abundant charged sugar groups in these adsorbed proteins give the deposits staining characteristics that were thought to resemble starch (amylose). Therefore, the deposits were called *amyloid*, a name that is firmly entrenched despite the realization that the deposits are unrelated to starch.

Amyloid is deposited in the extracellular space in various tissues and organs of the body in a variety of clinical settings. Because amyloid deposition appears insidiously and sometimes mysteriously, its clinical recognition ultimately depends on morphologic identification of this distinctive substance in appropriate biopsy specimens. With the light microscope and hematoxylin and eosin stains, amyloid appears as an amorphous, eosinophilic, hyaline, extracellular substance. *With progressive accumulation, it encroaches on and produces pressure atrophy of adjacent cells.* To differentiate amyloid from other hyaline materials (e.g., collagen, fibrin), a variety of histochemical techniques, described later, are used. Perhaps most widely used is the Congo red stain, which under ordinary light imparts a pink or red color to tissue deposits, but far more striking and specific is the green birefringence of the stained amyloid when observed by polarizing microscopy (see later).

Properties of Amyloid Proteins

Even though all amyloid deposits have a similar appearance and staining characteristics, amyloid is not a single chemical entity. In fact, more than 20 (at last count, 23) different proteins can aggregate and form fibrils with the appearance of amyloid. There are three major and several minor biochemical forms, which are deposited by different pathogenetic mechanisms. Therefore, amyloidosis should not be considered a single disease; rather it is a group of diseases having in common the deposition of similar-appearing proteins. At the heart of the morphologic similarity is the remarkably uniform physical organization of amyloid protein, which we consider first.

Physical Nature of Amyloid. By electron microscopy, all types of amyloid consist of continuous, nonbranching fibrils with a diameter of approximately 7.5 to 10 nm. X-ray crystallography and infrared spectroscopy demonstrate a characteristic cross-β-pleated sheet conformation (Fig. 6-44). This conformation is seen regardless of the clinical setting or chemical composition and is responsible for the distinctive Congo red staining and birefringence of amyloid.

Chemical Nature of Amyloid. Approximately 95% of the amyloid material consists of fibril proteins, the remaining 5% being the P component and other glycoproteins. The three most common forms of amyloid are the following:

- **The AL (amyloid light chain) protein is made up of complete immunoglobulin light chains, the amino-terminal fragments of light chains, or both.** Most of the AL proteins analyzed are composed of λ light chains or their fragments, but κ chains are present in some cases. The amyloid fibril protein of the AL type is produced from free Ig light chains secreted by a monoclonal population of plasma cells, and its deposition is associated with certain forms of plasma cell tumors (Chapter 13).

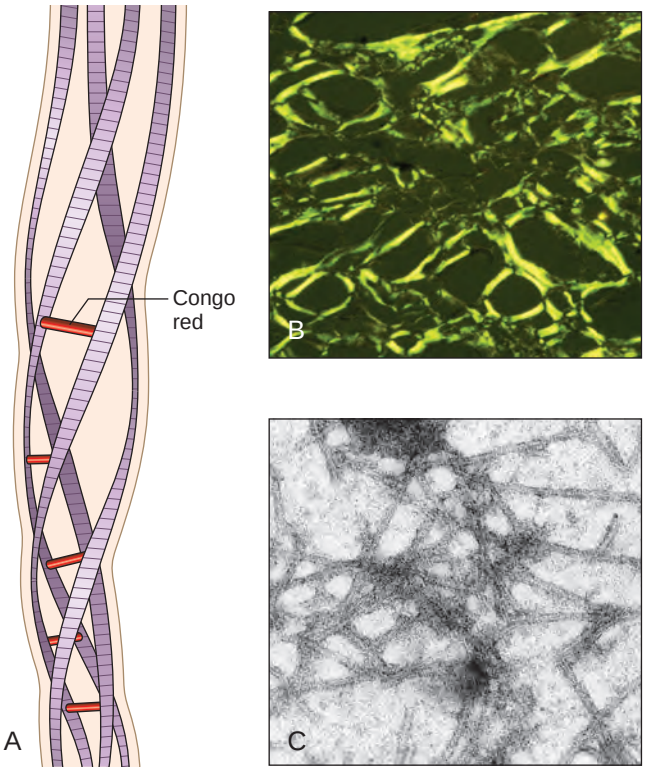

Figure 6-44 Structure of amyloid. **A,** A schematic diagram of an amyloid fiber showing four fibrils (there can be as many as six in each fiber) wound around one another with regularly spaced binding of the Congo red dye. **B,** Congo red staining shows apple-green birefringence under polarized light, a diagnostic feature of amyloid. **C,** Electron micrograph of 7.5- to 10-nm amyloid fibrils. (From Merlini G, Bellotti V: Molecular mechanisms of amyloidosis. N Engl J Med 2003;349:583-596, with permission of the Massachusetts Medical Society.)

- **The AA (amyloid-associated) type of amyloid fibril protein is derived from a unique non-Ig protein made by the liver.** It has a molecular weight of 8500 and consists of 76 amino acid residues. AA fibrils are derived by proteolysis from a larger (12,000 daltons) precursor in the serum called SAA (serum amyloid-associated) protein that is synthesized in the liver and circulates bound to high density lipoproteins. The production of SAA protein is increased in inflammatory states as part of the acute phase response; therefore, this form of amyloidosis is associated with chronic inflammation, and is often called *secondary amyloidosis*.
- **β-amyloid protein (Aβ) constitutes the core of cerebral plaques found in Alzheimer disease** as well as the amyloid deposited in walls of cerebral blood vessels in individuals with this disease. The Aβ protein is a 4000-dalton peptide that is derived by proteolysis from a much larger transmembrane glycoprotein, called *amyloid precursor protein*. This form of amyloid is discussed in Chapter 28.

As mentioned, multiple other biochemically distinct proteins can also deposit as amyloid in a variety of clinical settings. Among these rarer causes of amyloidosis, the proteins most often involved are the following: