Table 20-2 Glomerular Diseases

Primary Glomerulopathies
Acute proliferative glomerulonephritis
Postinfectious
Other
Rapidly progressive (crescentic) glomerulonephritis
Membranous nephropathy
Minimal-change disease
Focal segmental glomerulosclerosis
Membranoproliferative glomerulonephritis
Dense deposit disease
IgA nephropathy
Chronic glomerulonephritis
Systemic Diseases with Glomerular Involvement
Systemic lupus erythematosus
Diabetes mellitus
Amyloidosis
Goodpasture syndrome
Microscopic polyarteritis/polyangiitis
Wegener granulomatosis
Henoch-Schönlein purpura
Bacterial endocarditis
Hereditary Disorders
Alport syndrome
Thin basement membrane disease
Fabry disease

Structure of the Glomerulus

Many clinical manifestations of glomerular diseases result from perturbations of specific components of the glomerular tuft, so we before discussing these diseases we describe the key anatomic structures of glomeruli. The glomerulus consists of an anastomosing network of capillaries lined by fenestrated endothelium invested by two layers of epithelial cells (Fig. 20-1). The visceral epithelial cells (commonly referred to as *podocytes*) are incorporated into and become an intrinsic part of the capillary wall, separated from endothelial cells by a basement membrane. The parietal epithelium, situated on the Bowman capsule, lines the urinary space, the cavity in which plasma filtrate first collects.

The glomerular capillary wall is the filtering membrane and consists of the following structures (Fig. 20-2):

- There is a thin layer of fenestrated *endothelial cells*, with each fenestra being about 70 to 100 nm in diameter.

Table 20-3 Glomerular Syndromes

Syndrome	Manifestations
Nephritic syndrome	Hematuria, azotemia, variable proteinuria, oliguria, edema, and hypertension
Rapidly progressive glomerulonephritis	Acute nephritis, proteinuria, and acute renal failure
Nephrotic syndrome	>3.5 gm/day proteinuria, hypoalbuminemia, hyperlipidemia, lipiduria
Chronic renal failure	Azotemia → uremia progressing for months to years
Isolated urinary abnormalities	Glomerular hematuria and/or subnephrotic proteinuria

- A *glomerular basement membrane* (GBM) with a thick electron-dense central layer, the *lamina densa*, and thinner electron-lucent peripheral layers, the *lamina rara interna* and *lamina rara externa*. The GBM consists of collagen (mostly type IV), laminin, polyanionic proteoglycans (mostly heparan sulfate), fibronectin, entactin, and several other glycoproteins. Type IV collagen forms a network suprastructure to which other glycoproteins attach. The building block (monomer) of this network is a triple-helical molecule composed of one or more of six types of α chains (α_1 to α_6 or COL4A1 to COL4A6). Each molecule consists of a 7S domain at the N terminus, a triple-helical domain in the middle, and a globular noncollagenous domain (NC1) at the C terminus. The NC1 domain is important for helix formation and for assembly of collagen monomers into the basement membrane suprastructure. Glycoproteins (laminin, entactin) and proteoglycans (heparan sulfate, perlecan) attach to the collagenous suprastructure. The biochemical properties of these structural components are critical to understanding glomerular diseases. For example, antigens in the NC1 domain are the targets of antibodies in anti-GBM nephritis; genetic defects in the α-chains underlie some forms of hereditary nephritis; and the proteoglycan content of the GBM may contribute to its permeability characteristics.
- The *visceral epithelial cells* (podocytes) possess interdigitating processes embedded in and adherent to the lamina rara externa of the basement membrane (Fig. 20-1). Adjacent *foot processes* are separated by 20- to 30-nm–wide *filtration slits*, which are bridged by a thin diaphragm (Fig. 20-2).
- The entire glomerular tuft is supported by *mesangial cells* lying between the capillaries. Basement membrane–like *mesangial matrix* forms a meshwork in which the mesangial cells are embedded (Fig. 20-1). These cells, of mesenchymal origin, are contractile, phagocytic, and capable of proliferation, of laying down both matrix and collagen, and of secreting several biologically active mediators. Biologically, they are most akin to vascular smooth muscle cells and pericytes. They are important in many forms of glomerulonephritis.

The normal glomerulus is highly permeable to water and small solutes, because of the fenestrated nature of the endothelium, and impermeable to proteins of the size of albumin (~3.6-nm radius; 70 kilodaltons [kD] molecular weight) or larger. The permeability characteristics of the *glomerular filtration barrier* allow discrimination among various protein molecules, depending on their size (the larger, the less permeable) and charge (the more cationic, the more permeable). This size- and charge-dependent barrier function is accounted for by the structure of the capillary wall. The charge-dependent restriction is important in the virtually complete exclusion of albumin from the filtrate, because albumin is an anionic molecule.

The visceral epithelial cell is important for the maintenance of glomerular barrier function; its slit diaphragm presents a size-selective distal diffusion barrier to the filtration of proteins, and it is the cell type that is largely responsible for synthesis of GBM components. Proteins located in the slit diaphragm or present in assemblies of molecules within visceral epithelial cells that are attached