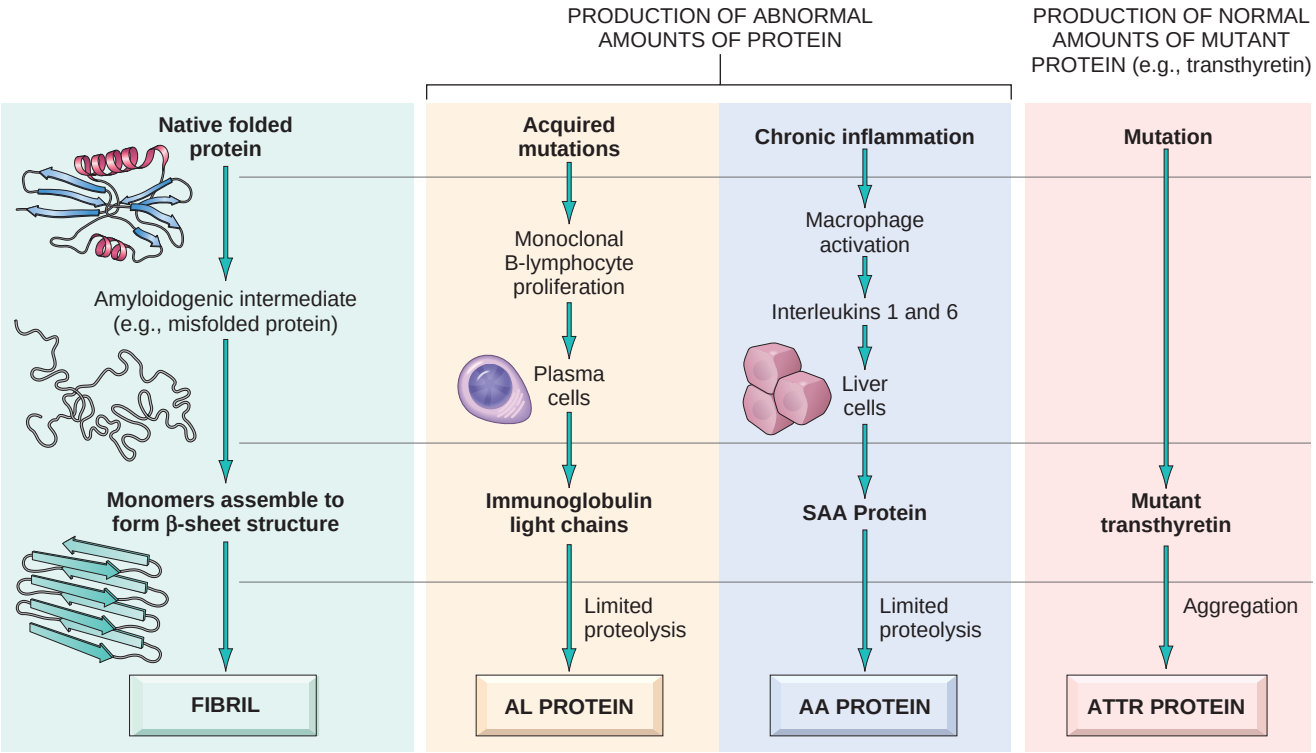

Figure 6-45 Pathogenesis of amyloidosis, showing the proposed mechanisms underlying deposition of the major forms of amyloid fibrils.

- *Transthyretin (TTR)* is a normal serum protein that binds and transports thyroxine and retinol. Several distinct mutant forms of TTR (and its fragments) are deposited in a group of genetically determined disorders referred to as familial amyloid polyneuropathies. Normal TTR is also deposited in the heart of aged individuals (senile systemic amyloidosis).
- *β_2-microglobulin*, a component of MHC class I molecules and a normal serum protein, has been identified as the amyloid fibril subunit ($A\beta_2m$) in amyloidosis that complicates the course of patients on long-term hemodialysis.
- In a minority of cases of prion disease in the central nervous system, the misfolded *prion proteins* aggregate in the extracellular space and acquire the structural and staining characteristics of amyloid protein.
- In addition, other minor components are always present in amyloid. These include serum amyloid P component, proteoglycans, and highly sulfated glycosaminoglycans. Serum amyloid P protein may contribute to amyloid deposition by stabilizing the fibrils and decreasing their clearance.

Pathogenesis and Classification of Amyloidosis

Amyloidosis results from abnormal folding of proteins, which become insoluble, aggregate, and deposit as fibrils in extracellular tissues. Normally, misfolded proteins are degraded intracellularly in proteasomes, or extracellularly by macrophages. It appears that in amyloidosis, these quality control mechanisms fail, leading to accumulation of a misfolded protein outside cells. The proteins that form amyloid fall into two general categories (Fig. 6-45): (1) normal proteins that have an inherent tendency to fold improperly, associate and form fibrils, and do so when they are produced in increased amounts; and (2) mutant proteins that are prone to misfolding and subsequent aggregation. The mechanisms of deposition of different types of amyloid are discussed below along with classification.

Because a given biochemical form of amyloid (e.g., AA) may be associated with amyloid deposition in diverse clinical settings, we follow a combined biochemical-clinical classification for our discussion (Table 6-17). Amyloid may be *systemic* (generalized), involving several organ systems, or it may be *localized*, when deposits are limited to a single organ, such as the heart.

On clinical grounds, the systemic, or generalized, pattern is subclassified into *primary amyloidosis*, when it is associated with some plasma cell disorder, or *secondary amyloidosis*, when it occurs as a complication of an underlying chronic inflammatory or tissue-destructive process. *Hereditary* or *familial amyloidosis* constitutes a separate, albeit heterogeneous group, with several distinctive patterns of organ involvement.

Primary Amyloidosis: Plasma Cell Disorders Associated with Amyloidosis. Amyloid in this category is usually systemic in distribution and is of the AL type. With approximately 2000 to 3000 new cases every year in the United States, this is the most common form of amyloidosis. In all cases, the disorder is caused by a clonal proliferation of plasma cells that synthesize an Ig that is prone to form amyloid due to its intrinsic physiochemical properties. Best defined is the occurrence of systemic amyloidosis in 5% to 15% of individuals with multiple myeloma, a plasma-cell