condition called *familial Mediterranean fever*. This is an "autoinflammatory" syndrome associated with excessive production of the cytokine IL-1 in response to inflammatory stimuli. It is characterized clinically by attacks of fever accompanied by inflammation of serosal surfaces, including peritoneum, pleura, and synovial membrane. The gene for familial Mediterranean fever encodes a protein called *pyrin* (for its relation to fever), which is one of a complex of proteins that regulate inflammatory reactions via the production of proinflammatory cytokines (Chapter 3). This disorder is encountered largely in individuals of Armenian, Sephardic Jewish, and Arabic origins. It is sometimes associated with widespread amyloidosis. The amyloid fibril proteins are made up of AA proteins, suggesting that this form of amyloidosis is related to the recurrent bouts of inflammation.

In contrast to familial Mediterranean fever, a group of autosomal dominant familial disorders is characterized by deposition of amyloid predominantly in peripheral and autonomic nerves. These familial amyloidotic polyneuropathies have been described in different parts of the world. As mentioned before, in all of these genetic disorders, the fibrils are made up of mutant TTRs. In these disorders, TTRs are deposited as amyloid fibrils because genetically determined alterations of structure appear to render the TTRs prone to misfolding and aggregation, and resistant to proteolysis.

Hemodialysis-Associated Amyloidosis. Patients on long-term hemodialysis for renal failure can develop amyloidosis as a result of deposition of β_2-microglobulin. This protein is present in high concentrations in the serum of persons with renal disease and in the past, it was retained in the circulation because it could not be filtered through dialysis membranes. Patients sometimes presented with carpal tunnel syndrome because of β_2-microglobulin deposition. With new dialysis filters, the incidence of this complication has decreased substantially.

Localized Amyloidosis. Sometimes, amyloid deposits are limited to a single organ or tissue without involvement of any other site in the body. The deposits may produce grossly detectable nodular masses or be evident only on microscopic examination. Nodular deposits of amyloid are most often encountered in the lung, larynx, skin, urinary bladder, tongue, and the region about the eye. Frequently, there are infiltrates of lymphocytes and plasma cells in the periphery of these amyloid masses. At least in some cases, the amyloid consists of AL protein and may therefore represent a localized form of plasma cell-derived amyloid.

Endocrine Amyloid. Microscopic deposits of localized amyloid may be found in certain endocrine tumors, such as medullary carcinoma of the thyroid gland, islet tumors of the pancreas, pheochromocytomas, and undifferentiated carcinomas of the stomach, and in the islets of Langerhans in individuals with type 2 diabetes mellitus. In these settings the amyloidogenic proteins seem to be derived either from polypeptide hormones (e.g., medullary carcinoma) or from unique proteins (e.g., islet amyloid polypeptide). In medullary carcinomas of the thyroid, the presence of amyloid is an essential diagnostic feature.

Amyloid of Aging. Several well-documented forms of amyloid deposition occur with aging. *Senile systemic amyloidosis* refers to the systemic deposition of amyloid in elderly patients (usually in their 70s and 80s). Because of the dominant involvement and related dysfunction of the heart, this form was previously called *senile cardiac amyloidosis*. Those who are symptomatic present with a restrictive cardiomyopathy and arrhythmias (Chapter 12). The amyloid in this form is derived from normal TTR. In addition to the sporadic senile systemic amyloidosis, another form, affecting predominantly the heart, that results from the deposition of a mutant form of TTR has also been recognized. Approximately 4% of the black population in the United States expresses this mutant form of TTR, and cardiomyopathy has been identified in both homozygous and heterozygous patients. The precise prevalence of patients with this mutation who develop clinically manifest cardiac disease is not known.

MORPHOLOGY

There are no consistent or distinctive patterns of organ or tissue distribution of amyloid deposits in any of the categories cited. Nonetheless, a few generalizations can be made. In amyloidosis secondary to chronic inflammatory disorders, kidneys, liver, spleen, lymph nodes, adrenals, and thyroid, as well as many other tissues, are typically affected. Although amyloidosis associated with plasma cell proliferations cannot reliably be distinguished from the secondary form by its organ distribution, it more often involves the heart, gastrointestinal tract, respiratory tract, peripheral nerves, skin, and tongue. The localization of amyloid deposits in the hereditary syndromes is varied. In familial Mediterranean fever the amyloidosis may be widespread, involving the kidneys, blood vessels, spleen, respiratory tract, and (rarely) liver. The localization of amyloid in the remaining hereditary syndromes can be inferred from the designation of these entities.

Whatever the clinical disorder, the amyloidosis may or may not be apparent on macroscopic examination. When amyloid accumulates in larger amounts, the organ is frequently enlarged and the tissue appears gray with a waxy, firm consistency. **Histologically, the amyloid deposition is always extracellular and begins between cells,** often closely adjacent to basement membranes (Fig. 6-46*A*). As the amyloid accumulates, it encroaches on the cells, in time surrounding and destroying them. In the form associated with plasma cell proliferation, perivascular and vascular deposits are common.

The histologic diagnosis of amyloid is based almost entirely on its staining characteristics. The most common staining technique uses the dye Congo red, which under ordinary light imparts a pink or red color to amyloid deposits. Under polarized light the Congo red-stained amyloid shows so-called apple-green birefringence (Fig. 6-46*B*). This reaction is shared by all forms of amyloid and is caused by the crossed β-pleated configuration of amyloid fibrils. Confirmation can be obtained by electron microscopy, which reveals amorphous nonoriented thin fibrils. AA, AL, and ATTR types of amyloid can also be distinguished by specific immunohistochemical staining.