Table 6-17 Classification of Amyloidosis

Clinicopathologic Category	Associated Diseases	Major Fibril Protein	Chemically Related Precursor Protein
Systemic (Generalized) Amyloidosis			
Immunocyte dyscrasias with amyloidosis (primary amyloidosis)	Multiple myeloma and other monoclonal plasma cell proliferations	AL	Immunoglobulin light chains, chiefly λ type
Reactive systemic amyloidosis (secondary amyloidosis)	Chronic inflammatory conditions	AA	SAA
Hemodialysis-associated amyloidosis	Chronic renal failure	$A\beta_2m$	β_2-microglobulin
Hereditary Amyloidosis			
Familial Mediterranean fever		AA	SAA
Familial amyloidotic neuropathies (several types)		ATTR	Transthyretin
Systemic senile amyloidosis		ATTR	Transthyretin
Localized Amyloidosis			
Senile cerebral	Alzheimer disease	Aβ	APP
Endocrine	Type 2 diabetes		
Medullary carcinoma of thyroid		A Cal	Calcitonin
Islets of Langerhans		AIAPP	Islet amyloid peptide
Isolated atrial amyloidosis		AANF	Atrial natriuretic factor

tumor characterized by multiple osteolytic lesions throughout the skeletal system (Chapter 13). The malignant plasma cells synthesize abnormal amounts of a single Ig (monoclonal gammopathy), producing an M (myeloma) protein spike on serum electrophoresis. In addition to the synthesis of whole Ig molecules, the malignant plasma cells often secrete free, unpaired κ or λ light chains (referred to as *Bence-Jones protein*). These may be found in the serum, and due to their small molecular size, Bence-Jones proteins are excreted and concentrated in the urine. In primary amyloidosis, the free light chains are not only present in serum and urine but are also deposited in tissues as amyloid. It should be noted, however, that the great majority of myeloma patients who have free light chains in serum and urine do not develop amyloidosis. Clearly, not all free light chains are equally likely to produce amyloid, and it is believed that the *amyloidogenic potential* of any particular light chain is largely determined by its specific amino acid sequence.

Most persons with AL amyloid do not have classic multiple myeloma or any other overt B-cell neoplasm; such cases have been traditionally classified as primary amyloidosis, because their clinical features derive from the effects of amyloid deposition without any other associated disease. In virtually all such cases, however, monoclonal immunoglobulins or free light chains, or both, can be found in the serum or urine. Most of these patients also have a modest increase in the number of plasma cells in the bone marrow, which presumably secrete the precursors of AL protein. Thus, these patients have an underlying monoclonal proliferation of plasma cells (*monoclonal gammopathy*) in which production of an abnormal protein, rather than production of tumor masses, is the predominant manifestation.

Reactive Systemic Amyloidosis. The amyloid deposits in this pattern are systemic in distribution and are composed of AA protein. This category was previously referred to as *secondary amyloidosis* because it is secondary to an associated inflammatory condition. At one time, tuberculosis, bronchiectasis, and chronic osteomyelitis were the most important underlying conditions, but with the advent of effective antimicrobial chemotherapy the importance of these conditions has diminished. More commonly now, reactive systemic amyloidosis complicates rheumatoid arthritis, other connective tissue disorders such as ankylosing spondylitis, and inflammatory bowel disease, particularly Crohn disease and ulcerative colitis. Among these the most frequent associated condition is rheumatoid arthritis. Amyloidosis is reported to occur in approximately 3% of patients with rheumatoid arthritis and is clinically significant in one half of those affected. Heroin abusers who inject the drug subcutaneously also have a high occurrence rate of generalized AA amyloidosis. The chronic skin infections associated with "skin-popping" of narcotics seem to be responsible for the amyloidosis. Reactive systemic amyloidosis may also occur in association with solid tumors, the most common being renal cell carcinoma and Hodgkin lymphoma.

In this form of amyloidosis, SAA synthesis by liver cells is stimulated by cytokines such as IL-6 and IL-1 that are produced during inflammation; thus, long-standing inflammation leads to a sustained elevation of SAA levels. However, increased production of SAA by itself is not sufficient for the deposition of amyloid. There are two possible explanations for this. According to one view, SAA is normally degraded to soluble end products by the action of monocyte-derived enzymes. Conceivably, individuals who develop amyloidosis have an enzyme defect that results in incomplete breakdown of SAA, thus generating insoluble AA molecules. Alternatively, a genetically determined structural abnormality in the SAA molecule may render it resistant to degradation by macrophages.

Heredofamilial Amyloidosis. A variety of familial forms of amyloidosis have been described. Most of them are rare and occur in limited geographic areas. The most common and best studied is an autosomal recessive