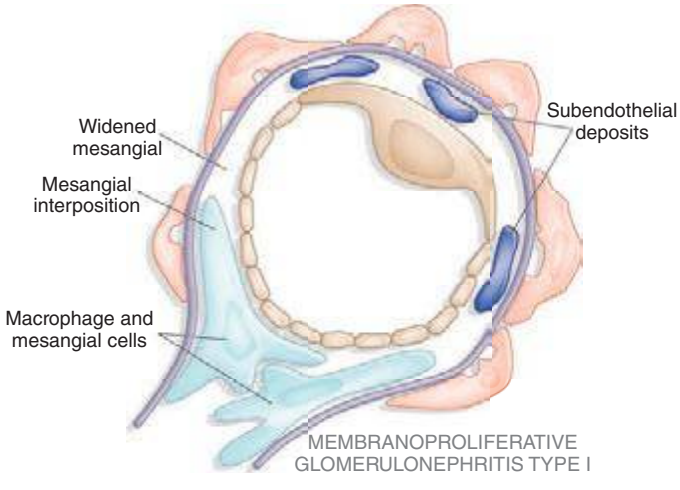
**TABLE 338-4 MEMBRANOPROLIFERATIVE GLOMERULONEPHRITIS**

| |
|---|
| **Type I Disease (Most Common)** |
| Idiopathic |
| Subacute bacterial endocarditis |
| Systemic lupus erythematosus |
| Hepatitis C ± cryoglobulinemia |
| Mixed cryoglobulinemia |
| Hepatitis B |
| Cancer: Lung, breast, and ovary (germinal) |
| **Type II Disease (Dense Deposit Disease)** |
| Idiopathic |
| $C_3$ nephritic factor–associated |
| Partial lipodystrophy |
| **Type III Disease** |
| Idiopathic |
| Complement receptor deficiency |

Type I MPGN, the most proliferative of the three types, shows mesangial proliferation with lobular segmentation on renal biopsy and mesangial interposition between the capillary basement membrane and endothelial cells, producing a double contour sometimes called *tram-tracking* (see Fig. 62e-9). (See Glomerular Schematic 3.) Subendothelial deposits with low serum levels of $C_3$ are typical, although 50% of patients have normal levels of $C_3$ and occasional intramesangial deposits. Low serum $C_3$ and a dense thickening of the GBM containing ribbons of dense deposits and $C_3$ characterize type II MPGN, sometimes called *dense deposit disease* (see Fig. 62e-10). Classically, the glomerular tuft has a lobular appearance; intramesangial deposits are rarely present and subendothelial deposits are generally absent. Proliferation in type III MPGN is less common than the other two types and is often focal; mesangial interposition is rare, and subepithelial deposits can occur along widened segments of the GBM that appear laminated and disrupted.

Type I MPGN is secondary to glomerular deposition of circulating immune complexes or their in situ formation. Types II and III MPGN may be related to "nephritic factors," which are autoantibodies that stabilize $C_3$ convertase and allow it to activate serum $C_3$. MPGN can also result from acquired or genetic abnormalities in the alternative complement pathway. Patients with MPGN present with proteinuria, hematuria, and pyuria (30%); systemic symptoms of fatigue and malaise that are most common in children with type I disease; or an acute nephritic picture with RPGN and a speedy deterioration in renal function in up to 25% of patients. Low serum $C_3$ levels are common. Fifty percent of patients with MPGN develop end-stage disease 10 years after diagnosis, and 90% have renal insufficiency after 20 years. Nephrotic syndrome, hypertension, and renal insufficiency all predict poor outcome. In the presence of proteinuria, treatment with inhibitors of the renin-angiotensin system is prudent. Evidence for treatment with dipyridamole, Coumadin (warfarin), or cyclophosphamide is not strongly established. There is some evidence supporting the efficacy of treatment of *primary MPGN* with steroids, particularly in children, as well as reports of efficacy with plasma exchange and other immunosuppressive drugs. If defects in the complement pathway are found, treatment with eculizumab is of hypothetical but unproven benefit. In *secondary MPGN,* treating the associated infection, autoimmune disease, or neoplasms is of demonstrated benefit. In particular, pegylated interferon and ribavirin are useful in reducing viral load. Although all primary renal diseases can recur over time in transplanted renal allografts, patients with MPGN are well known to be at risk for not only a histologic recurrence but also a clinically significant recurrence with loss of graft function.

Glomerular schematic 3




## MESANGIOPROLIFERATIVE GLOMERULONEPHRITIS

Mesangioproliferative glomerulonephritis is characterized by expansion of the mesangium, sometimes associated with mesangial hypercellularity; thin, single contoured capillary walls; and mesangial immune deposits. Clinically, it can present with varying degrees of proteinuria and, commonly, hematuria. Mesangioproliferative disease may be seen in IgA nephropathy, *Plasmodium falciparum* malaria, resolving postinfectious glomerulonephritis, and class II nephritis from lupus, all of which can have a similar histologic appearance. With these secondary entities excluded, the diagnosis of *primary mesangioproliferative glomerulonephritis* is made in less than 15% of renal biopsies. As an immune-mediated renal lesion with deposits of IgM, C1q, and $C_3$, the clinical course is variable. Patients with isolated hematuria may have a very benign course, and those with heavy proteinuria occasionally progress to renal failure. There is little agreement on treatment, but some clinical reports suggest benefit from use of inhibitors of the renin-angiotensin system, steroid therapy, and even cytotoxic agents.

## NEPHROTIC SYNDROME

Nephrotic syndrome classically presents with heavy proteinuria, minimal hematuria, hypoalbuminemia, hypercholesterolemia, edema, and hypertension. If left undiagnosed or untreated, some of these syndromes will progressively damage enough glomeruli to cause a fall in GFR, producing renal failure. Multiple studies have noted that the higher the 24-h urine protein excretion, the more rapid is the decline in GFR.

Therapies for various causes of nephrotic syndrome are noted under individual disease headings below. In general, all patients with hypercholesterolemia secondary to nephrotic syndrome should be treated with lipid-lowering agents because they are at increased risk for cardiovascular disease. Edema secondary to salt and water retention can be controlled with the judicious use of diuretics, avoiding intravascular volume depletion. Venous complications secondary to the hypercoagulable state associated with nephrotic syndrome can be treated with anticoagulants. The losses of various serum binding proteins, such as thyroid-binding globulin, lead to alterations in functional tests. Lastly, proteinuria itself is hypothesized to be nephrotoxic, and treatment of proteinuria with inhibitors of the renin-angiotensin system can lower urinary protein excretion.

### MINIMAL CHANGE DISEASE

Minimal change disease (MCD), sometimes known as *nil lesion,* causes 70–90% of nephrotic syndrome in childhood but only 10–15% of nephrotic syndrome in adults. Minimal change disease usually presents as a primary renal disease but can be associated with several other conditions, including Hodgkin's disease, allergies, or use of nonsteroidal anti-inflammatory agents; significant interstitial nephritis often accompanies cases associated with nonsteroidal drug use. Minimal change disease on renal biopsy shows no obvious glomerular lesion by light microscopy and is negative for deposits by immunofluorescent microscopy, or occasionally shows small amounts of IgM in the mesangium