobin and loss of flexibility of red cell membranes [23], and oxygen transport to the tissues is impaired [7]. Furthermore, endoneurial hypoxia has been demonstrated in association with reduced nerve blood flow in streptozotocin-diabetic rats [35]. There are also structural aspects of the endoneurial microcirculation which, in the presence of diabetic microangiopathy, may result in impaired vascular perfusion of the

Table 1. Microangiopathy in diabetic neuropathy. Endothelial proliferation and basal laminar thickening were identified by electron microscopy in every case and did not appear to correlate with the type or duration of diabetes mellitus

Case	Clinical					Pathological		
	Age	Sex	Duration of disease (yr)	Type of Diabetes		Nerve fiber loss	Endothelial proliferation	Basal laminar thickening
				IDDM	NIDDM			
1	65	M	1	+	−	+++	×	×
2	65	M	15	+	−	+++	×	×
3	56	M	7	+	−	+	×	×
4	62	M	20	−	+	++	×	×
5	82	F	−	−	+	+++	×	×
6	72	M	−	−	+	+++	×	×
7	62	M	1	−	+	+++	×	×
8	83	M	−	−	+	+	×	×
9	69	M	−	−	+	++++	×	×
10	74	F	−	+	−	+++	×	×
11	51	M	−	−	+	++++	×	×
12	43	M	7	+	−	++++	×	×
13	60	M	15	+	−	++++	×	×
14	59	M	1	+	−	++++	×	×
15	73	F	1	−	+	++	×	×
16	79	F	2	−	+	++	×	×
17	64	M	−	−	+	+	×	×

endoneurial contents [28 – 29]. In particular, the transperineurial "regional nutritive vessels" described by Lundborg et al. [17 – 20] are susceptible to perineurial distension [25, 26].

The purpose of this paper is to demonstrate microangiopathy and other aspects of neuropathy in human diabetic nerves embedded in plastic media for electron microscopy and to illustrate how mural thickening of these vessels may affect them as they pass through the perineurial sheath, which is also thickened in diabetes mellitus [15].

Material and Methods

Fascicular biopsies of sural nerve were fixed by immersion in 2.5% glutaraldehyde and subsequently processed for electron microscopy. After postfixation in osmium tetraoxide and dehydration in serial alcohols they were embedded in araldite resin. Once the resin hardened, 1-μm-thick sections were cut and stained with paraphenylene diamine. These sections were subsequently employed for morphometric analysis. Ultrathin sections for electron microscopy were stained with uranyl acetate and bismuth subnitrate. Studies were carried out on nerves from 17 diabetics and seven controls. Fourteen of the specimens were sural nerve biopsies, two were removed from amputated legs, and one was obtained at autopsy (Table 1).

Morphometry of endoneurial vessels was performed in nerves from 11 diabetics and seven controls (Table 1). Diabetics included both insulin-dependent (IDDM) and non-insulin-dependent (NIDDM) individuals (Table 1) in whom duration of the disease ranged from months to years. Controls consisted of biopsied nerves which were morphologically normal (five cases) and two biopsies which revealed nerve fiber loss, but normal-appearing vessels. Additional histometric studies in four diabetics and four age-matched non-diabetic controls included determination of fascicular area, enumeration of myelinated fibers, and estimation of fiber size. The number of vessels crossing the perineurium and vessels in the subperineurial area were also counted.

Prior to morphometry the sections were screened to ensure that the tissue, especially the perineurium, was intact. Photomicrographs were taken with a Zeiss Axiomat using high contrast black and white film. Each negative was mounted as a 35 mm slide and projected from beneath a glass screen overlaid by a digitizing pad. Morphometric analysis of vascular wall thickness was performed in 11 diabetics and seven controls. The thickness of the vessel wall was a linear measurement calculated after determining the areas of the vessel and substracting the luminal area. Vessels were identified, and their external circumference and luminal circumferences were measured. Enumeration of vessels crossing the perineurium and of vessels in the subperineurial space was accomplished by light microscopy with an oil immersion lens. The fascicular area was then calculated from the projected image. To assess the size of myelinated fibers, areas within the endoneurium were sampled using a random-numbers table to position a hexagonal lattice having 25 sampling crosshatchings. Once the lattice was correctly placed, myelinated fibers containing lattice crosshatchings were placed into one of three categories based on the diameter (6 μm, 12 μm, 18 μm) using an overlay template with the appropriate sizes marked on its surface. Four sample areas from each fascicle were used.

Results

Capillary mural thickening due to both endothelial proliferation and basal laminar thickening was noted in diabetics of both types (IDDM and NIDDM) and did not appear to correlate with the documented duration of disease (Table 1). Vessel walls in diabetics were

Table 2. Morphometric analysis of nerve capillaries. There was significant thickening of the vessel walls in diabetic nerves

Group	*N*	Mean (μm)	± SD (μm)	Significance
Wall thickness				
Control	58	6.9	4.1	
Diabetic	117	18.9	9.2	$P < 0.001$
Luminal diameter				
Control	58	4.1	5.6	
Diabetic	117	5.9	8.6	NS

Table 3. Morphometric analysis of human diabetic nerves. A severe reduction in the myelinated nerve fiber population was noted in diabetics as compared to age-matched, non-diabetic controls. In addition to the pathologic changes described above, there was an increase in the number of subperineurial vessels in diabetics

	Diabetic	Control	Significance
Myelinated fibers/ m^2 of fascicle area ($\times 10^3$)	1.078 ± 0.908	13.700 ± 5.291	$P \leqslant 0.01$
Number of vessels in the perineurium	0.732 ± 0.492	0.713 ± 0.468	NS
Number of vessels in the subperineurial space	3.457 ± 0.375	2.503 ± 0.589	$P \leqslant 0.05$

almost three times thicker than controls (Table 2). Vascular mural thickening averaged 18.9 ± 9.9 μm^2 in diabetics ($n = 11$) vs. 6.9 ± 4.1 μm^2 in non-diabetic vasa nervorum. Lumen diameters did not differ significantly. Vessels were more numerous in the subperineurial region (Table 3) in diabetics. Transverse sections of biopsied sural nerves of diabetic patients revealed a profound reduction of myelinated fibers compared to controls (Table 3). In most of the biopsied sural nerves there was a drastic reduction of myelinated fibers (Fig. 1), fewer than 10% remaining in the endoneurium in many of them (Table 1). The number of myelinated fibers per 1,000 μm^2 was 1.08 ± 0.91 in diabetics as compared to 13.7 ± 5.2 in controls, and this difference was statistically significant as determined by Student's unpaired *t*-test ($P < 0.01$).

Microscopic examination of 1-μm-thick plastic sections showed swollen axons and myelin ovoids, both consistent with active nerve fiber degeneration. Clusters of closely contiguous tiny axonal sprouts were present, and there was evidence of remyelination. Paraffin-embedded sections showed epineurial vasculitis in three cases but showed no endoneurial inflammatory changes, and Schwann cell nuclei were every numerous. Immunocytochemical staining for anti-insulin antibodies was negative in each of the three biopsies. The vasa nervorum were prominent, and plastic sections stained with methylene-blue azure II showed extensive mural thickening of capillaries (Figs. 2–3) due to accretion of redundant basal lamina. By electron microscopy, multiple supernumerary layers of redundant basal lamina were observed around capillaries (Figs. 4–7). Thickening and reduplication of basal lamina were associated with proliferation of capillary endothelium often to the point of occlusion of the vessel lumen (Figs. 8–10). Organelles within proliferated endothelium appeared within normal limits, and endothelial tight junctions appeared intact; however, in case 2 the unusual observation of fenestrated endoneurial endothelium was made (Fig. 11). Affected vascular endothelium was composed of discontinuous layers of cytoplasm overlying the basal lamina (Fig. 12). Occlusive changes of capillary endothelium were most pronounced in perineurial vessels in which endothelial proliferation combined with basal laminar thickening and reduplication of both vessels and perineurial sheath exacerbated the occlusive effects already described in endoneurial vessels. Thrombosis was not seen in any vessel. Thickening and luminal narrowing of perineurial vessels was observed in all diabetic cases. Endothelial proliferation was not observed in the controls used in this study, but there was some reduplication of basal lamina around capillary endothelium.

Aside from its basal lamina, the perineurial sheath also showed thickening (Fig. 8). Abnormalities of nerve fibers were noteworthy. These included numerous Büngner's bands, increase in endoneurial collagen, and accumulation of glycogen as well as dystrophic changes of axons (Figs. 13–16). Swollen axons packed with abnormal organelles were also observed in two of the diabetic nerves (Figs. 13–16). Accumulation of glycogen took the form of intramitochondrial masses of electron-dense granules within the external compartment of the organelle (Figs. 14, 15). However, in many instances, aggregations of glycogen were simply surrounded by unit membrane, and sometimes the axoplasm was filled with glycogen granules.

Discussion

Pathologic changes of endoneurial and perineurial vessels were present in each of 17 diabetic patients in

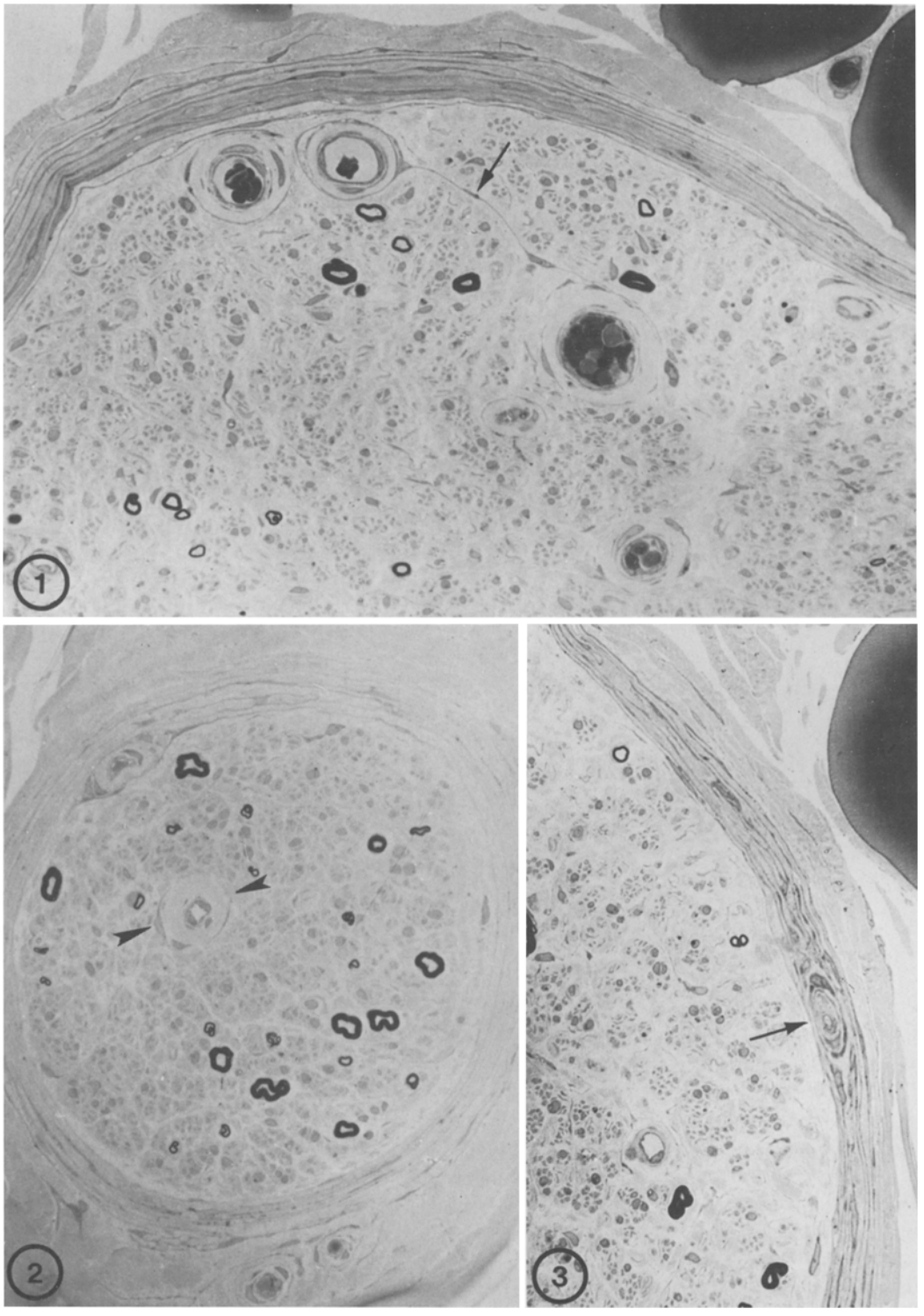


Fig. 1. Transverse section of biopsied sural nerve in human diabetic neuropathy. There is extreme reduction in the population of myelinated nerve fibers only, few of which remain. The vasa nervorum are prominent due to basal laminar and cellular proliferation. Adjacent vessels are linked by proliferated fibroblasts (*arrow*). One-micrometer-thick section of araldite-embedded nerve stained with paraphenylene diamine. ×1,120

Fig. 2. Massive thickening of the vessel walls by pale gray staining material consistent with basal lamina (*arrowheads*). Note the marked reduction in myelinated nerve fibers. One-micrometer-thick section stained with paraphenylene diamine. ×1,350

Fig. 3. This transverse section shows a perineurial vessel (*arrow*) with cellular proliferation and no visible lumen. Few myelinated fibers are present in the endoneurium which contains many bands of Bünger. ×1,120

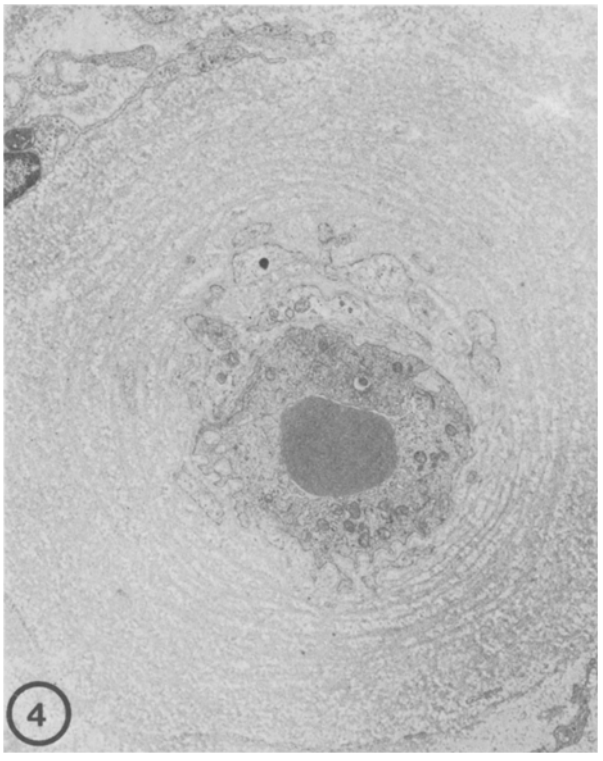


Fig. 4. Diabetic neuropathy. Perineurial capillary showing extensive reduplication and overall basal laminar thickening. ×6,300

whom severe loss of myelinated nerve fibers was also noted (Table 1). Increased thickness of vessel walls was not only due to abnormalities of basal laminae, but also the result of endothelial proliferation. The perineurial sheaths and their basal lamina underwent thickening with apparent narrowing of vessels which penetrate them. Myelinated nerve fibers were severely reduced in number (Table 3) and dystrophic changes of axons were observed by electron microscopy (Figs. 13–16).

Significance of Microangiopathy

Since the neurologic complications of diabetes chiefly affect the peripheral axon, sparing the CNS [4] it is conceivable that local factors in the microenvironment of peripheral nerve contribute to this regional axonopathy. Apart from biochemical abnormalities related to sorbitol or myoinositol metabolism [9], the most prominent structural change is microangiopathy of the vasa nervorum. Although microangiopathy is a major systemic complication of diabetes mellitus [3, 38, 40] its role in peripheral nerve has received comparatively little attention since Fagerberg's observations in 1959 [11].

Perineurial Vessels

Peripheral nerves have a dual blood supply, derived from both central, axial vessels passing down the trunk and from transperineurial vessels forming a dense anastomotic network on the surface of each fascicle. Insufficiency of central vessels, as demonstrated by Asbury et al. [2] may occur in diabetic mononeuropathy and results in degeneration of central myelinated fibers with sparing of the fibers subjacent to the perineurial sheath. More diffuse injury may be expected in the wake of damage to the transperineurial vessels which span the nerve surface. These small vessels form an anastomotic network between the epineurium and the endoneurium (Fig. 10), passing obliquely through openings in the perineurial membrane [17, 18], thereby constituting a "valve mechanism" [19]. These vessels are vulnerable to external pressure [19, 20] and to internal pressure associated with nerve edema [21, 24–26]. While neither of these mechanisms is necessarily involved in diabetic neuropathy, intramural changes in vessels with microangiopathy may have a similar effect. Not only thickening of basal lamina but also endothelial proliferation alter the size of the vessel and diminish the caliber of its lumen [38]. The impact of this change in peripheral nerve may be heightened by the constricting effect of a thickened perineurium as described by Johnson et al. [15]. Our pictures show uniform thickening of capillaries in the vasa nervorm due to endothelial proliferation as well as basal laminar widening and reduplication. This change appears to be compounded by associated perineurial cellular and basal laminar changes, hence the compression, and frequent obliteration (Figs. 4–6) of vessel lumens in capillaries and other small vessels penetrating the perineurial sheath. Endothelial proliferation may have its greatest impact in the perineurium, in which thickening of the normally flattened cells occurs as a result of an increase in the basal laminar thickness [15]. It was at this point that the most severe reduction in luminal size was observed and may alter nerve blood flow.

Endoneurial Vessels

An increase in the number of vessels in the subperineurial region was also detected by morphometry (Table 3). Its significance is uncertain but may be related to generalized changes in the microvascular bed, including increased tortuosity of vessels as well as thickening of their walls.

Fenestrated endoneurial endothelium was observed by electron microscopy in one diabetic patient (Figs. 11, 12). This unusual observation is of interest since the vasa nervorum are normally lined by continuous, non-fenestrated endothelium comprising one ele-

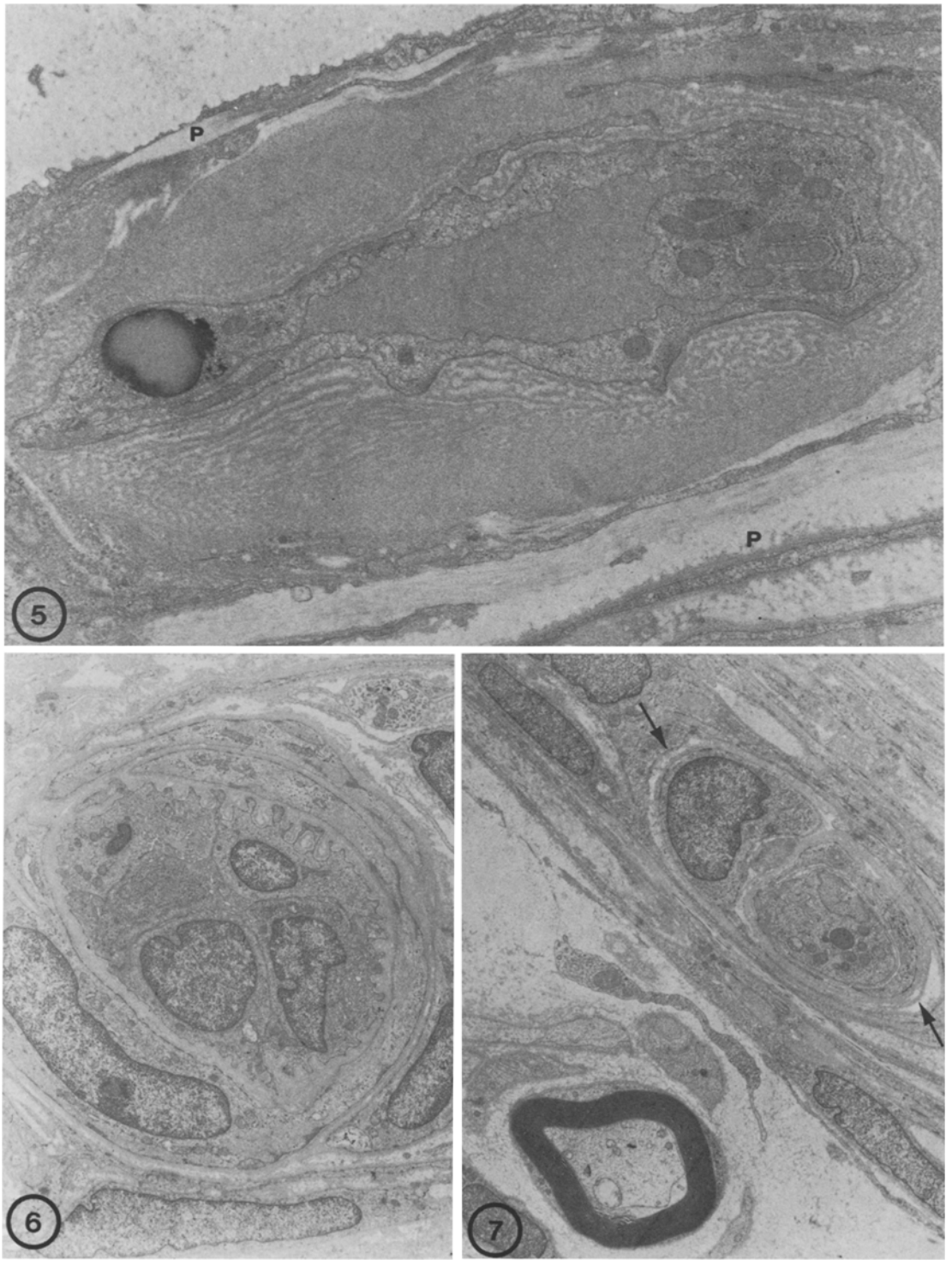


Fig. 5. Diabetic neuropathy. Massive basal laminar thickening in a perineurial vessel. The innermost basal lamina shows several reduplicated layers, while the outer portion appears homogeneous. Note the characteristic arrangement of perineurial cells (*P*) which are flattened and show basal lamina on both sides. ×15,300

Fig. 6. Diabethy. Endoneurial capillary showing endothelial proliferation, basal laminar thickening, and effacement of the capillary lumen. ×6,500

Fig. 7. Intraperineurial capillary. The vessel lumen is completely effaced by endothelial proliferation. ×7,200

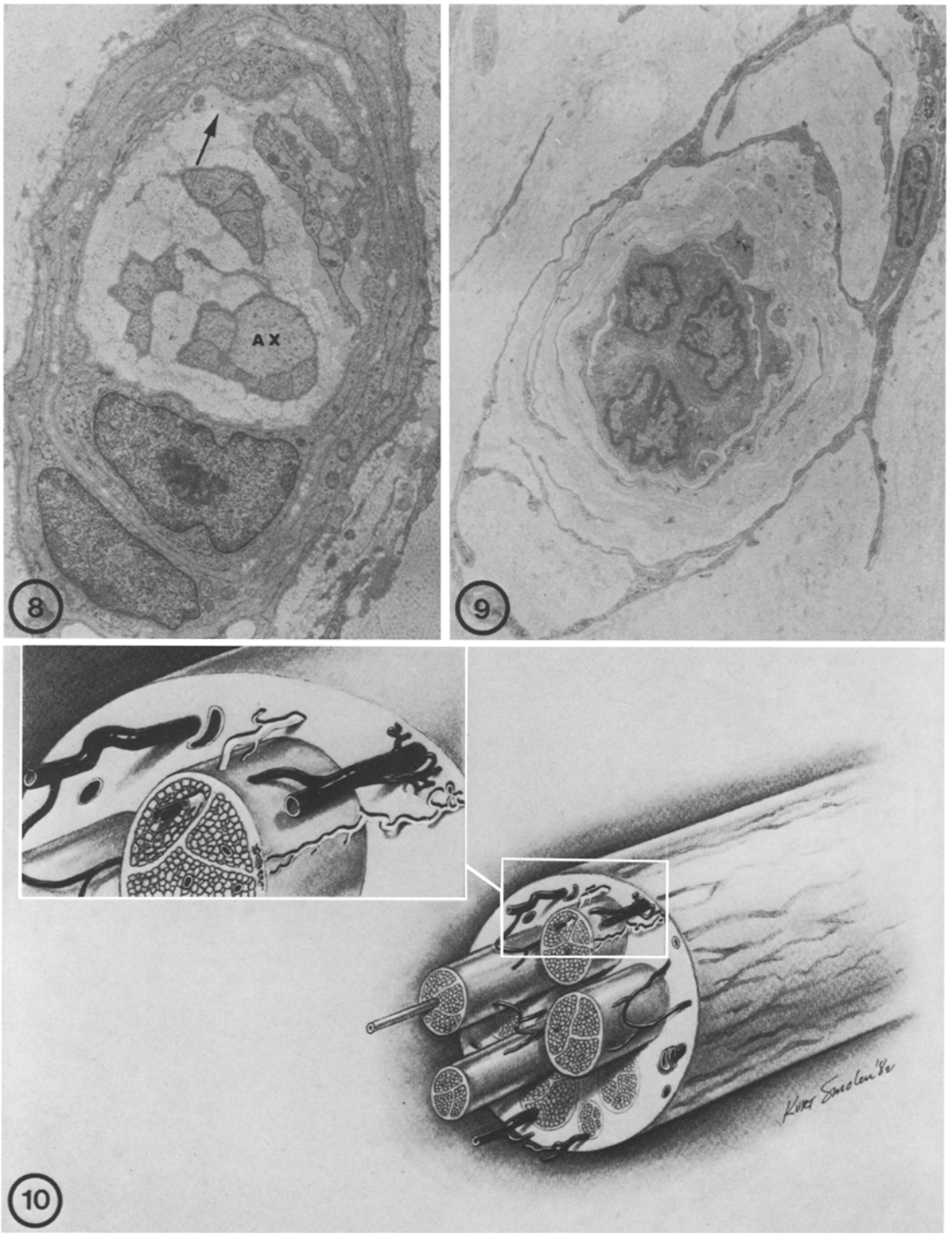
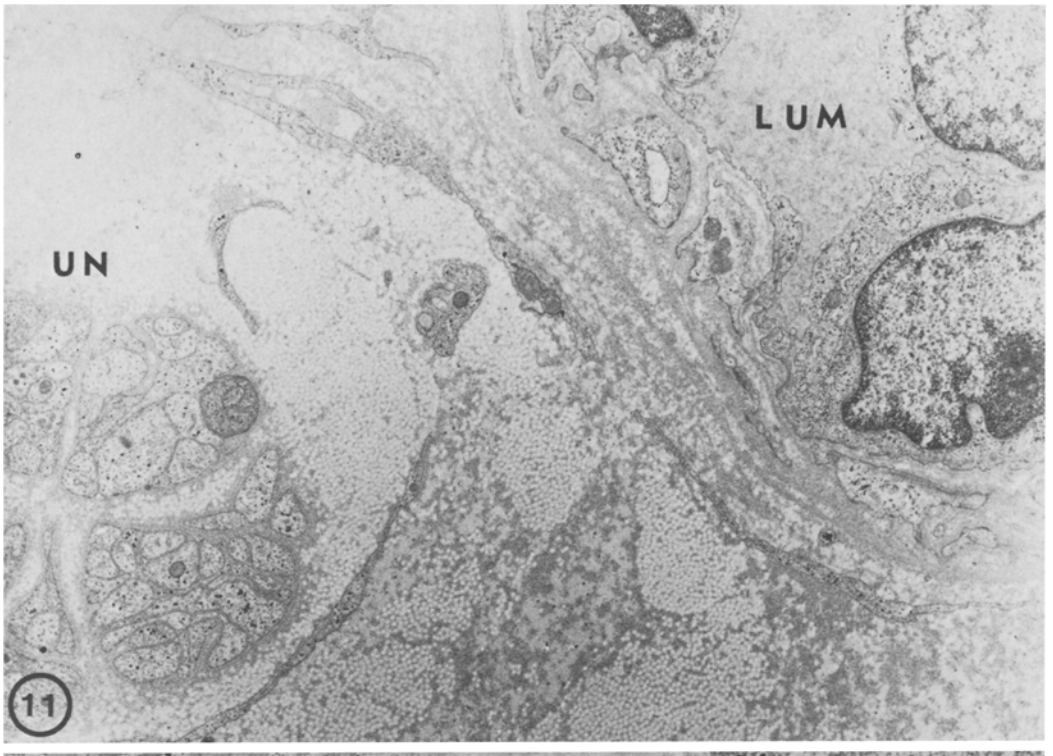


Fig. 8. Cross section through a nerve twig which contains portions of unmyelinated fiber (*AX*) and is surrounded by a disproportionately thick perineurial sheath in which cellular proliferation is accompanied by thickening of basal lamina (*arrow*). ×9,900

Fig. 9. Subperineurial capillary surrounded by a cuff of fibroblasts. There is endothelial proliferation and extensive thickening of endothelial basal lamina. ×5,850

Fig. 10. Diagrammatic representation of extrinsic and intrinsic blood vessels in peripheral nerve. A richly anastomosing vascular network is found in the epineurium. *Inset*: Oblique passage of vessels through the perineurial sheath



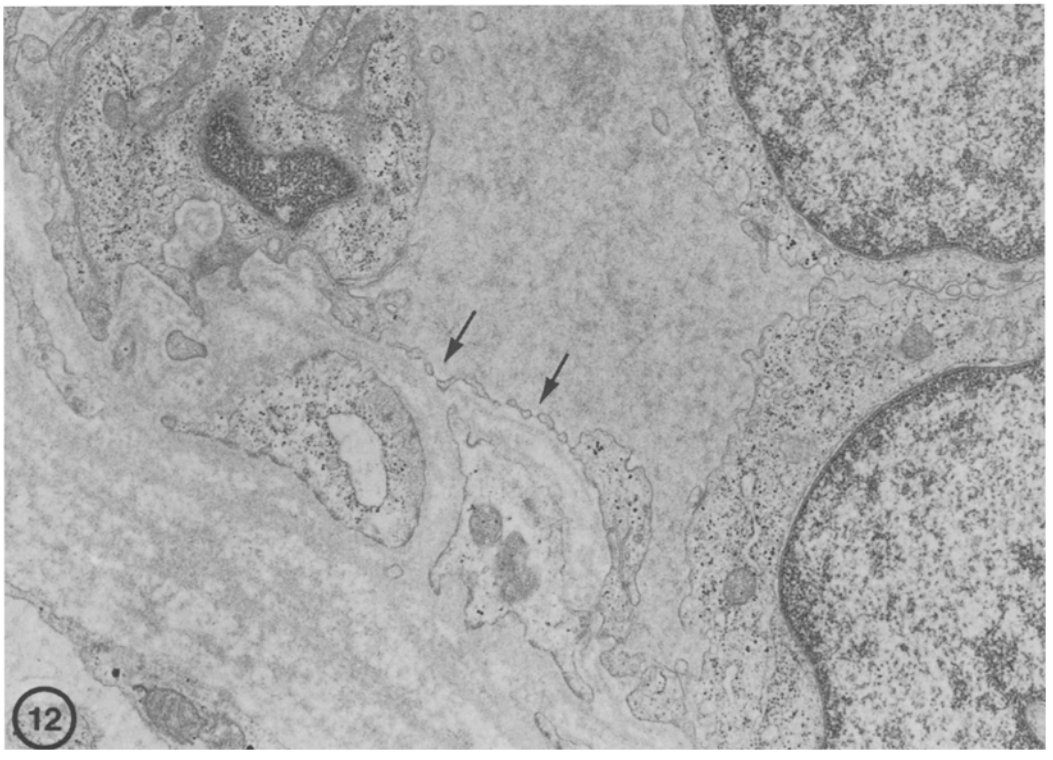


Fig. 11. Endoneurial capillary with fenestrated endothelium lining a portion of its lumen (*LUM*). Some unmyelinated nerve fibers (*UN*) are visible in the *left* of the picture. ×9,560

Fig. 12. Higher magnification of the fenestrated capillary. Note the discontinuous endothelial surface (*arrows*) and characteristic layer of elastin. ×19,000

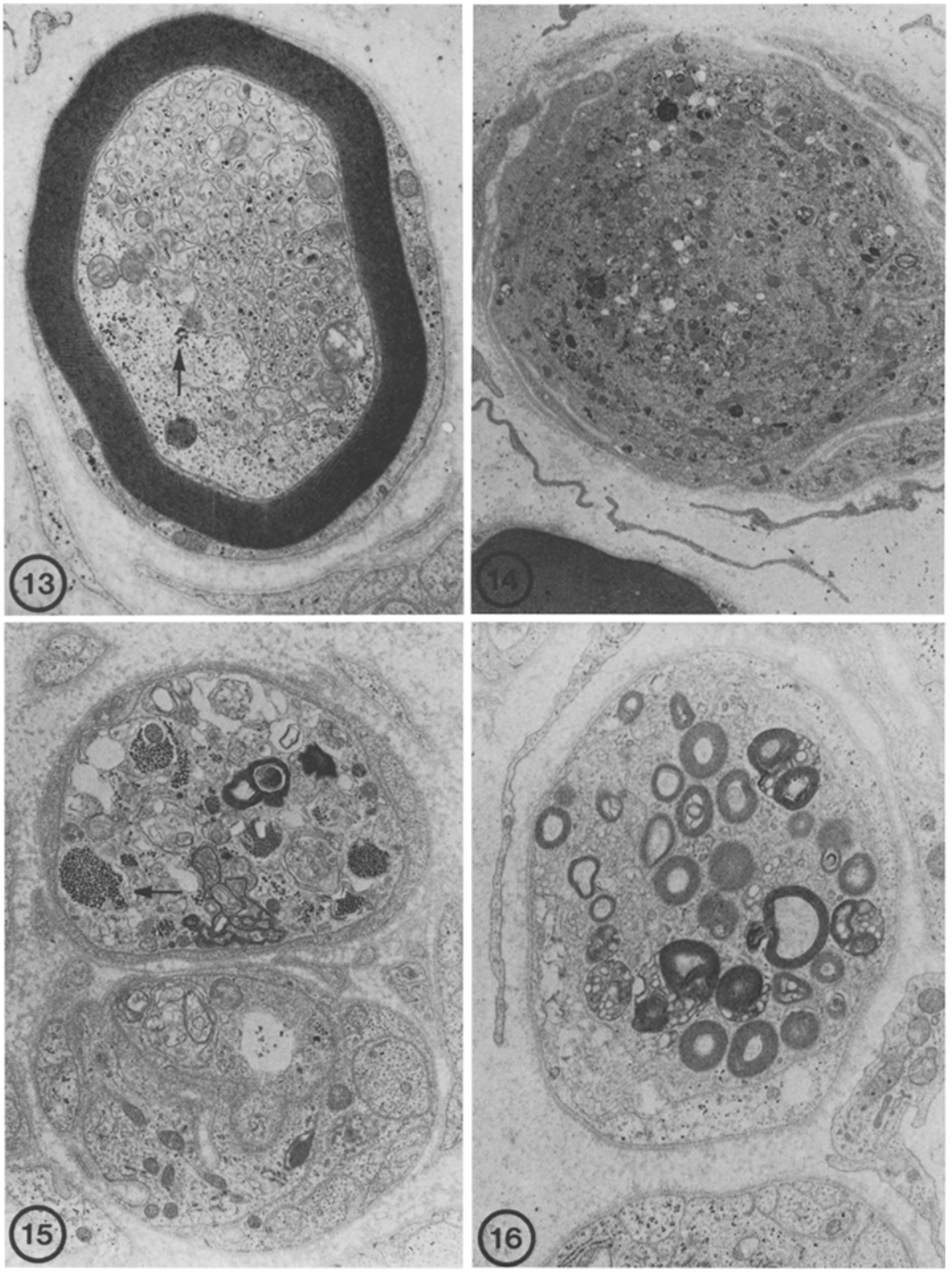


Fig. 13. Diabetic neuropathy. Electron micrograph of a dystrophic axon containing numerous organelles and membranous inclusions. Darkly staining glycogen granules are scattered through the axon. × 19,800

Fig. 14. Swollen axon packed with mitochondria, densely staining organelles, neurofilaments, and glycogen granules. Diabetic neuropathy. × 5,400

Fig. 15. Dystrophic axon containing lamellar debris and membrane-bound aggregates of glycogen granules diabetic axon. × 13,500

Fig. 16. Axonopathy of diabetic neuropathy, note the accumulated lamellar debris characteristic of axonal degeneration. × 14,700

ment of the blood-nerve barrier (BNB) [16]. It has been reported previously in a diabetic by Thomas and Elliason [34] and has been described in human macroglobulinemic neuropathy [14] as well as in the brains of animals with chronic experimental allergic encephalomyelitis [33]. It should be noted that the patient in whom we observed fenestrated endoneurial capillary endothelium did not have vasculitis.

Endothelial proliferation was observed in each diabetic biopsy and is a recognized complication of this disorder [3, 38]. Thickening of the walls of vasa nervorum can be observed in other chronic neurologic disorders, such as polyneuropathy associated with macroglobulinemia [30]. Unfortunately, there is little information available concerning the morphology of vasa nervorum in aging human and animals nerves. Morphometric analysis of cerebral capillaries in monkeys showed attenuation of vessel walls with age [6]. Thickening due to reduplication of basal lamina in rat cerebral capillaries can be seen by electron microscopy [6] but endothelial proliferation is not involved. Microangiopathy is important because there is a positive correlation between microangiopathy and hyperviscosity in diabetes [22]. Vascular proliferation may also be stimulated by increased sorbitol and glucose concentrations in the blood [36].

Pathology of Myelinated Nerve Fibers

These microcirculatory changes might be expected to result in loss of myelinated axons, which was severe in the diabetic specimens (Figs. 13–16, Table 3). In addition, many remaining axons showed dystrophic changes, such as swelling (Fig. 14) with accumulation of organelles, membranous complexes, and glycogen granules (Figs. 15, 16). Accumulation of intra-axonal glycogen in diabetic nerves has already been described in experimental animals [27] and in ultrastructural study of peripheral nerves of diabetic patients with ischemic vascular disease [37]. This change may also be seen in compression neuropathy in animals housed in wire-floored cages [12]. However, the presence of large deposits of glycogen in human diabetic sural nerve is consistent with some etiology other than simple compression. Glycogen accumulation in diabetic axons is not considered to be a direct effect of hyperglycemia, but rather an indirect complication, possibly due to tissue hypoxia [27]. Glycogen accumulation occurs in mitochondria, filling the inner compartments of these organelles [26]. This mitochondrial change can be reproduced in experimental hypoxic states [5]. There are several reasons for considering its pathogenesis in diabetic neuropathy as secondary to hypoxia. Firstly, severe microangiopathy complicated by perineurial thickening and compression of vessels penetration the perineurium may affect tissue perfusion. Reduced blood flow has been reported in muscle of patients with severe diabetic neuropathy and in streptozotocin-diabetic nerves [35], but as far as we know nerve blood flow has not yet been measured in human diabetics. Morphometric analysis of endoneurial capillaries by Dyck et al. [10] has shown "capillary closure" related to endothelial proliferation. These authors suggest an ischemic basis for diabetic polyneuropathy mediated through altered endoneurial capillaries.

Conclusions

The role of angiopathy in diabetic neuropathy has been emphasized by authors, such as Fagerberg [11], who described thickening of small vessels associated with accumulation of periodic-acid-Schiff (PAS)-positive staining of their walls. Others, while confirming the intramural change in vasa nervorum, have disagreed with his conclusion [8, 13], because they did not see infarcts in their own material. Microinfarcts, associated with intravascular platelet thrombi, have been described subsequently by electron microscopy [39] in human biopsies and in experimental rats [32]. However, there are disturbances of the microcirculation which can diminish nerve blood flow and be associated with Wallerian degeneration [25] or demyelination [26] without actual infarction. The combined effects of microangiopathy, altered biorrheologic and other variables is likely to impair nerve blood flow. The observation that structural injury to nerve fibers is a late complication of diabetic neuropathy, rather than an initial finding, lends further support to the view that chronic diabetic neuropathy is partly attributable to diabetic angiopathy [28], whereas the predominantly functional changes of early diabetic neuropathy are of metabolic origin and develop in association with biochemical changes in the endoneurial microenvironment.

Acknowledgement. The authors thank the National Diabetes Research Interchange which provided cases 16 and 17.

References

1. Asbury L, Aldredge H, Hershberg R, Fisher CM (1970) Oculomotor palsy in diabetes mellitus: clinical and pathologic study. Brain 93:555–566
2. Asbury AK, Johnson PC (1978) Focal ischemic neuropathies. In: Asbury AK, Johnson PC (eds) Pathology of peripheral nerve. Major problems in pathology, vol 9. Saunders, Philadelphia, pp 102–119
3. Bischoff A (1968) Diabetische Neuropathie. Pathologische Anatomie, Pathophysiologie und Pathogenese aufgrund elektronenmikroskopischer Untersuchungen. Dtsch Med Wochenschr 93:237–241

4. Brown MR, Dyck PJ, McClearn GE, Sima AF, Powell HC, Porte D (1982) Central and peripheral nervous system complications. Diabetes [Suppl] 31:65–70
5. Buja LM, Ferrans VJ, Levitsky AS (1972) Occurrence of intramitochondrial glycogen in canine myocardium after prolonged anoxic cardiac arrest. J Mol Cell Cardiol 4:237–254
6. Burns EM, Kruckeberg TW, Gaetano PK, Shulman LM (1983) Morphological changes in cerebral capillaries with age. In: Cervos-Navarro J, Sarkander HI (eds) Brain aging: Neuropathology and Pharmacology, vol 21: Aging. Raven Press, New York, pp 115–119
7. Ditzel J (1980) Affinity hypoxia as a pathogenic factor of microangiopathy with particular reference to diabetic retinopathy. Acta Endocrinol [Supp] 238:39–55
8. Dolman CL (1963) The morbid anatomy of diabetic neuropathy. Neurology 13:135–146
9. Dyck PJ, Sherman WR, Hallcher LM, Service FJ, O'Brien PC, Grina LA, Palumbo PJ, Swanson CJ (1980) Human diabetic endoneurial sorbitol, fructose, and myo-inositol related to sural nerve morphometry. Ann Neurol 8:590–596
10. Dyck PJ, Yasuda H, Karnes J, Lais A, Service FJ (1985) Ischemia in the etiology of diabetic polyneuropathy. J Neuropathol Exp Neurol 44:346 [Abstr]
11. Fagerberg SE (1959) Diabetic neuropathy, a clinical and histological study on the significance of vascular affections. Acta Med Scand [Suppl 164] 345:1–97
12. Grover-Johnson N, Spencer PS (1981) Peripheral nerve abnormalities in aging rats. J Neuropathol Exp Neurol 40:155–165
13. Harriman D (1962) Ischemic factors in diabetic neuropathy. In: Jaw H (ed) Proceedings of the Fourth International Congress of Neuropathology. Thieme, Stuttgart, pp 164–168
14. Johnson PC (1977) Fenestrated endothelium in the peripheral nervous system. J Neuropathol Exp Neurol 36:607 (Abstract)
15. Johnson PC, Brendel AK, Meezan AE (1981) Human diabetic perineurial cell basement membrane thickening. Lab Invest 44:265–270
16. Lampert PW, Carpenter AS (1965) Electron microscope studies on vascular permeability and the mechanism of demyelination in experimental allergic encephalities. J Neuropathol Exp Neurol 24:11–24
17. Lundborg G (1970) Ischemic nerve injury. Scand J Plast Reconstruct Surg [Suppl] 6:1–113
18. Lundborg G, Nordborg C, Rydevik B, Olsson Y (1973) The effect of ischemia on the permeability of the perineurium to protein tracers in the rabbit tibial nerve. Acta Neurol Scand 49:287–294
19. Lundborg G (1975) Structure and function of the intraneural microvessels are related to trauma, edema formation, and nerve function. J Bone Joint Surg [Am] 57:938–948
20. Lundborg G (1979) The intrinsic vascularisation of human peripheral nerves, structural and functional aspects. J Hand Surg 41:34–41
21. Lundborg G, Myers RR, Powell HC (1983) Increased endoneurial fluid pressure in experimental entrapment neuropathy. J Neurol Neurosurg Psychiatry 40:1119–1124
22. McMillan DE (1982) Further observations on serum viscosity changes in diabetes mellitus. Metabolism 31:274–278
23. Miller JA, Pizzighella AS, Gravallese AE, Bunn HF (1980) Nonenzymatic glycosylation of erythrocyte membrane proteins. Relevance to diabetes. J Clin Invest 65:896–901
24. Myers RR, Powell HC, Shapiro HM, Costello ML, Lampert PW (1980) Changes in endoneurial fluid pressure, permeability, and peripheral nerve ultrastructure in experimental lead neuropathy. Ann Neurol 8:392–401
25. Myers RR, Mizisin AP, Powell HC, Lampert PW (1982) Reduced nerve blood flow in hexachlorophene neuropathy. Relationship to elevated endoneurial fluid pressure. J Neuropathol Exp Neurol 41:391–399
26. Myers RR, Powell HC (1984) Galactose neuropathy: impact of edema on nerve blood flow. Ann Neurol 16:587–594
27. Powell HC, Ward HW, Garrett RS (1979) Glycogen accumulation in the nerves and kidneys of chronically diabetic rats. A quantitative electron-microscopic study. J Neuropathol Exp Neurol 38:114–127
28. Powell HC (1983) Pathology of diabetic neuropathy: new observations new hypotheses. Lab Invest 49:515–518
29. Powell HC, Myers RR (1984) Axonopathy and microangiopathy in chronic alloxan diabetes. Acta Neuropathol (Berl) 65:128–137
30. Powell HC, Rodriguez M, Hughes RAC (1984) Microangiopathy of vasa nervorum in dysglobulinemic neuropathy. Ann Neurol 15:386–395
31. Raff MC, Sangalang V, Asbury AK (1968) Ischemic mononeuropathy multiplex associated with diabetes mellitus. Arch Neurol 18:487–499
32. Sima AAF, Thibert P (1982) Proximal motor neuropathy in the BB-Wistar rat. Diabetes 31:784–788
33. Snyder DH, Hirano A, Raine CS (1975) Fenestrated CNS blood vessels in chronic experimental allergic encephalomyelitis. Brain Res 100:645–649
34. Thomas PK, Elliason S (1984) Diabetic neuropathy. In: Dyck PJ, Thomas PK, Lambert EH, Bunge RP (eds) Peripheral neuropathy, chapter 76. Saunders, Philadelphia, pp 1776–1810
35. Tuck RR, Schmelzer JD, Low PA (1984) Endoneurial blood flow and oxygen tension in the sciatic nerves of rats with experimental diabetic neuropathy. Brain 107:913–950
36. Turner JL, Bierman EL (1978) Effects of glucose and sorbitol on proliferation of cultured human skin fibroblasts and arterial smooth muscle cells. Diabetes 27:583–588
37. Vital C, Brechenmacher C, Servise JM, Bellance R, Vital A, Dartignes JF, Boissieras P (1983) Ultrastructural study of peripheral nerve in arteritic diabetic patients. Acta Neuropathol (Berl) 61:225–231
38. Vracko R (1982) A comparison of the microvascular lesions in diabetes mellitus with those of normal aging. J Am Geriatr Soc 30:201–205
39. Williams E, Timperley WR, Ward JD, Duckworth T(1980) Electron-microscopic studies of vessels in diabetic peripheral neuropathy. J Clin Pathol 33:462–470
40. Williamson JR, Kilo C (1980) Vascular complications of diabetes mellitus. N Engl J Med 302:399–400

Received April 15, 1985/Accepted July 29, 1985