Clinical Features. Amyloidosis may be found as an unsuspected anatomic change, having produced no clinical manifestations, or it may cause serious clinical problems and even death. The symptoms depend on the magnitude of the deposits and on the sites or organs affected. Clinical manifestations at first are often entirely nonspecific, such as weakness, weight loss, light-headedness, or syncope. Somewhat more specific findings appear later and most often relate to renal, cardiac, and gastrointestinal involvement.

Renal involvement gives rise to proteinuria that may be severe enough to cause the nephrotic syndrome (Chapter 20). Progressive obliteration of glomeruli in advanced cases ultimately leads to renal failure and uremia. Renal failure is a common cause of death. *Cardiac amyloidosis* may present as an insidious congestive heart failure. The most serious aspects of cardiac amyloidosis are conduction disturbances and arrhythmias, which may prove fatal. Occasionally, cardiac amyloidosis produces a restrictive pattern of cardiomyopathy and masquerades as chronic constrictive pericarditis (Chapter 12). *Gastrointestinal amyloidosis* may be entirely asymptomatic, or it may present in a variety of ways. Amyloidosis of the tongue may cause sufficient enlargement and inelasticity to hamper speech and swallowing. Depositions in the stomach and intestine may lead to malabsorption, diarrhea, and disturbances in digestion. *Vascular amyloidosis* causes vascular fragility that may lead to bleeding, sometimes massive, that can occur spontaneously or following seemingly trivial trauma. Additionally, in some cases AL amyloid binds and inactivates factor X, a critical coagulation factor, leading to a life-threatening bleeding disorder.

The diagnosis of amyloidosis depends on the histologic demonstration of amyloid deposits in tissues. The most common sites biopsied are the kidney, when renal manifestations are present, or rectal or gingival tissues in patients suspected of having systemic amyloidosis. Examination of abdominal fat aspirates stained with Congo red can also be used for the diagnosis of systemic amyloidosis. The test is quite specific, but its sensitivity is low. In suspected cases of AL amyloidosis, serum and urine protein electrophoresis and immunoelectrophoresis should be performed. Bone marrow aspirates in such cases often show monoclonal plasmacytosis, even in the absence of overt multiple myeloma. Scintigraphy with radiolabeled serum amyloid P (SAP) component is a rapid and specific test, since SAP binds to the amyloid deposits and reveals their presence. It also gives a measure of the extent of amyloidosis and can be used to follow patients undergoing treatment.

The prognosis for individuals with generalized amyloidosis is poor. Those with AL amyloidosis (not including multiple myeloma) have a median survival of 2 years after diagnosis. Persons with myeloma-associated amyloidosis have an even poorer prognosis. The outlook for individuals with reactive systemic amyloidosis is somewhat better and depends to some extent on the control of the underlying condition. Resorption of amyloid after treatment of the associated condition has been reported, but this is a rare occurrence. New therapeutic strategies aimed at correcting protein misfolding and inhibiting fibrillogenesis are being developed.

KEY CONCEPTS

Amyloidosis

- Amyloidosis is a disorder characterized by the extracellular deposits of misfolded proteins that aggregate to form insoluble fibrils.
- The deposition of these proteins may result from: excessive production of proteins that are prone to misfolding and aggregation; mutations that produce proteins that cannot fold properly and tend to aggregate; defective or incomplete proteolytic degradation of extracellular proteins.
- Amyloidosis may be localized or systemic. It is seen in association with a variety of primary disorders, including monoclonal B-cell proliferations (in which the amyloid deposits consist of immunoglobulin light chains); chronic inflammatory diseases such as rheumatoid arthritis (deposits of amyloid A protein, derived from an acute-phase protein produced in inflammation); Alzheimer disease (amyloid b protein); familial conditions in which the amyloid deposits consist of mutants of normal proteins (e.g., transthyretin in familial amyloid polyneuropathies); amyloidosis associated with dialysis (deposits of β_2-microglobulin, whose clearance is defective).
- Amyloid deposits cause tissue injury and impair normal function by causing pressure on cells and tissues. They do not evoke an inflammatory response.

SUGGESTED READINGS

Innate Immunity

Goubau D, Deddouche S, Reis E, et al: Cytosolic sensing of viruses. *Immunity* 38:855–69, 2013. *[An excellent review on the numerous mechanisms used by cells to recognize viral DNA and RNA.]*

Kumar H, Kawai T, Akira S: Pathogen recognition by the innate immune system. *Int Rev Immunol* 30:16–34, 2011. *[A comprehensive review of the receptors used by the innate immune system to sense microbes.]*

Park H, Bourla AB, Kastner DL, et al: Lighting the fires within: the cell biology of autoinflammatory diseases. *Nat Rev Immunol* 12:570–80, 2012. *[A discussion of the inflammasome, and autoinflammatory diseases resulting from gain-of-function mutations in components of the inflammasome as well as other disorders involving abnormal inflammasome activity.]*

Schenten D, Medzhitov R: The control of adaptive immune responses by the innate immune system. *Adv Immunol* 109:87–124, 2011. *[A thoughtful discussion of how innate immune responses provide the danger signals that stimulate adaptive immunity.]*

Walker JA, Barlow JL, McKenzie AN: Innate lymphoid cells–how did we miss them? *Nat Rev Immunol* 13:75–87, 2013. *[A discussion of a recently appreciated family of cells of innate immunity, and their functions in host defense and immune regulation.]*

Cell-Mediated Immunity

Liao W, Lin JX, Leonard WJ: Interleukin-2 at the crossroads of effector responses, tolerance, and immunotherapy. *Immunity* 38:13–25, 2013. *[An excellent review of the established and newly discovered functions of a well-known cytokine, IL-2.]*

O'Shea JJ, Paul WE: Mechanisms underlying lineage commitment and plasticity of helper CD4+ T cells. *Science* 327:1098, 2010. *[An excellent review of the development and functions of helper T cell subsets, and the uncertainties in the field.]*

Pulendran B, Artis D: New paradigms in type 2 immunity. *Science* 337:431–5, 2012. *[A discussion of the mechanisms and functions of TH2 responses.]*

(Note: articles on TH17 cells are listed below, under "Other Hypersensitivity Reactions".)