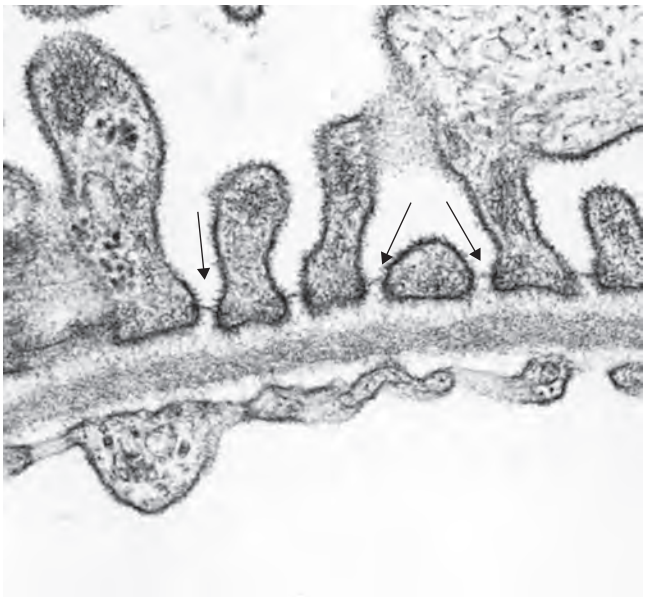

Figure 20-2 Glomerular filter consisting, from bottom to top, of fenestrated endothelium, basement membrane, and foot processes of epithelial cells. Note the filtration slits *(arrows)* and diaphragm situated between the foot processes. Note also that the basement membrane consists of a central lamina densa, sandwiched between two looser layers, the lamina rara interna and lamina rara externa. (Courtesy Dr. Helmut Rennke, Brigham and Women's Hospital, Boston, Mass.)

to the slit diaphragm are illustrated in Figure 20-3. Nephrin is a transmembrane protein with a large extracellular portion made up of immunoglobulin (Ig)-like domains. Nephrin molecules extend toward each other from neighboring foot processes and dimerize across the slit diaphragm. Within the cytoplasm of the foot processes, nephrin forms molecular connections with podocin, CD2-associated protein, and ultimately the actin cytoskeleton of the visceral epithelial cells. More slit diaphragm proteins continue to be identified, and comprehensive descriptions of their structure and interactions have been published. The importance of the slit diaphragm proteins in maintaining glomerular permeability is demonstrated by the observation that mutations in the genes encoding them give rise to defects in permeability and the nephrotic syndrome (discussed later).

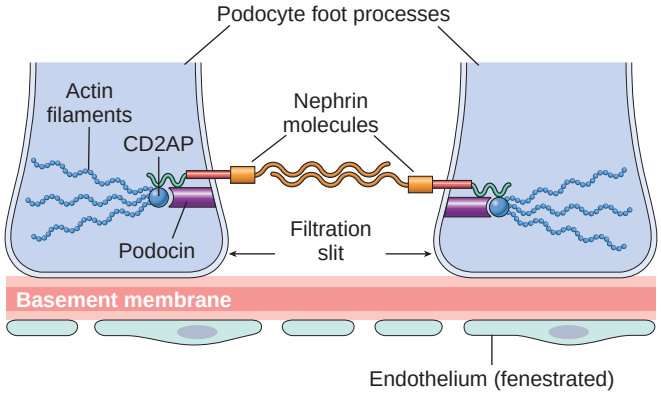

Figure 20-3 A simplified schematic diagram of some of the best-studied proteins of the glomerular slit diaphragm. CD2AP, CD2-associated protein.

Pathologic Responses of the Glomerulus to Injury

Various types of glomerulopathies are characterized by one or more of four basic tissue reactions.

Hypercellularity. Some *inflammatory diseases* of the glomerulus are characterized by an increase in the number of cells in the glomerular tufts. This hypercellularity results from one or more of the following:

- *Proliferation* of mesangial or endothelial cells.
- *Infiltration of leukocytes,* including neutrophils, monocytes, and, in some diseases, lymphocytes. The combination of infiltration of leukocytes and swelling and proliferation of mesangial and/or endothelial cells is often referred to as *endocapillary proliferation*.
- *Formation of crescents.* These are accumulations of cells composed of proliferating glomerular epithelial cells (predominately parietal but including some visceral cells) and infiltrating leukocytes. The epithelial cell proliferation that characterizes crescent formation occurs following an immune/inflammatory injury involving the capillary walls. Plasma proteins leak into the urinary space, where it is believed that exposure to procoagulants such as tissue factor leads to fibrin deposition. Activation of coagulation factors such as thrombin is suspected of being a trigger for crescent formation, but the actual mechanisms are still unknown. Molecules that have been implicated in recruitment of leukocytes into crescents include multiple proinflammatory cytokines.

Basement Membrane Thickening. By light microscopy, this change appears as thickening of the capillary walls, best seen in sections stained with periodic acid-Schiff (PAS). By electron microscopy such thickening takes one of three forms:

- Deposition of amorphous electron-dense material, most often immune complexes, on the endothelial or epithelial side of the basement membrane or within the GBM itself. Fibrin, amyloid, cryoglobulins, and abnormal fibrillary proteins may also deposit in the GBM.
- Increased synthesis of the protein components of the basement membrane, as occurs in diabetic glomerulosclerosis.
- Formation of additional layers of basement membrane matrices, which most often occupy subendothelial locations and may range from poorly organized matrix to fully duplicated lamina densa, as occurs in membranoproliferative glomerulonephritis.

Hyalinosis and Sclerosis. *Hyalinosis*, as applied to the glomerulus, denotes the accumulation of material that is homogeneous and eosinophilic by light microscopy. *Hyalin* is an extracellular, amorphous material composed of plasma proteins that have insudated from the circulation into glomerular structures. When extensive, these deposits may obliterate the capillary lumens of the glomerular tuft. Hyalinosis is usually a consequence of endothelial or capillary wall injury and typically the end result of various forms of glomerular damage.