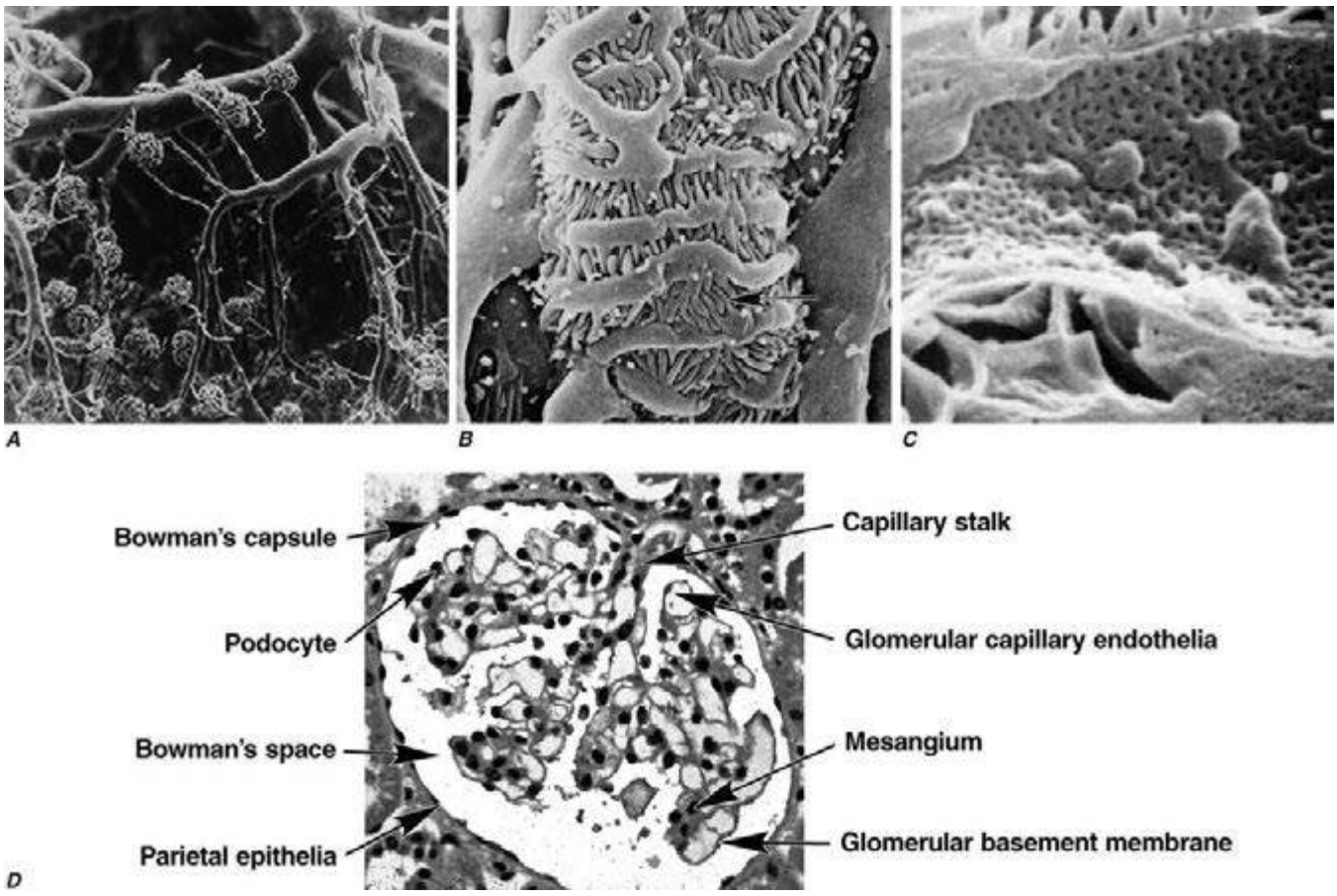

FIGURE 338-1 Glomerular architecture. ***A.*** The glomerular capillaries form from a branching network of renal arteries, arterioles, leading to an afferent arteriole, glomerular capillary bed (tuft), and a draining efferent arteriole. *(From VH Gattone II et al: Hypertension 5:8, 1983.)* ***B.*** Scanning electron micrograph of podocytes that line the outer surface of the glomerular capillaries (*arrow* shows foot process). ***C.*** Scanning electron micrograph of the fenestrated endothelia lining the glomerular capillary. ***D.*** The various normal regions of the glomerulus on light microscopy. *(A–C: Courtesy of Dr. Vincent Gattone, Indiana University; with permission.)*

tubules. Most large proteins and all cells are excluded from filtration by a physicochemical barrier governed by pore size and negative electrostatic charge. The mechanics of filtration and reclamation are quite complicated for many solutes **(Chap. 325)**. For example, in the case of serum albumin, the glomerulus is an imperfect barrier. Although albumin has a negative charge, which would tend to repel the negatively charged GBM, it only has a physical radius of 3.6 nm, while pores in the GBM and slit-pore membranes have a radius of 4 nm. Consequently, variable amounts of albumin inevitably cross the filtration barrier to be reclaimed by megalin and cubilin receptors along the proximal tubule. Remarkably, humans with normal nephrons excrete on average 8–10 mg of albumin in daily voided urine, approximately 20–60% of total excreted protein. This amount of albumin, and other proteins, can rise to gram quantities following glomerular injury.

The breadth of diseases affecting the glomerulus is expansive because the glomerular capillaries can be injured in a variety of ways, producing many different lesions. Some order to this vast subject is brought by grouping all of these diseases into a smaller number of clinical syndromes.

PATHOGENESIS OF GLOMERULAR DISEASE

There are many forms of glomerular disease with pathogenesis variably linked to the presence of genetic mutations, infection, toxin exposure, autoimmunity, atherosclerosis, hypertension, emboli, thrombosis, or diabetes mellitus. Even after careful study, however, the cause often remains unknown, and the lesion is called *idiopathic*. Specific or unique features of pathogenesis are mentioned with the description of each of the glomerular diseases later in this chapter.

Some glomerular diseases result from genetic mutations producing familial disease or a founder effect: congenital nephrotic syndrome from mutations in *NPHS1* (nephrin) and *NPHS2* (podocin) affect the slit-pore membrane at birth, and *TRPC6* cation channel mutations produce *focal segmental glomerulosclerosis (FSGS)* in adulthood; polymorphisms in the gene encoding apolipoprotein L1, *APOL1*, are a major risk for nearly 70% of African Americans with nondiabetic end-stage renal disease, particularly FSGS; mutations in complement factor H associate with *membranoproliferative glomerulonephritis (MPGN)* or *atypical hemolytic uremic syndrome (aHUS)*, type II partial lipodystrophy from mutations in genes encoding lamin A/C, or PPARγ cause a metabolic syndrome associated with MPGN, which is sometimes accompanied by dense deposits and C3 nephritic factor; Alport's syndrome, from mutations in the genes encoding for the α3, α4, or α5 chains of type IV collagen, produces *split-basement membranes* with *glomerulosclerosis;* and lysosomal storage diseases, such as α-galactosidase A deficiency causing Fabry's disease and *N* -acetylneuraminic acid hydrolase deficiency causing nephrosialidosis, produce FSGS.

Systemic hypertension and atherosclerosis can produce pressure stress, ischemia, or lipid oxidants that lead to *chronic glomerulosclerosis. Malignant hypertension* can quickly complicate glomerulosclerosis with fibrinoid necrosis of arterioles and glomeruli, thrombotic microangiopathy, and acute renal failure. *Diabetic nephropathy* is an acquired sclerotic injury associated with thickening of the GBM secondary to the long-standing effects of hyperglycemia, advanced glycosylation end products, and reactive oxygen species.

Inflammation of the glomerular capillaries is called *glomerulonephritis*. Most glomerular or mesangial antigens involved in *immune-mediated glomerulonephritis* are unknown **(Fig. 338-2)**. Glomerular epithelial or mesangial cells may shed or express epitopes that mimic