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K. D. Jhaveri

Zucker School of Medicine at Hofstra/Northwell

S. Fishbane

Zucker School of Medicine at Hofstra/Northwell

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Glomerular Diseases: Entering a New Era

[Kenar D. Jhaveri](#) and [Steven Fishbane](#)[✉]

Department of Medicine, Division of Kidney Diseases and Hypertension, Hofstra North Shore-Long Island Jewish Health System School of Medicine, Great Neck, New York

[✉]Corresponding author.

Correspondence: Dr. Steven Fishbane, Hofstra North Shore-Long Island Jewish Health System School of Medicine, 100 Community Drive, Second Floor, Great Neck, NY 11021. Email: sfishbane@nshs.edu

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Diseases of the glomerulus have always held a special place of interest for nephrologists. At first glance the glomerulus is a simple filtering structure connected to a couple of pipes, like so many manmade fluid-filtering systems. Of course, on closer inspection, advancement in science has revealed much of the beauty and complexity of this structure.

In 1697, proteinuria was first mentioned in a clinical context (1). Initial studies on albuminuria were performed in 1814 by Jack Blackall (1). One hundred thirty years after proteinuria was first reported, Richard Bright established its relation to renal disease; John Bostock then showed how loss of protein through the urine could lead to a decrease in the amount of protein in the blood (2).

Each individual glomerulus works with its millions of counterparts adjusting to a multitude of physiologic disruptions, reliably helping to maintain homeostatic equilibrium. Yet the glomerulus is also prone to injury, particularly related to autoimmunity and inflammation.

Interestingly, in 1905, one of the first descriptions by Muller (3) to classify glomerular diseases was simple: degenerative versus inflammatory.

The glomerulus is a tuft of capillaries connected to the afferent and efferent arterioles. The capillary wall differs from other capillaries by having three instead of two layers. A fenestrated endothelium, similar to that found in the liver, partially covers the glomerular basement membrane (GBM), and its importance is generally underappreciated. The GFR is proportional to the total area of fenestrations, and disorders of fenestrations play a role in proteinuria and loss of renal function. The second layer of the capillary wall, the GBM, is composed of a variety of proteins, most importantly type IV collagen, which forms the membrane's ultrastructure. The GBM serves several functions, including vital aspects of size and charge filtration selectivity. Heparin moieties provide a barrier to the vectorial movement of certain negatively charged molecules. Perhaps the first major advances in the pathobiology of glomerular diseases came with the discovery of how alterations in type IV collagen components led to structural and functional changes that result in Alport syndrome. The third and final component of the capillary wall is the epithelial cell or podocyte, a terminally differentiated cell that projects foot processes over the GBM. Gaps, or slits, between these cells, covered by thin-slit diaphragms, are the route for regulated filtration. The podocyte has a critical role in the filtration barrier, forming a highly organized structure, disorders of which cause proteinuria. Taken together the glomerular capillary wall is a remarkable structure that allows for high-volume filtration while maintaining charge and size selectivity and preventing loss of significant quantities of protein.

During the prebiopsy era, clinical observations helped define different forms of classification of glomerular diseases. In 1913, lipoid nephrosis was first described, and in 1927 came the first delineation of nephrotic versus nephritic syndrome (4). The procedure that revolutionized glomerular disease was the development of the kidney biopsy in the 1950s (5). This led to not only an expansion of disease categories but the rise of nephropathology.

Glomerular diseases are a result of infections, autoimmunity, chronic illnesses, or cancer. Although secondary causes have slowly increased in number, the search for what activates the immune system remained puzzling. While the science of immunology showed progress, the glomerular diseases needed a new leaf of understanding.

In the prebiopsy era, Thomas Addis recognized in his earliest book three major forms of disease: hemorrhagic, degenerative, and arteriosclerosis (6). He called his classification “last arrangement” and categorized patients with proteinuria in accordance with its causation. In 1955, the first descriptions of diabetic nephropathy appeared, classification of lupus nephritis was mentioned, and treatment strategies were proposed (7). Glomerular disease research blossomed in this era. Many advances in vasculitis and anti-GBM disease (8) were made in the ensuing years, but the pathobiology of three common causes of glomerular diseases—membranous nephropathy, FSGS, and minimal-change disease—remained obscure.

For most of the brief history in which we have had some awareness of the glomerulus and its diseases, our treatments have been decidedly crude and inelegant. Steroids, cyclophosphamide, and chlorambucil have been bombs tossed in darkness at hidden enemies, occasionally hitting their targets, just as often causing substantial collateral damage. But now the situation is changing. In recent years understanding of the pathophysiology and of treatment of glomerular diseases has advanced rapidly.

Ultimately, knowledge of the pathobiology of the glomerular diseases is required for treatment precision and greater efficacy and safety. The progress here has been substantial and is the reason for this Moving Points series. In membranous nephropathy, Beck *et al.* (9) recently described M-type phospholipase A2 receptor as the primary target antigen. Subsequent work has led to an understanding that approximately 80% of patients with membranous nephropathy produce antibodies against this glomerular antigen, and rapidly growing evidence shows the primary causal role these antibodies play. Next it will be important to understand why antibodies against a normal component of the glomerular epithelial cells develop. In membranoproliferative GN, two important breakthroughs have changed our understanding; first the discovery of the key role of the hepatitis C virus and next, elucidation of pathobiologic effects of complement dysregulation. The latter finding has already been exploited therapeutically by the use of biologics that inhibit formation of the membrane attack complex. In addition, a novel classification for membranoproliferative GN has been proposed (10). Last but not least, the *APOLI* gene discovery, which has contributed to the understanding of the genetic basis of FSGS (11) in African Americans, and the urokinase receptor relationship to FSGS (12) complete a series of superb discoveries in glomerular diseases.

In this series of articles, Masani, Ponticelli, Appel, Cattran, and coauthors describe four glomerular diseases with special attention to recent developments in understanding pathobiology: membranous nephropathy, FSGS, IgA nephropathy, and membranoproliferative GN. Other glomerular diseases are no less important but are not included because they have been recently covered in detail in other *CJASN* articles. These articles point to important advances that make this an exciting time to be caring for patients with these disorders and point to a promising future.

Footnotes

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References

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1. Dock W: Proteinuria: The story of 280 years of trials, errors, and rectifications. *Bull N Y Acad Med* 50: 659–666, 1974 [PMCID: PMC1749399] [PubMed: 4597329]
2. Bright R: *Report of Medical Cases with a View of Illustrating the Symptoms and Cure of Disease by a Reference to Morbid Anatomy* London, Longman, Rees, Orme, Brown and Green, 1827
3. Muller F. Morbus brightii. *Verhandl d Deutsch Path Geselisch* 1905;9:64:99
4. Black D: The story of nephrology. *J R Soc Med* 73: 514–518, 1980 [PMCID: PMC1437709] [PubMed: 7014891]
5. Iversen P, Brun C: Aspiration biopsy of the kidney. *Am J Med* 11: 324–330, 1951 [PubMed: 14877837]
6. Addis T: *Glomerular Nephritis*, New York, MacMillan Company, 1948
7. Kark RM, Pirani CL, Pollak VE, Muehrcke RC, Blainey JD: The nephrotic syndrome in adults: a common disorder with many causes. *Ann Intern Med* 49: 751–754, 1958 [PubMed: 13583770]
8. Falk RJ, Jennette JC: Anti-neutrophil cytoplasmic autoantibodies with specificity for myeloperoxidase in patients with systemic vasculitis and idiopathic necrotizing and crescentic glomerulonephritis. *N Engl J Med* 318: 1651–1657, 1988 [PubMed: 2453802]
9. Beck LH, Jr, Bonegio RG, Lambeau G, Beck DM, Powell DW, Cummins TD, Klein JB, Salant DJ: M-type phospholipase A2 receptor as target antigen in idiopathic membranous nephropathy. *N Engl J Med* 361: 11–21, 2009 [PMCID: PMC2762083] [PubMed: 19571279]
10. Sethi S, Fervenza FC: Membranoproliferative glomerulonephritis—a new look at an old entity. *N Engl J Med* 366: 1119–1131, 2012 [PubMed: 22435371]
11. Genovese G, Friedman DJ, Ross MD, Lecordier L, Uzureau P, Freedman BI, Bowden DW, Langefeld CD, Oleksyk TK, Uscinski Knob AL, Bernhardt AJ, Hicks PJ, Nelson GW, Vanhollebeke B, Winkler CA, Kopp JB, Pays E, Pollak MR. Association of trypanolytic ApoL1 variants with kidney disease in African Americans. *Science*. 2010;329:841–845 [PMCID: PMC2980843] [PubMed: 20647424]
12. Wei C, El Hindi S, Li J, Fornoni A, Goes N, Sageshima J, Maignel D, Karumanchi SA, Yap HK, Saleem M, Zhang Q, Nikolic B, Chaudhuri A, Daftarian P, Salido E, Torres A, Salifu M, Sarwal MM, Schaefer F, Morath C, Schwenger V, Zeier M, Gupta V, Roth D, Rastaldi MP, Burke G, Ruiz P, Reiser J: Circulating urokinase receptor as a cause of focal segmental glomerulosclerosis. *Nat Med* 17: 952–960, 2011 [PMCID: PMC4089394] [PubMed: 21804539]

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