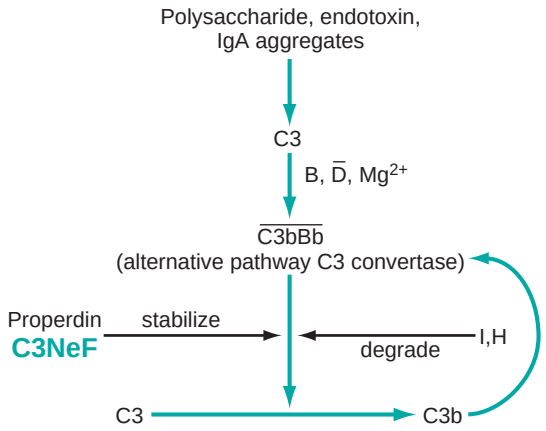

Figure 20-18 The alternative complement pathway in dense deposit disease (Type II MPGN). Note that C3NeF, an antibody present in the serum of individuals with membranoproliferative glomerulonephritis, acts at the same step as properdin, serving to stabilize the alternative pathway C3 convertase, thus enhancing C3 activation and consumption, causing hypocomplementemia.

Secondary MPGN

Secondary MPGN (invariably type I) is more common in adults and arises in the following settings:

- Chronic immune complex disorders, such as SLE; hepatitis B infection; hepatitis C infection, usually with cryoglobulinemia; endocarditis; infected ventriculoatrial shunts; chronic visceral abscesses; HIV infection; and schistosomiasis
- α_1-Antitrypsin deficiency
- Malignant diseases, particularly lymphoid tumors such as chronic lymphocytic leukemia, which are commonly complicated by development of autoantibodies

Dense Deposit Disease

Most patients with dense-deposit disease (formerly called type II MPGN) have abnormalities resulting in excessive activation of the alternative complement pathway. These patients have a consistently decreased serum C3 but normal C1 and C4, the early components of complement. They also have diminished serum levels of Factor B and properdin, components of the alternative complement pathway. In the glomeruli, C3 and properdin are deposited, but IgG is not. Recall that in the alternative complement pathway, C3 is directly cleaved to C3b (Fig. 20-18; see also Chapter 3, Fig. 3-12). The reaction depends on the initial activation of C3 by such substances as bacterial polysaccharides, endotoxin, and aggregates of IgA via a pathway involving Factors B and D. This leads to the generation of C3bBb, the alternative pathway C3 convertase. Normally, this C3 convertase is labile, but more than 70% of patients with dense-deposit disease have a circulating autoantibody termed *C3 nephritic factor (C3NeF)* that binds the alternative pathway C3 convertase and protects it from inactivation (Fig. 20-18). This favors persistent C3 activation and hypocomplementemia. There is also decreased C3 synthesis by the liver, further contributing to the profound hypocomplementemia. The precise nature of the dense deposits is unknown. Mutations in components of the alternate pathway such as Factor H have also been associated with dense deposit disease.

MORPHOLOGY

While some cases of dense deposit disease share histologic features with MPGN, there is a wider spectrum of histologic alterations in dense deposit disease. Many cases have a predominately mesangial proliferative pattern of injury, while others have an inflammatory and focally crescentic appearance. In some cases, dense deposits of a cellular material can be seen permeating the glomerular basement membranes in histologic sections. The defining feature is revealed by election microscopy, which demonstrates permeation of the lamina densa of the GBM by a ribbon-like, homogeneous, extremely electron-dense material of unknown composition (Fig. 20-17*B*). By immunofluorescence C3 is present in irregular granular or linear foci in the basement membranes on either side but not within the dense deposits. C3 is also present in the mesangium in characteristic circular aggregates (mesangial rings). IgG is usually absent, as are components of the classical pathway of complement activation (such as C1q and C4). C3 glomerlopathies other than dense deposit disease can have a similar distribution, with mesangial and capillary wall involvement, but lack the extremely electron dense deposits that define dense deposit disease.

Clinical Features. Dense deposit disease primarily affects children and young adults. The clinical presentation of nephritic syndrome with hematuria and/or nephrotic syndrome with proteinuria overlaps with that of MPGN. The prognosis is poor, with about half of these patients progressing to end-stage renal disease. There is a high incidence of recurrence in transplant recipients; dense deposits may recur in 90% of such patients, although renal failure in the allograft is much less common.

KEY CONCEPTS

The Nephrotic Syndrome

- **Membranous nephropathy** is caused by an autoimmune response, most often directed against the phospholipase A2 receptor on podocytes; it is characterized by granular subepithelial deposits of antibodies with GBM thickening and loss of foot processes but little or no inflammation; the disease is often resistant to steroid therapy.
- The nephrotic syndrome is characterized by proteinuria, which results in hypoalbuminemia and edema.
- Podocyte injury is an underlying mechanism of proteinuria, and may be the result of nonimmune causes (as in minimal-change disease and FSGS) or immune mechanisms (as in membranous nephropathy).
- **Minimal change disease** is the most frequent cause of nephrotic syndrome in children; it is manifested by proteinuria and effacement of glomerular foot processes without antibody deposits; the pathogenesis is unknown; the disease responds well to steroid therapy.
- **Focal and segmental glomerulosclerosis** (FSGS) may be primary (podocyte injury by unknown mechanisms) or secondary (e.g., as a consequence of prior glomerulonephritis, hypertension or infection such as HIV); glomeruli show focal and segmental obliteration of capillary lumens, and loss of foot processes; the disease is often resistant to therapy and may progress to end-stage renal disease.