point of focus here. Each of these disorders is also discussed in more detail in Chapter 8.

Leprosy (Hansen Disease)

Peripheral nerves are involved in both lepromatous and tuberculoid leprosy (discussed in Chapter 8).

- In *lepromatous leprosy,* Schwann cells are invaded by *Mycobacterium leprae*, which proliferate and eventually infect other cells. There is evidence of segmental demyelination and remyelination and loss of both myelinated and unmyelinated axons. As the infection advances, endoneurial fibrosis and multilayered thickening of the perineurial sheaths occur. Affected individuals develop a symmetric polyneuropathy that is most severe in the relatively cool distal extremities and in the face because lower temperatures favor mycobacterial growth. The infection prominently involves pain fibers, and the resulting loss of sensation contributes to injury, since the patient is rendered unaware of injurious stimuli and damaged tissues. Thus, large traumatic ulcers may develop.
- *Tuberculoid leprosy* is characterized by an active cell-mediated immune response to *M. leprae* that is usually manifest as dermal nodules containing granulomatous inflammation. The inflammation injures cutaneous nerves in the vicinity; axons, Schwann cells, and myelin are lost, and there is fibrosis of the perineurium and endoneurium. In tuberculoid leprosy, affected individuals have much more localized nerve involvement.

Lyme Disease

Lyme disease causes various neurologic manifestations in the second and third stage of the disease. These include polyradiculoneuropathy and unilateral or bilateral facial nerve palsies.

HIV/AIDS

Patients infected with human immunodeficiency virus (HIV) develop several patterns of peripheral neuropathy that are poorly understood, but all appear to be related in some way to immune dysregulation. Early stage HIV infection can be associated with mononeuritis multiplex and demyelinating disorders that may resemble Guillain-Barré syndrome or chronic inflammatory demyelinating polyradiculoneuropathy. More commonly, later stages of HIV infection are associated with a distal sensory neuropathy that is often painful.

Diphtheria

Diphtheria is most commonly found in the developing world and is a continuing medical problem because of incomplete immunization or waning immunity in adults. *Peripheral nerve dysfunction results from the effects of the diphtheria exotoxin.* It produces an acute peripheral neuropathy associated with prominent bulbar and respiratory muscle dysfunction, which can lead to death or long-term disability. The mechanism of action of diphtheria toxin is described in Chapter 8.

Varicella-Zoster Virus

Varicella-zoster is one of the most common viral infections of the peripheral nervous system. Following chickenpox, a latent infection persists within neurons of sensory ganglia. If the virus is reactivated, sometimes many years later, it may be transported along the sensory nerves to the skin. Here it infects keratinocytes, leading to a *painful, vesicular skin eruption (shingles) in a distribution that follows sensory dermatomes.* Most common is the involvement of thoracic or trigeminal nerve dermatomes. The factors underlying reactivation of the virus are not fully understood, but decreased cell-mediated immunity is suspected to play a role. In a small proportion of patients, weakness is also apparent in the same distributions. Affected ganglia show neuronal death, usually accompanied by abundant mononuclear inflammatory cell infiltrates; focal necrosis and hemorrhage may also be found. Peripheral nerves show degeneration of the axons that belong to the dead sensory neurons. Focal destruction of the large motor neurons of the anterior horns or cranial nerve motor nuclei may be seen at the corresponding levels. Intranuclear inclusions generally are not found in the peripheral nervous system.

Metabolic, Hormonal, and Nutritional Neuropathies

Diabetes

Diabetes is the most common cause of peripheral neuropathy. The prevalence of this complication depends on the duration of the disease; up to 50% of patients with diabetes overall and up to 80% of those who have had the disease for more than 15 years have clinical evidence of peripheral neuropathy. Patients with type 1 and type 2 diabetes are affected (Chapter 24). Several distinct clinicopathologic patterns of diabetes-related peripheral neuropathy are recognized (described later), but the most common by far is an ascending distal symmetric sensorimotor polyneuropathy.

Pathogenesis. The mechanism of diabetic neuropathy is complex and not completely resolved; both metabolic and secondary vascular changes are believed to contribute to the damage of neurons and Schwann cells. Hyperglycemia causes the nonenzymatic glycosylation of proteins, lipids, and nucleic acids. The resulting advanced glycosylation end products (AGEs) may interfere with normal protein function and activate inflammatory signaling through the receptor for AGE. Excess glucose within cells is reduced to sorbitol, a process that depletes NADPH and increases intracellular osmolality. These and other metabolic disturbances may predispose peripheral nerves to injury by reactive oxygen species. In addition, the vascular injuries that occur in chronic diabetes due to hyperlipidemia and other metabolic alterations may cause ischemic damage of the nerves.

MORPHOLOGY

In individuals with a **distal symmetric sensorimotor neuropathy,** the predominant pathologic finding is an axonal neuropathy. Nerve biopsies show reduced numbers of axons. Variable degrees of ongoing axonal damage, marked by degenerating myelin sheaths and regenerative axonal clusters, may be present. Endoneurial arterioles show thickening, hyalinization, and intense periodic acid–Schiff positivity of their walls and extensive reduplication of basement membranes (Fig. 27-6).