Sclerosis is characterized by deposition of extracellular collagenous matrix. It may be confined to mesangial areas, as is often the case in diabetic glomerulosclerosis, involve the capillary loops, or both. The sclerosing process may also result in obliteration of some or all of the capillary lumens in affected glomeruli.

Many primary glomerulopathies are classified by their histology, as seen in Table 20-2. The histologic changes can be further subdivided by their distribution into the following categories: *diffuse*, involving all of the glomeruli in the kidney; *global*, involving the entirety of individual glomeruli; *focal*, involving only a fraction of the glomeruli in the kidney; *segmental*, affecting a part of each glomerulus; and *capillary loop* or *mesangial*, affecting predominantly capillary or mesangial regions.

KEY CONCEPTS

Injury of Glomerular Structures

- The glomerular basement membrane is composted of type IV collagen molecules and other matrix proteins. These proteins can be the target of antibodies in some types of glomerulonephritis; genetic abnormalities in their composition are the basis for some forms of hereditary nephritis.
- Visceral epithelial cells (podocytes) are a critical component of the glomerular filtration barrier, and injury to these cells leads to leakage of proteins into the urinary space, clinically manifest as proteinuria.
- The acute glomerular response to injury includes hypercellularity with proliferation of mesangial and/or endothelial cells, influx of leukocytes, and, in severe injuries, formation of crescents.
- Chronic glomerular responses to injury include basement membrane thickening, hyalinosis, and sclerosis.

Pathogenesis of Glomerular Injury

Although much remains unknown about etiologic agents and triggering events, it is clear that **immune mechanisms underlie most forms of primary glomerulopathy and many of the secondary glomerular disorders** (Table 20-4). Glomerulonephritis can be readily induced experimentally by antigen-antibody reactions. Furthermore, glomerular deposits of immunoglobulins, often with components of complement, are found in the majority of individuals with glomerulonephritis. Cell-mediated immune reactions also may play a role, usually in concert with antibody-mediated events. We begin this discussion with a review of antibody-instigated injury.

Two forms of antibody-associated injury have been established: (1) injury by *antibodies reacting in situ within the glomerulus,* either binding to insoluble fixed (intrinsic) glomerular antigens or extrinsic molecules planted within the glomerulus, and (2) injury resulting from *deposition of circulating antigen-antibody complexes in the glomerulus.* It is clear that the major cause of glomerulonephritis resulting from formation of antigen-antibody complexes is the consequence of in situ immune complex formation, and not deposition of circulating complexes as was once thought.

Table 20-4 Immune Mechanisms of Glomerular Injury

Antibody-Mediated Injury
In Situ Immune Complex Deposition
Fixed intrinsic tissue antigens
NC1 domain of type IV collagen antigen (anti-GBM nephritis)
PLA_2R antigen (membranous glomerulopathy)
Mesangial antigens
Others
Planted antigens
Exogenous (infectious agents, drugs)
Endogenous (DNA, nuclear proteins, immunoglobulins, immune complexes, IgA)
Circulating Immune Complex Deposition
Endogenous antigens (e.g., DNA, tumor antigens)
Exogenous antigens (e.g., infectious products)
Cell-Mediated Immune Injury
Activation of Alternative Complement Pathway

GBM, glomerular basement membrane.

Diseases Caused by In Situ Formation of Immune Complexes

In this form of injury, immune complexes are formed locally by antibodies that react with intrinsic tissue antigen or with extrinsic antigens "planted" in the glomerulus from the circulation. Membranous nephropathy is the classic example of glomerular injury resulting from local formation of immune complexes. It has a well-studied experimental counterpart in the Heymann nephritis rat model, from which much of the underlying pathophysiology of glomerular immune complex–mediated diseases has been deduced.

The Heymann model of glomerulonephritis is induced by immunizing rats with an antigen, now known to be *megalin*, that is present in epithelial cell foot processes (Fig. 20-4C). The rats develop antibodies to this antigen, and disease develops from the reaction of antibody with the megalin-containing protein complex located on the basal surface of visceral epithelial cells, leading to localized immune complex formation. A major advance in our understanding of glomerulonephritis came from the identification of the M-type phospholipase A_2 receptor (PLA_2R) as the antigen that underlies most cases of primary human membranous nephropathy. Antibody binding to PLA_2R present in the glomerular epithelial cell membrane is followed by complement activation and then shedding of the immune aggregates from the cell surface to form characteristic deposits of immune complexes along the *subepithelial aspect* of the basement membrane (Fig. 20-4C). On electron microscopy the glomerulopathy is characterized by the presence of numerous discrete subepithelial electron-dense deposits (made up largely of immune reactants). **The pattern of immune deposition by immunofluorescence microscopy is granular rather than linear, reflective of the very localized antigen-antibody interaction.** These subepithelial complexes, with resultant host responses, can result in a thickened basement membrane appearance by light microscopy; hence the term *membranous nephropathy* has been applied to both the experimental model and human disease.

In humans, primary membranous nephropathy is an autoimmune disease, caused by antibodies to endogenous