MORPHOLOGY

The dominant histopathologic finding is **inflammation of peripheral nerves**, manifested as perivenular and endoneurial infiltration by lymphocytes, macrophages, and a few plasma cells. Segmental demyelination affecting peripheral nerves is the most prominent lesion, but damage to axons is also seen, particularly when the disease is severe. Electron microscopy has identified an early effect on myelin sheaths. The cytoplasmic processes of macrophages penetrate the basement membrane of Schwann cells, particularly in the vicinity of the nodes of Ranvier, and extend between the myelin lamellae, stripping the myelin sheath from the axon. Ultimately, the remnants of the myelin sheath are engulfed by the macrophages. Inflammation and demyelination can be widespread in the peripheral nervous system but are typically most prominent proximally, close to the nerve roots.

Clinical Features. The clinical picture is dominated by ascending paralysis and areflexia. Deep tendon reflexes disappear early in the process. Sensory involvement, including loss of pain sensation, is often present but is usually not a prominent feature. Nerve conduction velocities are slowed because of multifocal destruction of myelin segments in many axons within a nerve. Cerebrospinal fluid (CSF) protein levels are elevated due to inflammation and altered permeability of the microcirculation within the spinal roots as they traverse the subarachnoid space. Inflammatory cells, on the other hand, remain confined to the roots, therefore, there is little or no CSF pleocytosis. Many patients spend weeks in hospital intensive-care units before recovering normal function. With improved supportive respiratory care, cardiovascular monitoring, and prophylaxis against deep venous thrombosis, the mortality rate has fallen. Plasmapheresis and intravenous immunoglobulin appear to be beneficial, apparently because these remove pathogenic antibodies and suppress immune function, respectively. However, 2% to 5% of affected patients still die of respiratory paralysis, autonomic instability, cardiac arrest, or related complications, and up to 20% of hospitalized survivors suffer long-term disability.

Chronic Inflammatory Demyelinating Poly(radiculo)neuropathy

This is the most common chronic acquired inflammatory peripheral neuropathy, characterized by symmetrical mixed sensorimotor polyneuropathy that persists for 2 months or more. By definition, signs and symptoms must be present for at least 2 months but often the disease evolves over years, usually with relapses and remissions. While typically there is a symmetric, mixed sensorimotor polyneuropathy, some patients may present with predominantly sensory or motor impairment. Clinical remissions can often be achieved with immunosuppressive therapies, such as glucocorticoids, intravenous immunoglobulin, plasmapheresis, and biologic agents directed against T cells or B cells. The time course and the response to steroids distinguish chronic inflammatory demyelinating polyradiculoneuropathy from Guillain-Barré syndrome.

Pathogenesis. T cells as well as humoral factors are implicated in the inflammatory process. Molecules expressed at the Schwann cell-axon junction and in noncompact areas of myelin appear to be the target of the immune response. Complement-fixing IgG and IgM can be found on the myelin sheath, and the deposition of these opsonins leads to recruitment of macrophages that strip myelin from axons. Sural nerve biopsies show evidence of recurrent demyelination and remyelination associated with proliferation of Schwann cells. When excessive, this proliferation leads to the formation of so-called *onion-bulbs* – structures in which multiple layers of Schwann cells wrap around an axon like the layers of an onion (Fig. 27-5).

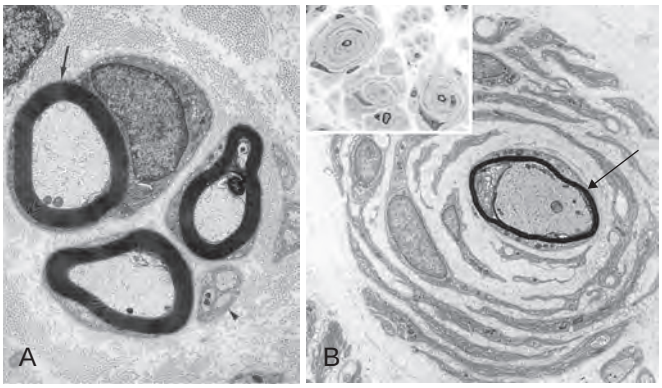

Figure 27-5 Onion bulb neuropathy. Compared with the normal ultrastructure of axons in a nerve **(A),** an "onion bulb" **(B)** is composed of a thinly myelinated axon (*arrow*) surrounded by multiple concentrically arranged Schwann cells. *Inset*, Light-microscopic appearance of an onion bulb neuropathy, characterized by "onion bulbs" surrounding axons. (**B,** Courtesy G. Richard Dickersin, MD, from Diagnostic Electron Microscopy: A Text Atlas. New York, Igaku-Shoin Medical Publishers, 2000, p 984.)

Neuropathy Associated with Systemic Autoimmune Diseases

Systemic autoimmune diseases like rheumatoid arthritis, Sjögren syndrome, or systemic lupus erythematosus (SLE) can be associated with peripheral neuropathies that often take the form of distal sensory or sensorimotor polyneuropathies. These neuropathies are distinct from vasculitic peripheral neuropathies, which can arise as secondary manifestations of these same diseases.

Neuropathy Associated with Vasculitis

Vasculitis is a noninfectious inflammation of blood vessels that can involve and damage peripheral nerves. About one third of patients with vasculitis have peripheral nerve involvement, and neuropathy may be the presenting feature. Vasculitis often presents as mononeuritis multiplex, but mononeuritis and polyneuropathy are also encountered.

Peripheral nerves involved by vasculitis typically show patchy axonal degeneration and loss, with some fascicles being more severely affected than others. Perivascular inflammatory infiltrates are often present. Identification of blood vessels with characteristic forms of acute or chronic damage (Chapter 11) helps establish the diagnosis.

Infectious Neuropathies

Many infectious processes affect peripheral nerves. Among these, leprosy, diphtheria, and varicella-zoster cause relatively specific pathologic changes in nerves that are the