EDITORIALS

Human Idiopathic Membranous Nephropathy — A Mystery Solved?

Richard J. Glassock, M.D.

Just over 50 years ago, the late David Jones[1] identified (using the periodic acid–Schiff and methenamine silver stains) the unique glomerular pathologic features of membranous nephropathy, thus distinguishing it from other causes of "nephrotic glomerulonephritis." Subsequent immunofluorescence and electron-microscopical studies established that membranous nephropathy was also characterized by striking granular aggregations of IgG and electron-dense deposits along the outer (or subepithelial) aspect of the glomerular basement membrane. These glomerular IgG deposits were initially believed to represent an accumulation of immune complexes arising from the circulation, as is found with glomerulonephritis in a rabbit model (chronic serum sickness).

In 1959, Heymann et al.[2] described a rat model of membranous nephropathy, similar to the disease in humans, induced by active immunization with crude kidney extracts in complete Freund's adjuvant. Initially, this model was also believed to be due to deposition of immune complexes from the circulation. Subsequently, however, Van Damme et al.[3] and Couser et al.[4] demonstrated that a circulating antibody reacted with and bound to the primary antigenic target located on podocytes — the visceral epithelial cells of the glomerulus — indicating that the disease was caused by the in situ formation of immune complexes. Others soon showed that additional antigens, normally extrinsic to the kidney, that were "planted" artificially in the glomeruli (the glomerular basement membrane or podocyte) through biophysical attraction to the capillary wall could provoke an identical lesion (Fig. 1).

Both the target antigen and the autoantibody operative in Heymann's model were eventually characterized; thus, all of Witebsky's postulates[5] were fulfilled, defining the autoimmune nature of the disease in the rat model.

However, translation of the pathogenesis of the rat model to idiopathic membranous nephropathy in humans proved difficult. The target antigen responsible for Heymann's model appeared to be absent in human kidneys.[6] Diligent searches for the autoantibody against the "Heymann" antigen (now known to be megalin [glycoprotein 330]) were unrewarding.[6] Thus, the true pathogenesis of human idiopathic membranous nephropathy remained unresolved.

Now, this long-lasting mystery may well have been solved by Beck et al.,[7] as reported in this issue of the *Journal.* Autoantibodies against an antigen normally expressed on the podocyte cell membrane in humans, the M-type phospholipase A_2 receptor (PLA_2R), appear to circulate and bind to a conformational epitope (or epitopes) present on PLA_2R, producing in situ deposits characteristic of those associated with membranous nephropathy. These autoantibodies are largely, but not exclusively, immunoglobulins of the IgG4 subclass, similar to those seen in most instances of idiopathic membranous nephropathy in patients. Other renal diseases and secondary forms of membranous nephropathy (such as lupus membranous nephropathy) do not appear to involve such autoantibodies.

Beck et al. also present preliminary indications of an association between the clinical features of the disease (proteinuria and the nephrotic syndrome) and the presence and titer of the circulating autoantibodies. If the disease can be transferred to nonhuman primates that express the PLA_2R antigen on podocytes or if the subepithelial deposits can be shown to recur rapidly in a kidney transplanted from a normal donor to a

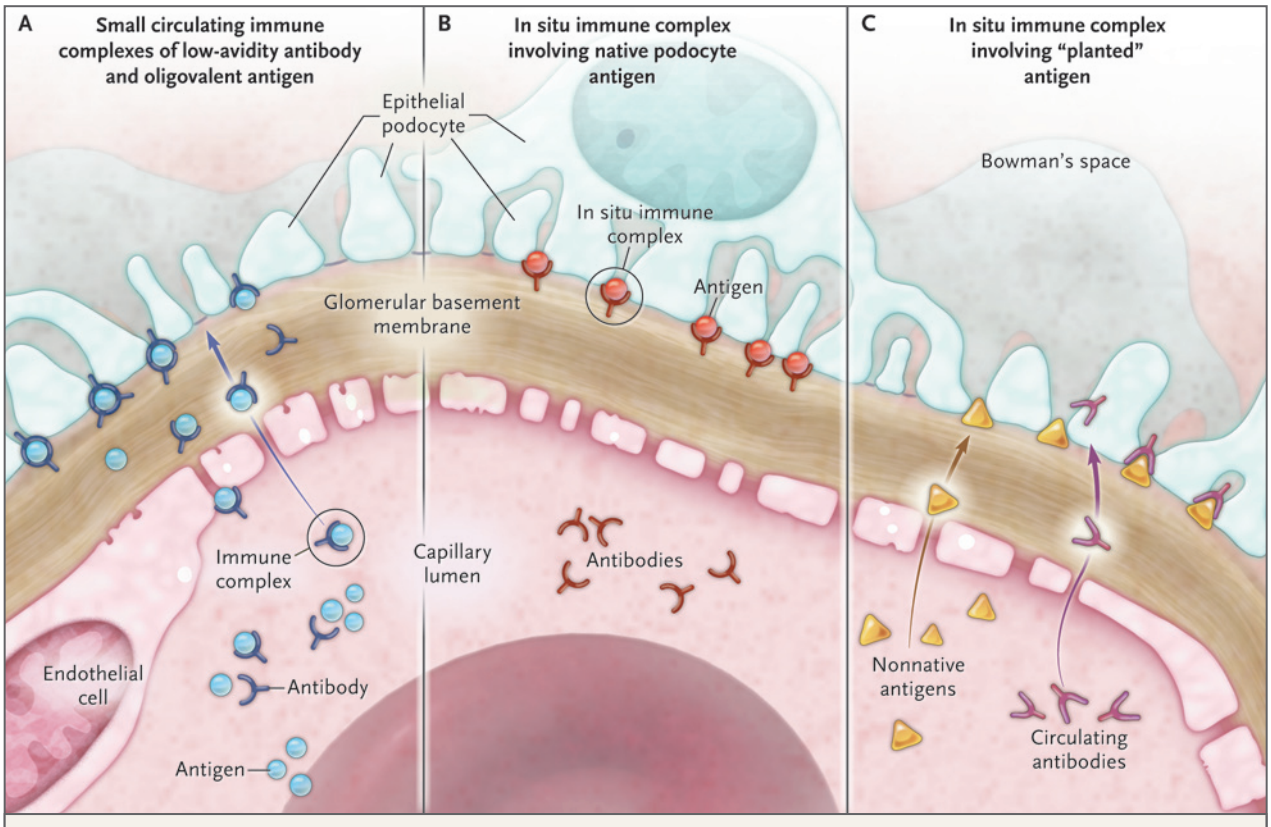

Figure 1. Possible Mechanisms of the Formation of Subepithelial Deposits in Experimental Models of, and Patients with, Membranous Nephropathy.

Panel A shows the deposition of immune complexes from the circulation. Panel B shows the in situ formation of immune complexes through the reaction of circulating autoantibody to a native glomerular (podocyte) antigen. Panel C shows formation of immune complexes with a nonnative (extrinsic) antigen artificially bound to the capillary wall.

recipient with membranous nephropathy whose circulation contains auto–anti-PLA_2R antibodies, all of Witebsky's postulates[5] would be fulfilled for the disease in humans. In addition, anti-PLA_2R autoantibodies would be proven as the circulating vector, and podocyte PLA_2R would be proven as the target autoantigen, in membranous nephropathy. Even without this proof, the present observations of Beck et al. represent a major breakthrough that will almost certainly initiate a new era of investigation into human membranous nephropathy.

However, several additional mysteries remain to be resolved. First, what proportion of cases of what we call "idiopathic" membranous nephropathy is caused by anti-PLA_2R autoantibodies? Next, what triggers the production of these autoantibodies? Third, how do the autoantibodies produce the enhanced glomerular permeability to protein?

Beck et al. suggest that at least 70% of cases of idiopathic membranous nephropathy are due to anti-PLA_2R autoantibodies.[7] Preliminary observations suggest that many patients with idiopathic membranous nephropathy also have circulating autoantibodies reactive with neutral endopeptidase, another podocyte antigen previously implicated in alloimmune congenital membranous nephropathy.[8,9] Sorting out this apparent conundrum will require the sharing of serum samples between laboratories studying membranous nephropathy and independent confirmation in another population of patients with idiopathic membranous nephropathy, with the use of both anti-PLA_2R and anti–neutral endopeptidase assays simultaneously. In addition, an older observation regarding a putative role for anti–α-enolase autoantibodies found in Japanese patients with membranous nephropathy should be reexamined.[10] The variety of autoantibodies seen in patients with idiopathic membranous nephropathy may represent the phenomenon of epitope spread-

ing, as observed in other chronic autoimmune diseases.[11] Serial examination of serum samples obtained and stored years before the apparent onset and diagnosis of membranous nephropathy should be enlightening in testing this hypothesis.[12]

Better understanding of the potential autologous or environmental triggers of autoantibody production in patients with membranous nephropathy may uncover possible targets for preventing the disease. The binding of the autoantibody to its relevant antigen on the podocyte cell surface may be sufficient to initiate the disease process. However, much data from experimental and clinical investigations suggest that in situ activation of the complement cascade and generation of the membrane-attack complex of complement in the capillary wall play important roles in the ensuing glomerular permeability defects that lead to proteinuria. This poses a dilemma, since the IgG4 subclass is known to activate complement only poorly, if at all, yet the dominant autoantibodies in the circulation and in the deposits are of the IgG4 subclass.[7] Perhaps the concomitant production of IgG1 or IgG2 autoantibodies is required for the full expression of the abnormal glomerular permeability.

Future investigations will undoubtedly yield answers to these tantalizing questions. Meanwhile, it is likely that the seminal observations of Beck et al. will have a profound effect on how clinicians approach the diagnosis and treatment of membranous nephropathy. Assays for anti-PLA_2R autoantibody (and perhaps anti–neutral endopeptidase as well) may permit the noninvasive diagnosis of membranous nephropathy as well as provide a convenient way to follow the activity of the disease in response to treatment. Five decades after its initial recognition, membranous nephropathy is now entering an exciting and dynamic new era.

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From the David Geffen School of Medicine at UCLA, Los Angeles.

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Diabetes Complications and the Renin–Angiotensin System

Bruce A. Perkins, M.D., M.P.H., Lloyd Paul Aiello, M.D., Ph.D., and Andrzej S. Krolewski, M.D., Ph.D.

The hypothesis that inhibition of the renin–angiotensin system may be effective in preventing diabetic nephropathy was based on a large body of evidence.[1] Positive findings from studies in animal models and subsequent clinical trials fostered enthusiastic hope that systematic use of agents blocking the renin–angiotensin system in the management of diabetic nephropathy would reduce the risk of end-stage renal disease.[2-4] Out of such studies was born a concept that gained wide acceptance: inhibition of the renin–angiotensin system in patients with diabetes is beneficial with regard to both early and advanced stages of nephropathy. As an extension, studies were initiated to investigate the mechanism and role of inhibition of the renin–angiotensin system in other complications of diabetes, such as retinopathy and neuropathy.[5,6]

The study by Mauer et al.[7] in this issue of the *Journal* (ClinicalTrials.gov number, NCT00143949)