catheter procedures and severe aortic atherosclerosis are probably the most important risk factors in susceptible patients. Biopsy of an affected nerve and muscle shows cholesterol crystals in the lumina of epineurial and epimysial vessels accompanied by necrotizing arteritis and foreign body giant cell reaction (Fig. 6). It can be argued that intraluminal deposition of cholesterol leads to arteritis rather than a coincidence of two separate disorders. Cholesterol clefts are not seen in other arteritic processes that result in the entrapment of cholesterol crystals. Similar pathologic findings in animals occur after injection of human atheromata. Necrotizing arteritis was noted at other sites of the peripheral nervous system in patients with cholesterol emboli neuropathy, including the lumbar plexus and skeletal muscles, and in other organs at postmortem examination.

**Familial Amyloid Polyneuropathy and Primary Systemic Amyloidosis**

Familial amyloid polyneuropathy is a group of autosomal dominant disorders characterized by deposits of amyloid fibrils in the peripheral nerve (24, 25). The amyloid fibrils are derived from mutant forms of a plasma protein transthyretin or prealbumin (26). The various familial amyloid polynepathy phenotypes differ in the clinical presentation of neuropathy, age at onset from the third to seventh decade, and the pattern of systemic involvement, variably affecting skin, liver, heart, vitreous, and other organs. Although the polyneuropathy is mainly sensory, one reported patient with an Asp 70 mutation presented with carpal tunnel syndrome followed by generalized weakness, wasting, and fasciculation, suggesting prominent motor nerve involvement (27). Sural nerve biopsy in that patient revealed axonopathy with homogenous masses of hyaline, deeply eosinophilic material deposited in the endoneurium and epineurium, typical tinctorial and optical properties of amyloid, and immunoreactivity to transthyretin antisera (Fig. 7). By electron microscopy, the

**FIG. 6.** Cholesterol emboli syndrome. A cross-section of gastrocnemius muscle stained with hematoxylin and eosin demonstrates active and healed arteritis in the vicinity of a cholesterol cleft (circle).

**FIG. 7.** Familial amyloidotic polyneuropathy. A longitudinal section of sural nerve stained with Congo red and viewed under crossed polarized lenses demonstrates endoneurial (n) amyloid deposition immediately subjacent to the perineurium (p).
Amyloid deposits appeared as fine, haphazard, non-branched filaments with a diameter of 8 to 10 nm.

Painful small-fiber neuropathy with progressive autonomic involvement is a common presenting feature of primary systemic amyloidosis. It results from the excessive production of immunoglobulin light chains due to plasma cell dyscrasias and is detectable by immunohistochemical analysis of a nerve biopsy specimen. In one patient with generalized weakness and wasting, laboratory studies suggested a neuropathic cause; however, electrodiagnostic studies were more compatible with a myopathic process, and muscle biopsy instead showed amyloid deposits in myofibers (Fig. 8A and B).

**Adult Polyglucosan Body Disease**

Adult polyglucosan body disease is a rare neurologic disorder characterized clinically by peripheral neuropathy with motor and sensory loss, corticospinal tract signs, urinary incontinence, and dementia and pathologically by polyglucosan bodies distributed in the peripheral and central nervous system of affected patients. One patient with autopsy proven adult polyglucosan body disease simulated amyotrophic lateral sclerosis (ALS) clinically and pathologically (28). At postmortem examination, polyglucosan bodies were found extensively in neuronal and astrocytic processes, nerve roots, and peripheral nerves. A second similar patient had polyglucosan bodies in myelinated axons in a sural nerve biopsy (Fig. 9A and B).

**Neurolymphomatosis**

Neurolymphomatosis is defined histologically by lymphomatous infiltration of the nerve in a biopsy specimen or at postmortem examination. Virtually all patients present with signs of peripheral neuropathy. Of 41 histologically proven cases, 16 were diagnosed antemortem by nerve biopsy and the remainder at postmortem examination; all but one had non-Hodgkin's lymphoma (29,30). Less than one half of patients have known lymphoma; therefore, nerve biopsy is crucial in establishing the diagnosis and prompting effective therapy. One recently studied patient with progressive leg weakness was found to have B-cell non-Hodgkin's lymphoma in a superficial peroneal nerve biopsy (Fig. 10A and B). He improved neurologically with intravenous cyclophosphamide therapy, but a higher grade of lymphoma appeared 6 months later as an isolated neck mass prompting further therapy.

**Charcot-Marie-Tooth Neuropathies**

Prominent motor involvement is the cause of the common foot deformity, pes cavus, and the “inverted champagne bottle” appearance of the leg in long-standing cases of Charcot-Marie-Tooth (CMT) neuropathy. The classification of the CMT neuropathies historically relied on the concordance of the clinical aspects, inheritance patterns, and electrophysiologic and nerve biopsy findings. However, modern genetic analysis added a fifth criterion, demonstration of the responsible gene defect. These include point mutations, duplications, overexpressions, and other alterations in the responsible gene loci for peripheral myelin protein 22, Po, and connexin 32 situated, respectively, on chromosomes 17, 1, and the X chromosome; other gene defects have been reported on chromosome 3 and 8 (31). There is generally little difficulty in establishing the diagnosis of CMT in index cases of well-studied families. However, several clinical situations might constitute diagnostic dilemmas warranting nerve biopsy to provide clinicopathologic correlation, for example, index cases of CMT1A with de novo duplications at the 17p11.2-12; families with hereditary neu-

![FIG. 8. Amyloid myopathy. Vastus lateralis muscle viewed in cross-section (A) and in longitudinal section (B) shows amyloid deposition at the peripheral of myofibers stained with Masson trichrome (arrows).](image-url)
ropathy with liability to pressure palsy (HNPP) or so-called tomaculous neuropathy, in which linkage to chromosome 17p may be lacking; or patients with CMT2C that resemble hereditary juvenile hereditary spinal muscular atrophy clinically.

**Chronic Inflammatory Demyelinating Polyneuropathy**

Chronic inflammatory demyelinating polynyropathy (CIDP) is probably the most common cause of undiagnosed demyelinating neuropathy. The disorder is characterized clinically by slow or stepwise progressive or relapsing symmetric sensorimotor neuropathy with loss of tendon reflexes, elevation of the cerebrospinal fluid protein content, widespread slowing of nerve conduction velocities, and morphologic evidence of primary demyelination in a nerve biopsy. Several factors may contribute to the occurrence of prominent motor involvement in some affected patients (32). First, a relatively larger proportion of large myelinated motor fibers contained in mixed nerves could lead to a greater devastation of motor function. Second, motor fibers in the ventral roots may be selectively involved pathologically by inflammatory demyelinating lesions and axon loss. Third, demyelinated motor fibers might be selectively impaired due to their lower safety factor for impulse propagation. Fourth, depending on the fascicular arrangement of motor fibers in a given nerve trunk, inflammatory-demyelinating lesions might be relatively restricted to motor fascicles, leaving sensory fibers intact.

There is no general consensus as to the appropriateness of nerve biopsy in all patients with CIDP. However, most authorities would probably advocate biopsy of an affected nerve to confirm the diagnosis pathologically and to exclude other etiologies before commencing therapy. Nonetheless, nerve biopsy findings can be quite variable. Among 60 patients with CIDP (33), 48% had

**FIG. 9.** Adult polyglucosan body disease. A: A polyglucosan body is seen within a large myelinated axon from a ventral root in a semithin section stained with toluidine blue (arrow). B: Several polyglucosan bodies are seen within a myelinated axon stained with hematoxylin and eosin (arrow).

**FIG. 10.** Neurolymphomatosis. A: Superficial peroneal sensory nerve demonstrates an intense lymphocytic invasion stained with H&E, which in B stains positively for leukocyte common antigen (LCA). Further evaluation showed gene rearrangement indicative of a malignant non-Hodgkin lymphoma.