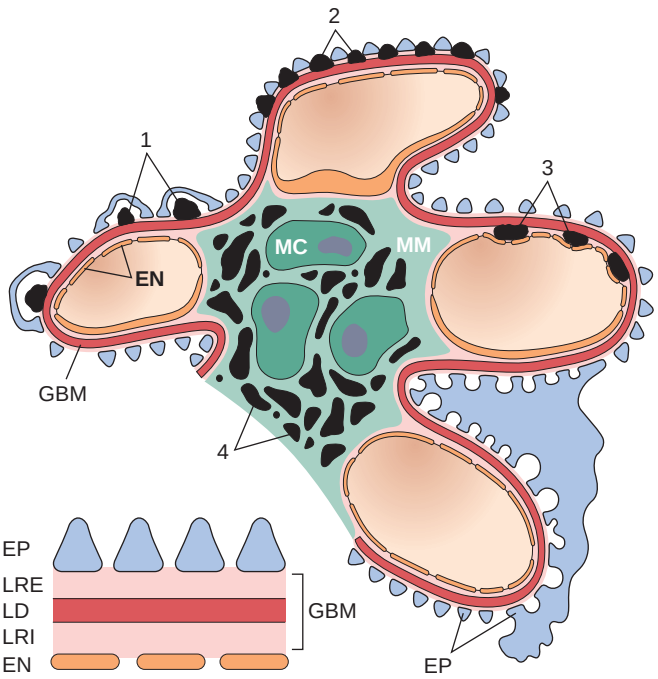

Figure 20-5 Localization of immune complexes in the glomerulus: (1) subepithelial humps, as in acute glomerulonephritis; (2) epimembranous deposits, as in membranous nephropathy and Heymann nephritis; (3) subendothelial deposits, as in lupus nephritis and membranoproliferative glomerulonephritis; (4) mesangial deposits, as in IgA nephropathy. *EN,* Endothelium; *EP,* epithelium; *GBM,* glomerular basement membrane; *LD,* lamina densa; *LRE,* lamina rara externa; *LRI,* lamina rara interna; *MC,* mesangial cell; *MM,* mesangial matrix. (Modified from Couser WG: Mediation of immune glomerular injury. J Am Soc Nephrol 1:13, 1990.)

usually nephritogenic, because they are cleared by the mononuclear phagocyte system and do not enter the GBM in significant quantities. The pattern of localization is also affected by changes in glomerular hemodynamics, mesangial function, and integrity of the charge-selective barrier in the glomerulus. These influences may underlie the variable pattern of immune reactant deposition in various forms of glomerulonephritis (Fig. 20-5). In turn, the distinct patterns of localization of immune complexes is a key determinant of the injury response and the histologic features that subsequently develop. Immune complexes located in subendothelial portions of capillaries and in mesangial regions are accessible to the circulation and more likely to be involved in inflammatory processes that require interaction and activation of circulating leukocytes. Diseases in which immune complexes are confined to the subepithelial locations and for which the capillary basement membranes may be a barrier to interaction with circulating leukocytes, as in the case of membranous nephropathy, typically have a noninflammatory pathology.

In summary, **most cases of immune complex mediated glomerulonephritis are a consequence of deposition of discrete immune complexes, which give rise to granular immunofluorescence staining along the basement membranes or in the mesangium.** However, it may be difficult to determine whether the deposition has occurred in situ, by circulating complexes, or by both mechanisms because, as we discussed earlier, trapping of circulating immune complexes can initiate further in situ complex formation. Single etiologic agents, such as hepatitis B and C viruses, can cause either a membranous pattern of glomerulonephritis, with subepithelial in situ deposition of antigens, or a membranoproliferative pattern, more indicative of subendothelial deposition of antigens or deposition of circulating complexes. It is best then to consider that **antigen-antibody deposition in the glomerulus is a major pathway of glomerular injury and that in situ immune reactions, trapping of circulating complexes, interactions between these two events, and local hemodynamic and structural determinants in the glomerulus all contribute to the diverse morphologic and functional alterations in glomerulonephritis.**

Cell-Mediated Immunity in Glomerulonephritis

Although antibody-mediated mechanisms may initiate many forms of glomerulonephritis, there is evidence that sensitized T cells cause glomerular injury and are involved in the progression of some glomerulonephritides. Clues to the role of cellular immunity include the presence of activated macrophages and T cells and their products in the glomerulus in some forms of human and experimental glomerulonephritis; in vitro and in vivo evidence of lymphocyte activation on exposure to antigen in human and experimental glomerulonephritis; abrogation of glomerular injury by lymphocyte depletion; and experiments in which glomerular injury may be induced by transfer of T cells from nephritic animals to normal recipients. The evidence is most compelling for certain types of experimental crescentic glomerulonephritis in which antibodies to GBM initiate glomerular injury and activated T lymphocytes then propagate the inflammation. Despite this body of suggestive evidence, proof of glomerulonephritis in humans resulting primarily from T-cell activation remains lacking.

KEY CONCEPTS

Pathogenesis of Immune-mediated Glomerular Injury

- Antibody-mediated immune injury is an important mechanism of glomerular damage, mainly via complement- and leukocyte-mediated pathways. Antibodies may also be directly cytotoxic to cells in the glomerulus.
- The most common forms of antibody-mediated glomerulonephritis are caused by the formation of immune complexes, which may involve either endogenous antigens (e.g., PLA_2R in membranous nephropathy) or exogenous (e.g., microbial) antigens. Immune complexes show a granular pattern of deposition by immunofluorescence.
- Autoantibodies against components of the GBM are the cause of anti–GBM antibody–mediated disease, often associated with severe injury. The pattern of antibody deposition is linear by immunofluorescence.

Activation of Alternative Complement Pathway

Alternative complement pathway activation occurs in the clinicopathologic entity called *dense-deposit disease,* until recently referred to as *membranoproliferative glomerulone-*