nucleosomes, and other nuclear proteins, which have an affinity for GBM components; bacterial products; large aggregated proteins (e.g., aggregated immunoglobulins), which deposit in the mesangium because of their size; and immune complexes themselves, since they continue to have reactive sites for further interactions with free antibody, free antigen, or complement.

There is no dearth of other possible planted antigens, including viral, bacterial, and parasitic products and drugs. As an example, membranous nephropathy develops in a small number of infants fed cow's milk. These children have been found to have antibodies to bovine albumin and their lesions contain bovine milk antigens, which presumably become lodged in the glomerular basement membrane following intestinal absorption, where they serve as the substrate for immune complex formation in situ. Antibodies that bind to these planted antigens induce a discrete pattern of Ig deposition detected as granular staining by immunofluorescence microscopy that is indistinguishable from the pattern of staining observed with immune complexes formed from intrinsic antigens.

Disease Caused by Antibodies Directed Against Normal Components of the Glomerular Basement Membrane

In anti-GBM antibody induced glomerulonephritis, antibodies bind to intrinsic antigens homogeneously distributed along the entire length of the GBM, resulting in a diffuse linear pattern of staining for the antibodies by immunofluorescence techniques (Fig. 20-4*B* and *E*). This contrasts with the granular pattern of immunofluorescence staining corresponding to the discrete immune complexes seen in membranous nephropathy, or other glomerular diseases in which large complexes of antigens and antibodies form in situ. These intrinsic, fixed antigens cannot be mobilized to form large, discrete complexes.

Often the anti-GBM antibodies cross-react with other basement membranes, especially those in the lung alveoli, resulting in simultaneous lung and kidney lesions *(Goodpasture syndrome)*. The GBM antigen that is responsible for classic anti-GBM antibody-induced glomerulonephritis and Goodpasture syndrome is a component of the noncollagenous domain (NC1) of the α_3 chain of type IV collagen that is critical for maintenance of GBM suprastructure. Although anti-GBM antibody-induced glomerulonephritis accounts for fewer than 5% of cases of human glomerulonephritis, it causes severe necrotizing and crescentic glomerular damage and the clinical syndrome of rapidly progressive glomerulonephritis.

Glomerulonephritis Resulting from Deposition of Circulating Immune Complexes

In this type of nephritis, glomerular injury is caused by the trapping of circulating antigen-antibody complexes within glomeruli. The antibodies have no immunologic specificity for glomerular constituents, and the complexes localize within the glomeruli because of their physicochemical properties and the hemodynamic factors peculiar to the glomerulus (Fig. 20-4*A*).

The antigens that trigger the formation of circulating immune complexes may be of endogenous origin, as in the glomerulonephritis associated with SLE or in IgA nephropathy, **or they may be exogenous**, as may occur in the glomerulonephritis that follows certain infections. Microbial antigens that are implicated include bacterial products (streptococcal proteins), the surface antigen of hepatitis B virus, hepatitis C virus antigens, and antigens of *Treponema pallidum*, *Plasmodium falciparum*, and several viruses. Some tumor antigens are also thought to cause immune complex-mediated nephritis. In many cases the inciting antigen is unknown. In most instances of immune complex–mediated glomerulonephritis associated with these systemic disorders, evidence is strongest that the inciting event underlying the glomerulonephritis is deposition of the antigens with subsequent formation of immune complexes in situ rather than deposition of preformed immune complexes from the circulation.

Mechanisms of Glomerular Injury Following Immune Complex Formation

The pathogenesis of immune complex diseases is discussed in Chapter 6. Here we briefly review the salient features that relate to glomerular injury. **Whatever the antigen may be, antigen-antibody complexes formed or deposited in the glomeruli may elicit a local inflammatory reaction that produces injury.** It has long been thought that the inflammation and injury are mediated and amplified by the binding of complement, but recent studies in knockout mice also point to the importance of engagement of Fc receptors on leukocytes and perhaps glomerular mesangial or other cells as mediators of the injury process. The glomerular lesions may exhibit leukocytic infiltration and proliferation of mesangial and endothelial cells.

Electron microscopy reveals electron-dense deposits, presumably containing immune complexes, that may lie in the mesangium, between the endothelial cells and the GBM (subendothelial deposits), or between the outer surface of the GBM and the podocytes (subepithelial deposits). Deposits may be located at more than one site in a given case. By immunofluorescence microscopy the immune complexes are seen as granular deposits along the basement membrane (Fig. 20-4*D*), in the mesangium, or in both locations. Once deposited in the kidney, immune complexes may eventually be degraded, mostly by infiltrating neutrophils and monocytes/macrophages, mesangial cells, and endogenous proteases, and the inflammatory reaction may then subside. Such a course occurs when the exposure to the inciting antigen is short-lived and limited, as in most cases of poststreptococcal glomerulonephritis. However, if immune complexes are deposited for prolonged periods, as may be seen in SLE or viral hepatitis, repeated cycles of injury may occur, leading to a more chronic membranous or membranoproliferative type of glomerulonephritis.

Several factors affect glomerular localization of antigen, antibody or immune complexes. The molecular charge and size of these reactants are clearly important. Highly cationic antigens tend to cross the GBM, and the resultant complexes eventually reside in a subepithelial location. Highly anionic macromolecules are excluded from the GBM and are trapped subendothelially or are not nephritogenic at all. Molecules of neutral charge and immune complexes containing these molecules tend to accumulate in the mesangium. Large circulating complexes are not