Table 20-7 Cause of Nephrotic Syndrome

Causes	Approximate Prevalence (%)*	
	Children	Adults
Primary Glomerular Disease		
Membranous nephropathy	3	30
Minimal-change disease	75	8
Focal segmental glomerulosclerosis	10	35
Membranoproliferative glomerulonephritis and dense deposit disease†	10	10
Other proliferative glomerulonephritides (focal, "pure mesangial," IgA nephropathy)†	2	17
Systemic Diseases		
Diabetes mellitus		
Amyloidosis		
Systemic lupus erythematosus		
Drugs (nonsteroidal anti-inflammatory, penicillamine, heroin)		
Infections (malaria, syphilis, hepatitis B and C, HIV)		
Malignant disease (carcinoma, lymphoma)		
Miscellaneous (bee-sting allergy, hereditary nephritis)		

*Approximate prevalence of primary disease = 95% of nephrotic syndrome in children, 60% in adults. Approximate prevalence of systemic disease = 5% in children, 40% in adults.
†Membranoproliferative and other proliferative glomerulonephritides may result in mixed nephrotic/nephritic syndromes.

Membranous Nephropathy

Membranous nephropathy is characterized by diffuse thickening of the glomerular capillary wall due to the accumulation of deposits containing Ig along the subepithelial side of the basement membrane. Approximately 75% of cases of membranous nephropathy are primary. The remaining cases occur in association with other systemic diseases and have identifiable etiologic agents, and hence are referred to as secondary membranous nephropathy. The most notable of these associations are as follows:

- *Drugs* (penicillamine, captopril, gold, nonsteroidal anti-inflammatory drugs (NSAIDs). From 1% to 7% of patients with rheumatoid arthritis treated with penicillamine or gold (drugs now used infrequently for this purpose) develop membranous nephropathy.
- *Underlying malignant tumors*, particularly carcinomas of the lung and colon, and melanoma. According to some studies, these are present in as many as 5% to 10% of adults with membranous nephropathy.
- *SLE.* About 10% to 15% of glomerulonephritis in SLE is of the membranous type.
- *Infections* (chronic hepatitis B, hepatitis C, syphilis, schistosomiasis, malaria)
- *Other autoimmune disorders* such as thyroiditis can be associated with secondary membranous nephropathy.

Pathogenesis. Membranous nephropathy is a form of chronic immune complex-mediated disease. In secondary membranous nephropathy, the inciting antigens can sometimes be identified in the immune complexes. The antigens may be endogenous or exogenous. The endogenous antigens may be renal or non renal. For example, membranous nephropathy in SLE is associated with deposition of complexes of self nuclear proteins and autoantibodies. Another example of an endogenous antigen is neutral endopeptidase, a membrane protein recognized by placentally transferred maternal antibodies in cases of neonatal membranous nephropathy. Exogenous antigens include those derived from hepatitis B virus and *Treponema pallidum* in patients infected with these microbes.

Primary (also called idiopathic) membranous nephropathy, long thought to be of unknown cause, is now considered to be an *autoimmune disease linked to certain HLA alleles such as HLA-DQA1 and caused in most cases by antibodies to a renal autoantigen.* In many adult cases the autoantigen is the phospholipase A_2 receptor. The lesions bear a striking resemblance to those of experimental Heymann nephritis, which, as you might recall, is induced by antibodies to the megalin antigenic complex present in the rat podocyte, which is the antigenic counterpart of the human phospholipase A_2 receptor.

How does the glomerular capillary wall become leaky in membranous nephropathy? There is a paucity of neutrophils, monocytes, or platelets in glomeruli. The virtually uniform presence of complement and corroborating experimental work suggest that the complement C5b-C9 membrane attack complex has an important role. It is postulated that C5b-C9 activates glomerular epithelial and mesangial cells, inducing them to liberate proteases and oxidants, which cause capillary wall injury and increased protein leakage. A subclass of IgG, IgG4, which differs from other IgG subclasses in being a poor activator of the classical complement pathway, is the principal immunoglobulin deposited in cases of primary membranous nephropathy. How IgG4 may activate the complement system is not clear. Perhaps other modes of complement activation may be harnessed.

MORPHOLOGY

By light microscopy the glomeruli either appear normal in the early stages of the disease or exhibit **uniform, diffuse thickening of the glomerular capillary wall** (Fig. 20-12*A*). By electron microscopy the thickening is seen to be caused by irregular electron dense also deposits containing immune complexes between the basement membrane and the overlying epithelial cells, with effacement of podocyte foot processes (Fig. 20-12*B* and *D*). Basement membrane material is laid down between these deposits, appearing as irregular spikes protruding from the GBM. These spikes are best seen by silver stains, which color the basement membrane, but not the deposits, black. In time, these spikes thicken to produce domelike protrusions and eventually close over the immune deposits, burying them within a markedly thickened, irregular membrane. Immunofluorescence microscopy demonstrates that the granular deposits contain both immunoglobulins and complement (Fig. 20-12*C*). As the disease advances segmental sclerosis may occur; in the course of time glomeruli may become totally sclerosed. The epithelial cells of the proximal tubules contain protein reabsorption droplets, and there may be considerable interstitial mononuclear cell inflammation.

Clinical Features. This disorder usually presents with the insidious onset of the nephrotic syndrome or, in 15% of patients, with nonnephrotic proteinuria. Hematuria and mild hypertension are present in 15% to 35% of cases. It is necessary in any patient to first rule out the secondary causes described earlier, since treatment of the underlying