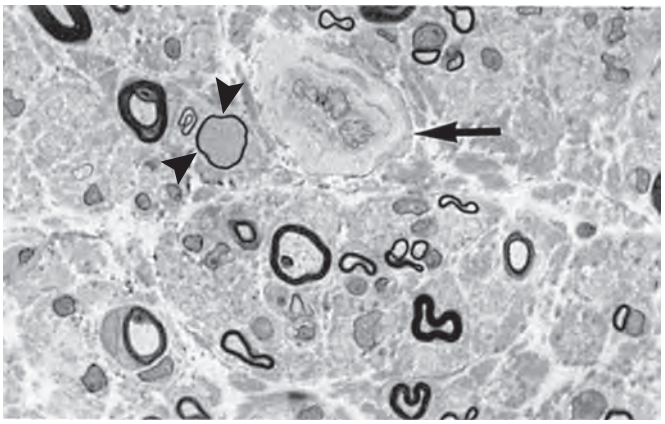

**Figure 27-6** Diabetic neuropathy with marked loss of myelinated fibers, a thinly myelinated fiber (*arrowheads*), and thickening of endoneurial vessel wall (*arrow*).

***Clinical Features.*** *Distal symmetric diabetic polyneuropathy* typically presents with sensory symptoms, like numbness, loss of pain sensation, difficulty with balance, and paresthesias or dysesthesias. Paresthesias or dysesthesias are so called "positive" symptoms—painful sensations that result from abnormal discharges of damaged nerves. Neuropathy leads to considerable morbidity, in particular an increased susceptibility to foot and ankle fractures and chronic skin ulcers, which may eventually lead to amputations.

Another manifestation is *dysfunction of the autonomic nervous system*; this affects 20% to 40% of individuals with diabetes mellitus, nearly always in association with a distal sensorimotor neuropathy. Diabetic autonomic neuropathy has protean manifestations, including postural hypotension, incomplete emptying of the bladder (resulting in recurrent infections), and sexual dysfunction. Some affected individuals, especially older adults with a long history of diabetes, develop a peripheral neuropathy that manifests with asymmetric presentations, including *mononeuropathy*, *cranial neuropathy* and *radiculoplexus neuropathy*. The latter is a devastatingly painful acute disorder that presents in the distribution of the brachial or lumbosacral nerve plexus. It is often monophasic and can improve over several months. These asymmetric manifestations may be caused by microvascular disease.

### Other Metabolic, Hormonal, and Nutritional Neuropathies

A diverse group of metabolic, hormonal, and nutritional disorders are associated with peripheral neuropathy, including the following:

- *Uremic neuropathy.* Most individuals with renal failure have a peripheral neuropathy. Typically this is a distal, symmetric neuropathy that may be asymptomatic or may be associated with muscle cramps, distal dysesthesias, and diminished deep tendon reflexes. In these patients axonal degeneration is the primary event; occasionally there is secondary demyelination. Regeneration and recovery are common after dialysis.
- *Thyroid dysfunction.* Hypothyroidism can lead to compression mononeuropathies such as carpal tunnel syndrome or cause a distal symmetric predominantly sensory polyneuropathy. In rare cases, hyperthyroidism is associated with a neuropathy resembling Guillain-Barré syndrome.
- *Vitamin $B_{12}$ (cyanocobalamin) deficiency* classically results in subacute combined degeneration with damage to long tracts in the spinal cord (Chapter 28), and also peripheral nerves.
- *Deficiencies of vitamin $B_1$ (thiamine), vitamin $B_6$ (pyridoxine), folate, vitamin E, copper, and zinc* have all been associated with peripheral neuropathy.

#### *Toxic Neuropathies*

Peripheral neuropathies may appear after *exposure to industrial or environmental chemicals, biologic toxins, or therapeutic drugs.* Important causes of toxic peripheral nerve damage include alcohol (independent of associated nutritional deficiencies), heavy metals (lead, mercury, arsenic, and thallium), and organic solvents. Various medications can cause toxic nerve damage, but the most notorious are chemotherapeutic agents. These include vinca alkaloids and taxanes, microtubule inhibitors that interfere with axonal transport, and cisplatin, which may cause a neuronopathy.

#### *Neuropathies Associated with Malignancy*

Neuropathies associated with cancers may stem from local effects, complications of therapy, paraneoplastic effects, or (in the case of B-cell tumors) tumor-derived immunoglobulins.

- *Direct infiltration or compression of peripheral nerves* by tumor is a common cause of mononeuropathy and may be a presenting symptom of cancer. These neuropathies include *brachial plexopathy* from neoplasms of the apex of the lung, *obturator palsy* from pelvic malignant neoplasms, and *cranial nerve palsies* from intracranial tumors or tumors of the base of the skull. A *polyradiculopathy* involving the lower extremity may develop when the cauda equina is involved by meningeal carcinomatosis.
- In addition to complications of chemotherapy (discussed earlier), damage to nerves in cancer patients may be caused by *radiation*, *poor nutrition* and *infection*.
- *Paraneoplastic neuropathies*. These can occur at any time during the patient's course, but often precede the diagnosis of the underlying tumor. *Sensorimotor neuronopathy is the most common paraneoplastic form,* but a chronic inflammatory demyelinating polyradiculoneuropathy-like picture, plexopathy, and autonomic neuropathy may also be seen. Paraneoplastic sensorimotor neuronopathy is most commonly associated with small cell lung cancer. Antibodies that recognize proteins expressed by cancer cells and normal neurons (for example anti-Hu antibodies) are often present, but the damage appears to be mediated by a CD8+ cytotoxic T-cell attack on dorsal root ganglion cells. Sensory symptoms usually start distally in an asymmetric and multifocal pattern. Other patients with so-called anti-CV2 autoantibodies (which recognize CRMP5, an intracellular signaling protein) tend to present with a mixed axonal and demyelinating sensorimotor neuropathy.