The Peripheral Nerve Vasculature

6

6.1 Normal Structure and Function

6.1.1 Vascular Anatomy

Nutrient arteries arise from major vessels and penetrate the nerve trunk roughly perpendicular to its axis. These vessels are highly variable in caliber (up to 1 mm) and in location, both between and within (from side to side) individuals. The median and ulnar nerves, for example, have 1–11 (mean 3.24) and 2–19 (mean 7.75) such nutrient arteries in their forearm segments, respectively (Sunderland 1978). After entering the nerve trunk, the nutrient vessels divide into longitudinal ascending and descending branches and supply several arrays of vessels which run along the nerve and interconnect via oblique or laterally directed channels.

Lundborg (Lundborg 1970; Lundborg and Branemark 1968) has divided the neural vascular system into extrinsic and intrinsic parts. The extrinsic system consists of the "… regional nutrient arteries which supply the Intraneural vascular bed at varying intervals." The intrinsic system is contained within the nerve and consists of longitudinal arrays of vessels running along the nerve, with abundant anastomosing channels between them. This system includes both epineurial and endoneurial vessels. More recently, some authors have used the term "intrinsic" to mean the intrafascicular vascular plexus (McManis et al. 1993; Olsson 1972).

The epineurial (extrafascicular) intrinsic vessels include arterioles which run longitudinally at the most superficial aspects of the epineurium. These arterioles are sometimes visible on the surface of the nerve. The epineurial intrinsic vessels (Fig. 6.1a) also include an array of arterioles deeper within the nerve, located between individual fascicles and vasculature within perineurial septa (Fig. 6.1b). A cross section of the nerve trunk may show several arterioles, but one usually dominates (arrowhead, Fig. 6.1a). The lack of an elastic lamina distinguishes venules which outnumber arterioles (Figs. 6.1a and 6.2a, b).

An endoneurial capillary system runs longitudinally with numerous oblique and transverse anastomoses among vessels (Figs. 6.1a and 6.3). The literature is somewhat unclear about whether arterioles are found in the endoneurium. Bell and Weddell (1984) described endoneurial arterioles having one or two layers of smooth muscle cells and an incomplete internal elastic lamina, but Sunderland (1978) has stated that arterioles are not seen in the endoneurium. This disagreement may simply be a nosologic issue, depending on the definition of endoneurium and of arterioles. Beggs et al. (1991) noted that true arterioles, when found inside a fascicle, are confined to intrafascicular perineurial septa and are not in the endoneurium, strictly speaking (Fig. 6.4). Moreover, the presence of arterioles may vary depending on the nerve trunk and species under study (Beggs et al. 1991), for the studies of Bell and Weddell (1984) were performed on sciatic nerves of several species including humans. We have never found an intrafascicular arteriole outside a perineurial septum.

The endoneurial capillary density has been measured at 60–100 per mm^2 in human sural nerve, decreasing somewhat with age (Dyck et al. 1985; Giannini and Dyck 1993). These endoneurial microvessels differ from those of other organs (Bell and Weddell 1984). The presence of strong alkaline phosphatase activity suggests their essential capillary nature. However, most vessels are associated with a periendothelial cell with cytoplasm extending over 50 % or more of the circumference and are thus reminiscent of postcapillary venules. Furthermore, endoneurial microvessels are larger than those of other tissues, with a mean diameter of 9 μm vs. 5.2 μm in muscle, for example (Bell and Weddell 1984). Giannini and Dyck (1993) found endoneurial microvessel diameters ranging from 5 to 22 μm. Endoneurial capillaries are lined by a single layer of thin endothelial cells, about five per vessel cross section, linked by tight junctions at points of contact (Giannini and Dyck 1993) (Figs. 6.5, and 6.6a). Junctions are associated with a large variety of molecules (claudins 1,2,5,12,19; zona occludens (ZO) 1,2; and other adhesion molecules, Ubogu

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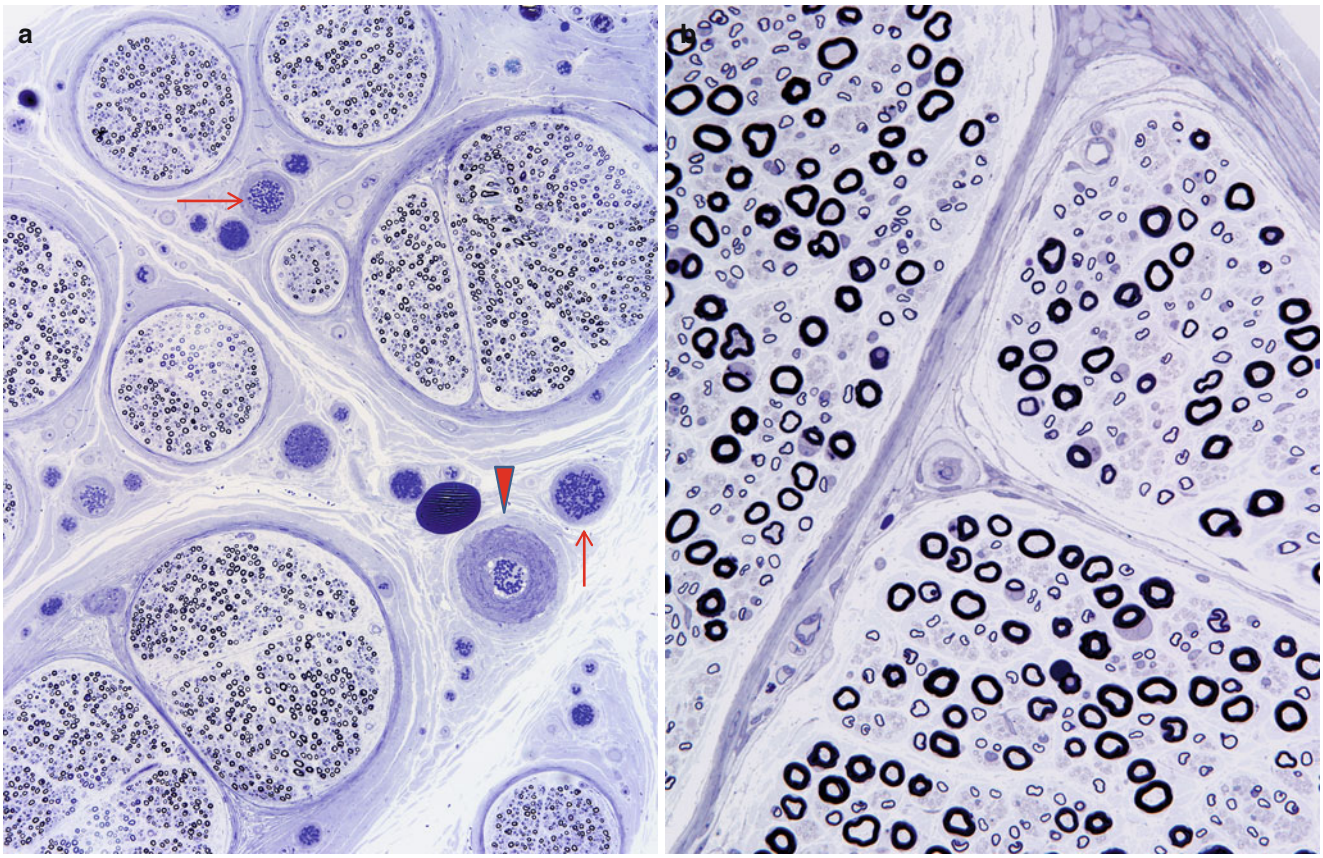

Fig. 6.1 One arteriole (*arrowhead*) and several venules (*arrows*) are shown in the epineurium (**a**). In (**b**) note vessels within perineurial septum (1 μm thick toluidine blue-stained plastic section, 1,000×)

2013). Capillary endothelial cells contain Weibel–Palade bodies (Fig. 6.6a) which are thought to produce factor VIII-related antigen (Rondaij et al. 2006). Endothelial cells may also express numerous chemokines, cytokines, and growth factors, which may participate in neuropathy. Normal endothelial cells of the epineurium and perineurium may demonstrate fenestrae, but those of the endoneurium do not. Immediately around the capillary is a condensation of the collagen found throughout the endoneurium. However, in contrast to vascular structures in the central nervous system, there is a generous extracellular space around vessels, and no "glial" cells invest the walls of the blood vessel.

Transperineurial arterioles connect the epineurial and endoneurial vessel arrays. Beggs and colleagues (1991) have defined transperineurial arterioles as vascular segments exhibiting a continuous smooth muscle coat and confined to the perineurial compartment, including all arterioles in the perineurium proper and arterioles within perineurial septa in the endoneurium (Fig. 6.5). These arterioles, which measure 10–25 μm in diameter, travel an oblique or transverse route through the perineurium (Beggs et al. 1991). The presence of axon terminals on the smooth muscle cells of these vessels suggests a potential for neurogenic regulation of their caliber (Beggs et al. 1991).

An incomplete smooth muscle cell layer and endothelial cells that are somewhat thinner than those of arterioles identified endoneurial venules (Bell and Weddell 1984). The endoneurial vessels drain into epineurial venules, which outnumber epineurial arterioles, and ultimately flow into large vessels which exit the nerve trunk along with the nutrient arteries.

A lymphatic drainage system has been described in the epineurium, but not in the endoneurium (Sunderland 1978). We have found that some large vessels in the epineurium demonstrate focal aggregations of cytoplasmic filaments in endothelial cells adjacent to focal condensation of basal

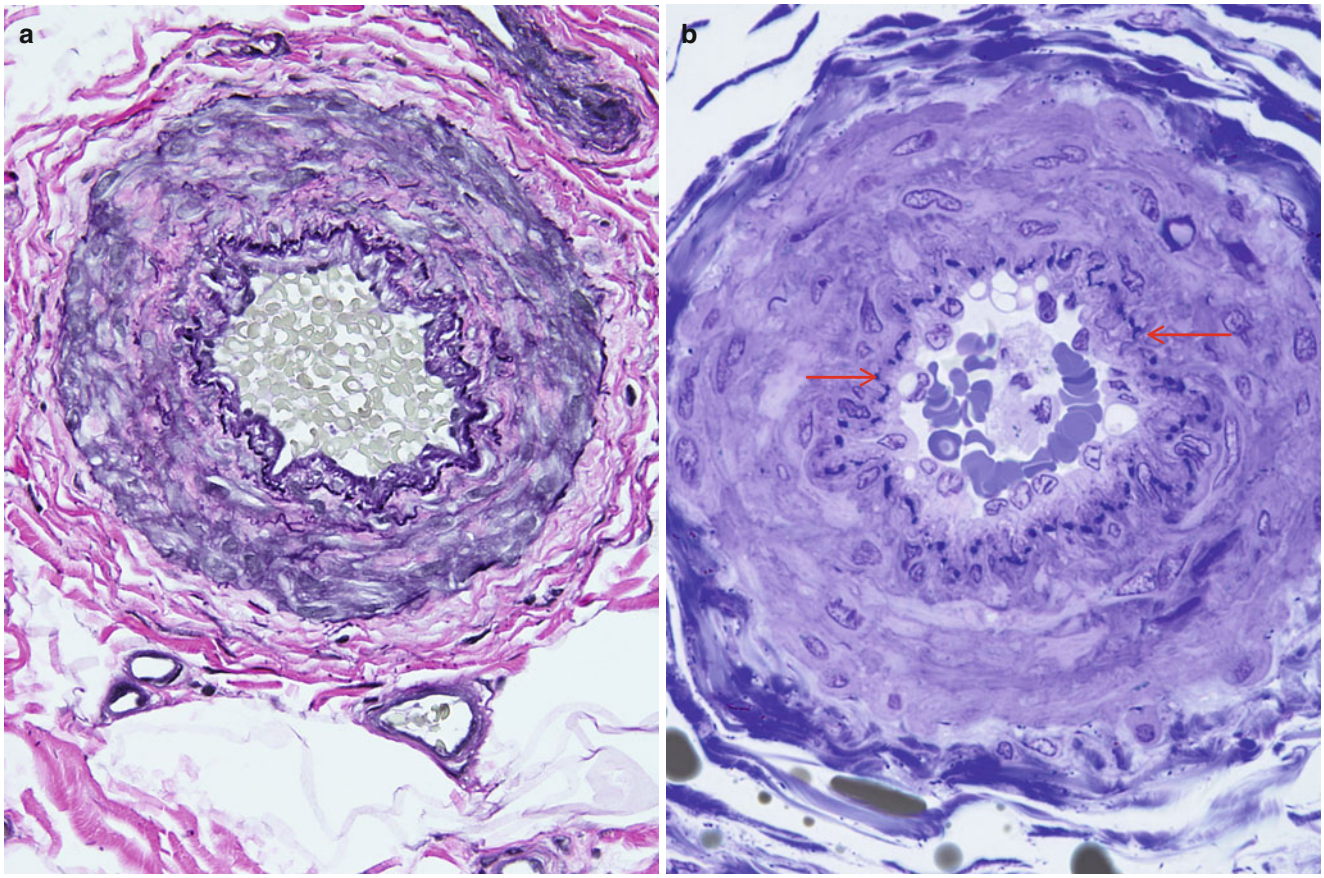

Fig. 6.2 (**a**) Epineurial arteriole is stained with Verhoeff–Van Gieson elastica. In semithin sections the internal elastic lamina (*arrow*) is less conspicuous (**b**) (**a**: paraffin, **b**: 1 μm thick toluidine blue-stained plastic section)

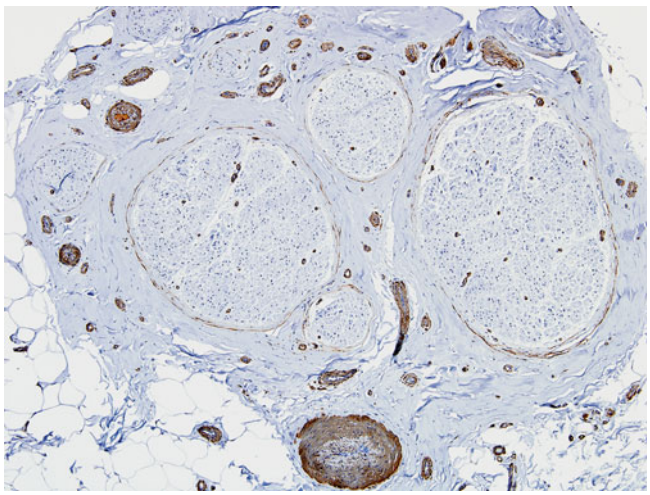

Fig. 6.3 Smooth muscle actin immunostaining highlights the epineurial and endoneurial microvasculature (paraffin, 100×)

lamina (Fig. 6.6b, c). The frequency with which these complexes are seen suggests that they are lymphatic vessels and a normal finding.

The endoneurium and subperineurial interstitial spaces are contiguous along the length of the nerve; consequently, material injected into the endoneurial compartment can be detected at considerable lengths up and down the nerve trunk, although it does not spread into the epineurium. Indeed, the endoneurial interstitial compartment is contiguous with the subarachnoid space (Olsson 1990).

6.1.2 Resistance of Peripheral Nerve to Ischemia

Overall then, there are four longitudinal arrays of vessels; superficial epineurial, deep epineurial, perineurial, and

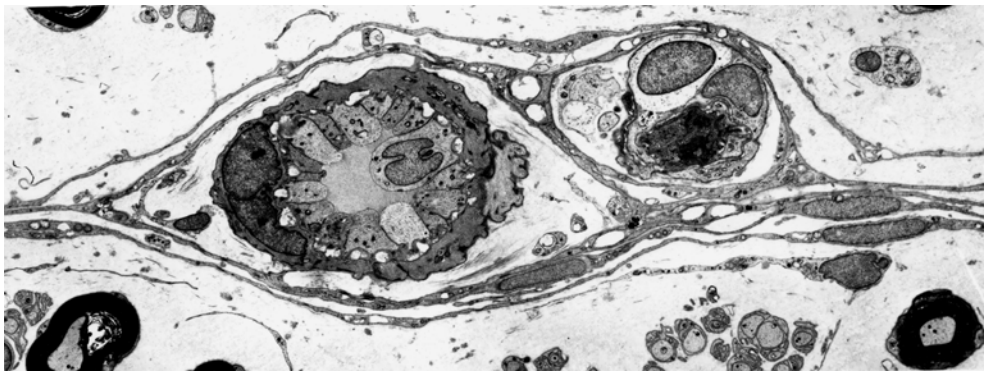

Fig. 6.4 Terminal arteriole in perineurial partition (2,070×)

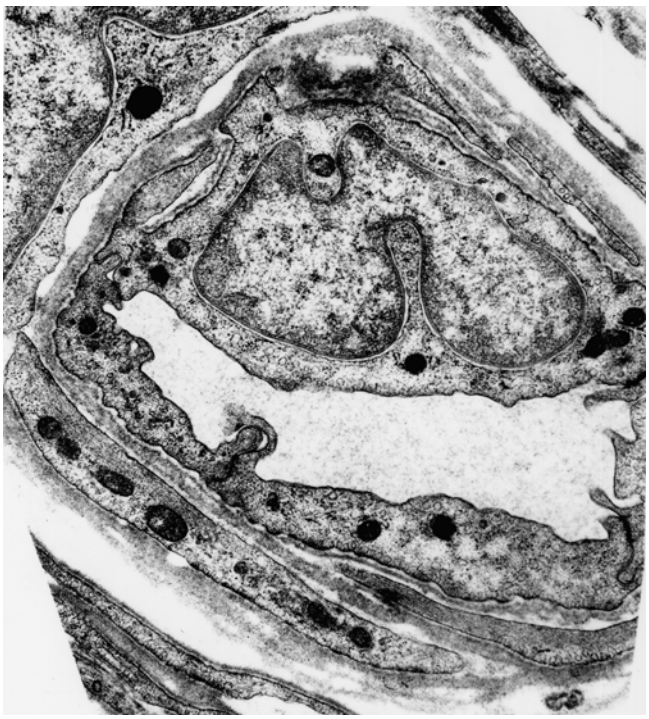

Fig. 6.5 Typical endoneurial microvessel displays intense pinocytotic activity, tight junctions, and pericytic component (1,3794×)

endoneurial, each of progressively lesser caliber. Typical lumina are 75–250 μm for epineurial arterioles, 10–25 μm for transperineurial arterioles, and 5–20 μm for endoneurial capillaries (Beggs et al. 1991; Dyck et al. 1972, 1985, 1987; Giannini and Dyck 1993). Numerous interconnections exist within and between the intra- and extrafascicular systems, providing the nerve with a high resistance to focal ischemia.

In vivo studies using rabbit tibial nerve demonstrate that occlusion of all nutrient vessels over a several centimeter segment does not cause visible change in blood flow, nor does the additional stripping of all epineurial vessels (Lundborg and Branemark 1968). Presumably, longitudinal flow within the intrafascicular circulation is able to compensate. Conversely, sectioning a nerve 3 cm above and below the observation point, thus eliminating the longitudinal intrafascicular blood flow, does not result in visible ischemia. Hypothetically, blood flow is maintained because the nutrient arteries feed the epineurial vessels, which interconnect readily with the intrafascicular capillaries. Indeed, two nutrient arteries are sufficient to maintain a nerve segment in the absence of the longitudinal intrafascicular circulation (Lundborg and Branemark 1968). Recent studies of peripheral nerve ischemia verify that endoneurial blood flow is dependent on both regional anastomoses with epineurial vessels through transperineurial arterioles and on longitudinal intrafascicular flow (Myers et al. 1991).

Peripheral nerve vasculature demonstrates an impressive functional reserve capacity, with numerous channels capable of opening in response to only a slight increase in nerve temperature or the sectioning of the other vessels (Lundborg 1970). Sympathetic activity also modulates the lumen of muscular vessels (epineurial, perineurial, transperineurial) and hence neural blood flow (Beggs et al. 1991; Kihara and Low 1990; Lundborg 1970).

6.1.3 The Blood–Nerve Barrier

The endoneurial compartment has a specialized ionic and macromolecular milieu (Ubogu 2013) thought to be important in nerve function, especially impulse propagation (Olsson 1972). Endoneurial fluid is under hydrostatic pressure greater than that of epineurial fluid, is hypertonic to plasma, and has less protein than plasma (Low et al. 1977; Myers et al. 1983). Maintenance of this unique composition requires isolation of the endoneurium from the vascular compartment and from the epineurium. Such isolation is a function of the blood–nerve barrier (BNB) and the perineurial barrier (PB) reviewed by Olsson (1990) and Ubogu (2013).

Early studies showed that, when injected into the experimental animal's circulation, various markers would penetrate minimally, or not at all, into the endoneurial compartment (Olsson 1972, 1990). Microscopic studies suggested that the

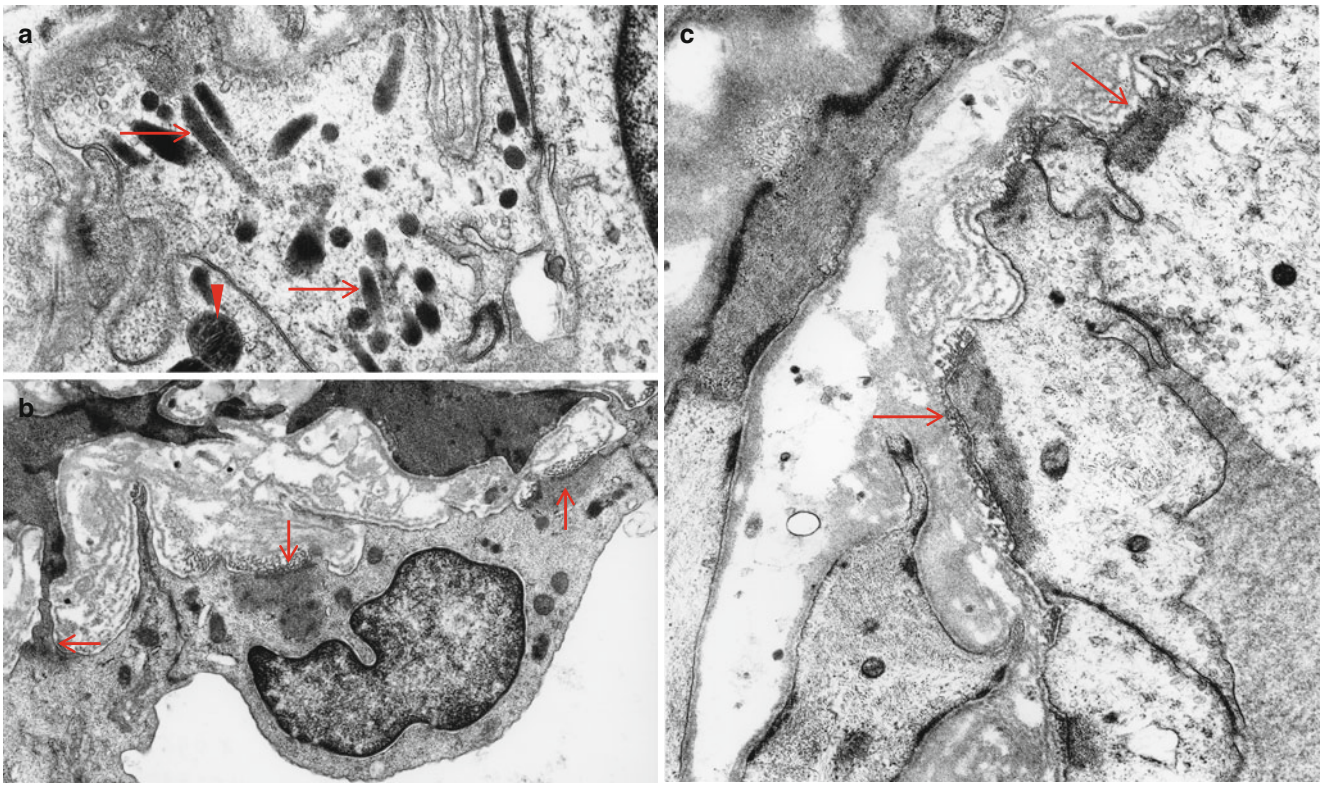

Fig. 6.6 (**a**) Large number of Weibel–Palade bodies (*arrows*) in endoneurial capillary endothelium. This patient suffered from Fabry disease: a single lipid inclusion is also seen (*arrowhead*). In (**b**, **c**) a complex of basal lamina condensation and anchoring filaments opposite focal filamentous accumulations (*arrows*) identifies these vessels as lymphatics (**a** 37,180×; **b** 19,760×)

site at which passage was blocked or markedly slowed was the innermost layer of the perineurium and the normally nonfenestrated endothelial cells of the endoneurium; the electron-dense tight junctions found at both of these sites form the anatomical basis of the PB and BNB, respectively. Vessels within the epineurium and perineurium contain numerous fenestrations and lack tight junctions. Studies using a mast cell degranulation promoting agent given intravascularly to experimental animals demonstrated that this structural barrier was also a functional barrier. Mast cell contents were liberated in the epineurium but not in the endoneurium (Olsson 1972). Substantial interspecies variation exists in the BNB (Olsson 1972). Consequently, the extent to which one can apply data derived from animals to human tissues in health and disease is uncertain.

Albumin can enter the endoneurium (Poduslo 1993), and immunohistochemical studies on normal nerve biopsy specimens suggest that IgG and to a lesser extent IgA also can penetrate this compartment, while IgM and complement (C3) probably cannot enter in significant amounts (Liebert et al. 1985; Schenone et al. 1988; Takatsu et al. 1985). These observations indicate that the BNB is a relative barrier, meaning that one macromolecule (e.g., IgA) might have a much slower diffusion or transport rate into the endoneurial compartment than another (e.g., IgG), but given sufficient time and a large enough concentration gradient between the two compartments, a certain amount of both macromolecules will accumulate (Mata et al. 1987). Accumulation of macromolecules in the subperineurial area is a common finding in normal and abnormal nerves (Graham and Johnson 1985; Liebert et al. 1985; Schenone et al. 1988; Van Lis and Jennekens 1977) and should not be ascribed undue significance.

This blood–nerve barrier is leaky in the spinal nerve roots and in the dorsal root and autonomic ganglia allowing access to exogenous tracers, some toxins, and plasma proteins. This has been attributed to a lack of tight junctions between the capillary endothelial cells of the endoneurial compartment at these sites.

6.2 Pathological Alterations

6.2.1 Alteration in the Blood–Nerve Barrier in Neuropathy

Many peripheral neuropathies alter the BNB. Diabetes, Guillain–Barré syndrome, paraproteinemic neuropathy, leprosy, and lead exposure are examples of extensively studied peripheral nerve diseases where careful observation of the

BNB indicates that it may be abnormal at times and that it potentially plays an important part in the pathogenesis of the neuropathy (see respective chapters for details). Whether such alterations in the BNB are primary or secondary to the neuropathy is a central question that has not been resolved in most cases (vide infra). In theory at least, an altered BNB can permit toxic substances to enter nerve and may cause increased endoneurial pressure with resultant reduced blood and nutrient flow, resulting in changes in the composition of the endoneurial milieu. These changes in turn may induce pathological processes such as fibrosis (Olsson 1990). An influx of vascular fluid into the endoneurium may result in alterations of the electrolyte concentration which permit the normal electrical function of peripheral nerve axons (Myers et al. 1983).

Immunohistological techniques permit study of alterations in the BNB in various human neuropathies (Liebert et al. 1985; Neuen et al. 1987; Van Lis and Jennekens 1977). IgM, ordinarily excluded from the endoneurium, frequently appears within it in inflammatory and vasculitic neuropathies. On the other hand, endoneurial IgM does not typically appear in metabolic, hereditary, or toxic neuropathies. An increase in the endoneurial content of smaller macromolecules such as IgG and albumin occurs in some noninflammatory neuropathies, representing perhaps a more subtle change in the BNB than the one which permits IgM to enter. In one study, the severity of disruption in the BNB correlated better with the presence of inflammation than with the severity of myelin or axon damage (Neuen et al. 1987).

An accumulation of macromolecules beneath the inner perineurial layer is commonly seen, perhaps due to entry via the endoneurial capillaries but blockage at the perineurium (Van Lis and Jennekens 1977). This accumulation of macromolecules seems to be particularly prominent in hypertrophic neuropathies (Van Lis and Jennekens 1977) and may correlate with the frequent finding of subperineurial edema in this setting.

Endoneurial vessel fenestration is always abnormal (Fig. 6.7). While more commonly associated with leprosy (Boddingius 1977, 1984), CIDP (Johnson 1977), and paraproteinemic neuropathy (Lach et al. 1993), this alteration is also found in diabetic neuropathy (Powell et al. 1985) and Wallerian degeneration (Ohara and Ikuta 1985). In addition to these settings, we have also found endoneurial fenestration in chronic axonal neuropathies of unknown etiology.

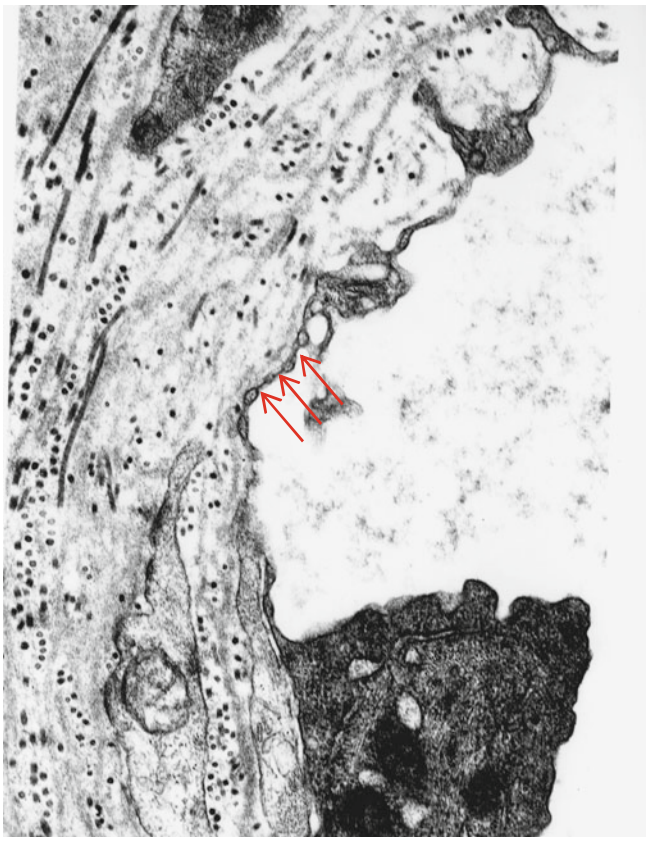

Fig. 6.7 Fenestration of endoneurial endothelium is shown (*arrows*) in a patient with CIDP (25,536×)

6.2.2 Endoneurial "Edema"

An increase in the amorphous or clear interstitial space of the endoneurium and subperineurial area is a common and nonspecific light microscopic finding. However, this finding is most closely associated with the hypertrophic neuropathies, familial or acquired (Behse et al. 1974; Matthews et al. 1970) (Fig. 6.8). The increased separation between nerve fibers and widening of the subperineurial space has been referred to as "endoneurial edema" and "subperineurial edema," respectively. This "edema" is lightly eosinophilic, stains weakly with Alcian blue or toluidine blue, and does not stain with PAS or Congo red (Asbury et al. 1971). Electron microscopy shows no specific features except for dispersal of normal elements, although at times a fine granular substance accumulates. Possibly this substance represents "acid mucopolysaccharide" material in keeping with the histostaining properties described above. Such granular material has not been a significant finding in biopsies we have examined; perhaps the granular appearance is an artifact related to fixation or preparation.

The tendency of macromolecules to accumulate in the subperineurial area in both normal and pathologically altered nerves (Van Lis and Jennekens 1977) may relate to the frequent observation of subperineurial "edema." Watanabe and Ohnishi (1979) demonstrated a significant enlargement of the subperineurial space in idiopathic polyradiculoneuropathy and thiamine deficiency-associated neuropathy. No correlation was found between prominence of subperineurial "edema" and severity of fiber damage or duration of illness (Watanabe and Ohnishi 1979). Such subperineurial space enlargement has also been described in a variety of inflammatory, toxic, metabolic, and inherited neuropathies.

Regions of endoneurial "edema" may be related to Renaut bodies. A fibrillar precursor of elastic fibers, oxytalan, is

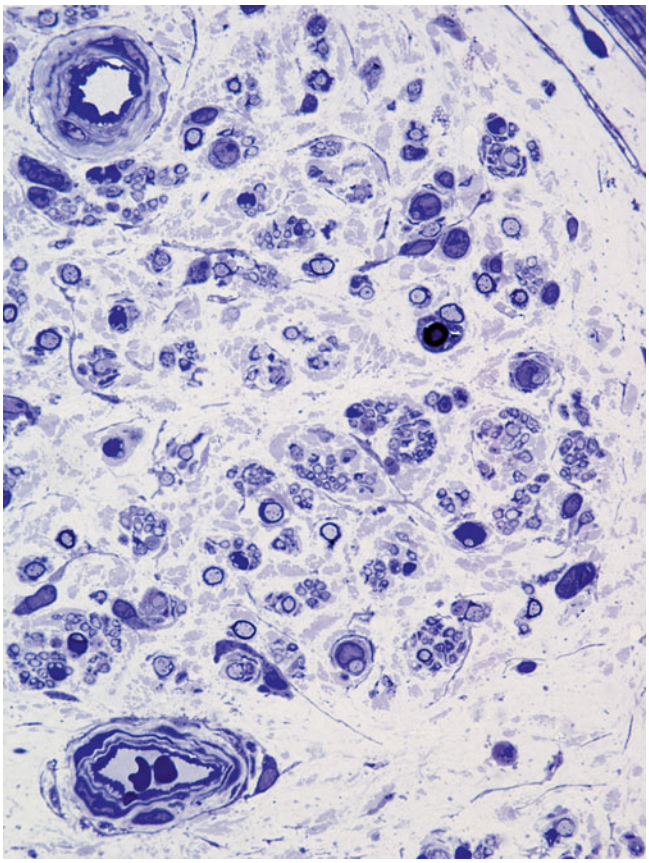

Fig. 6.8 Dispersion of endoneurial contents by increased intercellular matrix in CIDP (1 μm thick toluidine blue-stained plastic section, 1,000×)

frequently seen at sites of "edema" and in Renaut bodies. Fibroblasts with giant vacuoles are also often detected in both of these locations. Enlarged subperineurial regions devoid of axons and containing few or no cellular elements are often described as "subperineurial edema," but when fibroblastic configurations typical of Renaut bodies (Figs. 2.13c, d and 2.15a, b) are seen at this site, the distinction between "edema" and Renaut bodies becomes blurred. Certain ill-defined environmental conditions induce structural and functional changes in fibroblasts that result in the giant vacuolated appearance and in the production of acid mucopolysaccharide material and oxytalan (i.e., "edema"). In some instances, this process may proceed further to the formation of Renaut bodies. Indeed, precisely such a sequence of events has been reproduced experimentally in chronic nerve compression (Ortman et al. 1983).

While nerve "edema" may reflect deposition of acid mucopolysaccharides or oxytalan, or may represent a fixation artifact, it is also possible that this appearance may result from an osmotic increase in interstitial fluid. A balance of hydrostatic and osmotic pressures regulates endoneurial water content (Olsson 1990) and an increase in the macromolecular content of the interstitial compartment will cause an influx of fluid. This increase may result from pathological vascular permeability permitting an influx of albumin and other macromolecules, but can also theoretically occur without alteration in the BNB. For example, an influx of fluid could occur as a consequence of the release of macromolecules by endoneurial cells or the entrapment of macromolecules within the endoneurium by biochemical modification (Olsson 1990).

An increase in endoneurial interstitium is not always due to "edema." We have seen cases of IgM paraproteinemic neuropathy where massive buildup of IgM in the endoneurium was present and caused the neuropathy. In this setting the acellular spaces were PAS positive.

6.2.3 Significance of Alterations in the Blood–Nerve Barrier

A central question is whether the increase in BNB permeability seen in neuropathy is secondary to axon and/or myelin damage or whether the permeability change is primary, with resultant nerve damage. Studies of Wallerian degeneration and toxic neuropathy demonstrate that the BNB normally loses its integrity during the early phases of axonal degeneration or demyelination and gradually recovers over several months, usually in parallel with return of axons and their myelin sheaths (Bouldin et al. 1991; Ohara and Ikuta 1985; Seitz et al. 1989). Latker et al. (1991) showed that the BNB recovered in the absence of nerve fiber regeneration, while the PB did not. In a lead neuropathy model, permeability and fluid contents changed only after substantial quantities of lead had entered the endoneurial compartment (Poduslo 1993). Although such data suggests the primacy of axon and Schwann cell changes, alterations in vascular permeability and endoneurial fluid composition have frequently been postulated to be contributors to the severity of neuropathy, in diseases ranging from diabetes and inflammatory neuropathies to leprosy and amyloidosis (Boddingius 1977; Brosnan et al. 1990; Hahn et al. 1985; Koski 1992; Poduslo 1993). Computer models and in vivo experimental work suggest that transperineurial vessels, especially venules, will become distorted and compressed when endoneurial pressure is increased, possibly resulting in reduced blood flow and injury to neural elements (Kalichman and Myers 1991; Myers et al. 1986, 1991).

6.3 Focal Ischemic Injury of Peripheral Nerves

The vascular architecture of peripheral nerves results in a high degree of resistance to focal ischemia, as reviewed above. Furthermore, the metabolic demands of peripheral nerve are low relative to other neural tissues (Kihara and Low 1990). Nevertheless, acute ischemia is clinically

important (Olsson 1972), most obviously in the setting of vasculitic neuropathy and possibly in diabetic neuropathies. Numerous experimental models have explored nerve ischemia, but the interspecies variability in vascular structure and function should raise a flag of caution when extending such data to human ischemic neuropathy (Olsson 1972). Conversely, the possible confounding factor of nerve damage due to inflammatory mediators cannot be excluded in the human vasculitic neuropathies. Thus, a combination of human and experimental data is reviewed below in order to construct a picture of the effect of focal ischemia on peripheral nerve.

6.3.1 Fascicular Geography of Nerve Damage

6.3.1.1 Human Material

Dyck et al. studied limb nerves in autopsy material of patients with rheumatoid arthritis. With over 15,000 sections examined in one case, this work has yielded excellent insight into the distribution of nerve lesions in focal ischemia in human disease (Dyck et al. 1972). Various patterns of axonal injury occurred. In more proximal nerve segments, centrofascicular degeneration of fibers was the most common observation, but as the examination moved more distally, there was increasing admixture of intact and degenerating fibers. This increase presumably resulted from the inter- and intrafascicular intermingling that normally occurs as a nerve trunk progresses distally. Coagulative necrosis was not seen, and there was no correlation between regions of axonal degeneration and presence or absence of vascular occlusion. Similarly, in our experience with nerve biopsy in vasculitic neuropathies, the most typical pattern is multifocal Wallerian degeneration of variable severity in adjacent fascicles (Fujimura et al. 1991; Hawke et al. 1991). Much less frequently we have observed centrofascicular injury or wedge-shaped regions of axon loss that extend towards the perineurium. This observation is expected because the sural is a distal nerve trunk.

6.3.1.2 Experimental Material

In experimental animal models of large vessel occlusion, the centrofascicular pattern of axon degeneration has been produced most consistently, typically in large proximal nerve fascicles. On the other hand, distal nerve segments showed a more randomly disposed multifocal pattern of axonal degeneration (Hess et al. 1979; Korthals and Wisniewski 1975). A zone of more tenuous blood flow in the center of the nerve fascicle was shown to be models of ischemia produced by large vessel ligation (Sladky et al. 1985), thus providing an explanation for selective centrofascicular injury. Another possibility is that in endoneurial ischemia a simple transperineurial diffusion of oxygen supplies some of the nerve's requirements, thus protecting the subperineurial area (McManis et al. 1993). Alternatively, Nukada and Dyck (1984) found a higher capillary density in the subperineurial area than in the centrofascicular region. The studies of McManis and Low (1988) favor the importance of transperineurial oxygen diffusion. During acute ischemia there was no significant gradient between the subperineurial and centrofascicular regions in blood flow, but oxygen tension was clearly higher in the subperineurial area, presumably as a consequence of direct oxygen diffusion from the pool of oil in which the nerve fascicle was maintained (McManis and Low 1988). This explanation agrees with the observation that smaller fascicles are less severely affected than large fascicles (Korthals et al. 1978), since diffusion through the perineurium reaches a greater proportion of the fascicular contents in the former. A wedge-shaped or subperineurial region of axonal degeneration has been produced less frequently (Nukada et al. 1993). Occlusion of transperineurial arterioles, perhaps by a rise in endoneurial pressure, may result in subperineurial ischemia and axonal degeneration (Nukada et al. 1993).

To study microvessel occlusion Nukada and Dyck (1984) injected 15 μm microspheres into the arterial supply of rat sciatic nerve, producing blood flow deficits restricted to the capillary level. Obstruction of blood flow in individual microvessels did not induce fiber degeneration, but when sufficient vessels were occluded, a centrofascicular core of degenerating fibers emerged. Parry and Brown (1982) injected arachidonic acid into the femoral artery of rats, producing ischemia through "… platelet aggregation and occlusion of vasa nervorum." Again, a centrofascicular pattern of axonal degeneration was often identified.

Consequently, experimental and clinical data suggest that regardless of whether large or small vessels are occluded, the centers of nerve fascicles are more vulnerable to ischemia than the subperineurial area. However, this appearance is usually seen only at proximal "watershed" regions, and the intermingling of nerve fibers as the trunk courses distally results in the appearance of multifocal axonal degeneration as the consequence of more proximal ischemic events.

6.3.2 Involvement of Endoneurial Contents

6.3.2.1 Human Material

Reports on human biopsy material in vasculitic neuropathy are in conflict regarding the issue of whether there is preferential injury of any fiber type. Said, Fujimura, and colleagues demonstrated that large myelinated axons are more severely involved than small myelinated axons and that unmyelinated fibers are relatively spared except in the most severe cases (Fujimura et al. 1991; Said et al. 1988). However, other workers have not made this observation (Hawke et al. 1991;

Vital and Vital 1985). Segmental demyelination has been observed in vasculitic neuropathy and was thought to be secondary to axonal damage (Fujimura et al. 1991) or a primary effect of ischemia on Schwann cells (Vital and Vital 1985).

While axons and, to a lesser extent, Schwann cells are the principal targets of peripheral nerve ischemia, other cell types may be involved. The perineurium, in particular, may show focal damage and proliferation suggestive of reaction to a localized insult. Formation of a microneuroma is a rare but highly suggestive observation in vascular neuropathies (Figs. 17.2 and 17.4).

6.3.2.2 Experimental Material

Animal experiments have also been in conflict. No evidence of selective myelinated fiber loss was seen in the vessel ligation studies of Hess et al. (1979), but unmyelinated fibers were most often relatively spared. Parry and Brown (1982) used an arachidonic acid injection model and made the surprising observation that small myelinated and unmyelinated fibers were the most severely affected.

Intra-axonal accumulations of organelles are seen at the boundaries of ischemic regions, suggesting the presence of alterations in axoplasmic transport (Korthals et al. 1978; Nukada and Dyck 1987). In another experimental model of ischemia, the internodes just proximal to sites of axonal degeneration sometimes showed demyelination and remyelination, and less often this was seen even with no evidence of axonal degeneration (Hess et al. 1979). Similarly, the microsphere model of Nukada and Dyck (1987) demonstrated demyelination in association with accumulations of axonal organelles in the regions bordering severe ischemia. Such observations suggest that demyelination is secondary to axonal injury.

6.4 Chronic Vascular Insufficiency

In contrast to the clear-cut relation between acute ischemia and nerve damage, the importance of chronic ischemia due to vascular disease is difficult to quantify, reproduce, and interpret. Yet, this has been postulated as a causative factor in various neuropathies including diabetes, amyloidosis, leprosy, dysproteinemia, and in the "neuropathy of aging." Ischemic neuropathy may also follow aortic atherosclerosis, use of an intra-aortic balloon pump, abdominal aortic aneurysms or their repair, overall low cardiac output, hypercoagulable/hyperviscosity states, use of vasoconstrictors like methysergide, or prolonged tourniquet time in surgery (Laghi Pasini et al. 1996).

A study of 32 patients with severe symptomatic vascular disease of the legs and no other identifiable cause of neuropathy exemplifies the possible importance of chronic vascular insufficiency. The majority of patients suffered paresthesias and sensory loss, while half had weakness or wasting (Eames and Lange 1967). Ankle reflexes were reduced or absent in 13, and the presence of this finding correlated with the severity of vascular compromise in that limb. It appears that revascularization does not remedy the problem (Hunter et al. 1988).

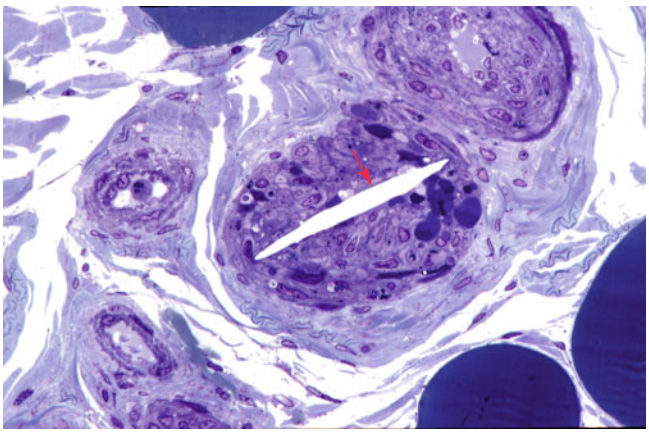

Fig. 6.9 Lucent cholesterol shard (*arrow*) within the lumen of a small arteriole in patient with cholesterol embolism (1 μm toluidine blue-stained plastic section, 1,000×)

Peripheral neuropathy has been described in a population of patients with a history of vascular catheterization or in patients with severe aortic atherosclerosis. In some of these patients, cholesterol clefts have been found in the lumina of small epineurial arteries (arrow, Fig. 6.9), cholesterol emboli syndrome, Bendixen et al. 1992), only occasionally resulting in necrotizing arteritis, but with chronic axonal degeneration involving peripheral and intramuscular nerves.

Investigators ascribe a broad spectrum of histological changes to chronic arterial insufficiency (Eames and Lange 1967; Farinon et al. 1984; Hunter et al. 1988; Vital et al. 1986). Variably severe active and chronic axonal loss has been described, ranging from no significant difference from controls (Chopra and Hurwitz 1969) to 50 % loss (Farinon et al. 1984; Hunter et al. 1988). Large myelinated fibers may be more severely involved, but this is not always the case (Vital et al. 1986). An increase in denervated Schwann cell bands and numerous dystrophic unmyelinated axons suggests that unmyelinated fibers are not spared (Vital et al. 1986). The severity of axonal loss is not correlated with the severity of vascular disease (Farinon et al. 1984). Regenerative activity may be very prominent (Gemignami et al. 1989). Nonspecific axonal changes including atrophy, organelle accumulations, and Schwann cell–axon networks are observed. A wide spectrum of segmental myelin changes has also been seen, including onion bulbs (Farinon et al. 1984).

Endoneurial capillaries show thickening and reduplication of basement membranes, hyperplasia and hypertrophy of endothelial cells, and projection of small endothelial cell

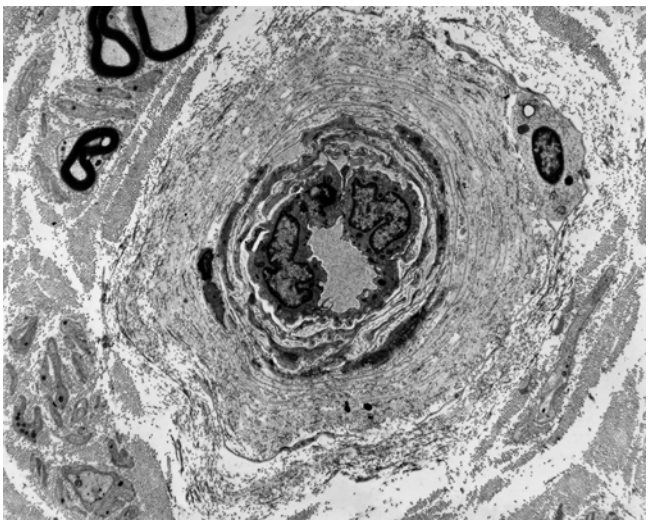

Fig. 6.10 Reduplication of basal lamina with intervening collagen in an endoneurial microvessel (3,830×)

processes into the vessel lumen (Fig. 6.10). Occasional sites of microvascular occlusion may be identified (Eames and Lange 1967; Hunter et al. 1988). Muscular vessels in the epineurium may show medial smooth muscle proliferation and disorganization of the layers composing the vessel wall.

The nonspecificity of such changes makes interpretation difficult. Most of the patients studied are over 60 years of age, and such alterations are also seen with normal aging. Indeed, chronic ischemia has been proposed to contribute to the "neuropathy of aging" and to diabetic neuropathy, with similar histological findings. Often, arteriopathic patients have concomitant small vessel disease, even in the absence of diabetes. Thus, at present there is little hard evidence to suggest that large vessel ischemia causes obvious peripheral nerve injury. In an animal model of chronic endoneurial ischemia, the predominant morphologic abnormality was axonal swelling and retraction with remodeling of myelin at the node of Ranvier, but without significant axonal loss (Sladky et al. 1991). This correlated with slowing of conduction.

6.5 Chronic Hypoxemia

Patients with chronic hypoxemic lung disease are sometimes found to have a mild neuropathy that cannot be ascribed to other causes (Appenzeller et al. 1968; Malik et al. 1990; Paramelle et al. 1986). Symptoms include mild sensory complaints, and objective signs are minimal, largely confined to distal sensory abnormalities or diminished ankle jerks. Electrophysiological tests reveal a distal predominantly axonal process.

The nerve biopsy alterations in these patients have correlated best with duration and severity of hypoxia (Appenzeller et al. 1968; Malik et al. 1990; Paramelle et al. 1986). Although Malik and co-workers (1990) found no significant alterations in myelinated fiber number and distribution, other workers have documented prominent chronic and active axonal degeneration (Appenzeller et al. 1968; Paramelle et al. 1986). An increase in denervated Schwann cell subunits and concurrent decrease in unmyelinated axons may occur (Paramelle et al. 1986). Teased nerve fibers have shown predominantly paranodal demyelination and a slight increase in the frequency of axonal degenerative changes (Malik et al. 1990). Significant perineurial thickening may be seen. Endoneurial vessels show hyperplasia and hypertrophy of endothelial cells and increased basement membrane thickness, resulting in narrowing of the vessel lumen (Malik et al. 1990; Paramelle et al. 1986; Stoebner et al. 1989). The significance of such changes is uncertain as the same caveats that were noted above for neural changes in chronic vascular insufficiency are applicable to the neural changes of chronic hypoxemia.

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