IgA Nephropathy: Progress Before and Since Berger

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Berger and the First Description of IgAN

The first public appearance of Berger's seminal observations was modest: an oral report to the Société de Néphrologie in Paris in winter 1968, followed by publication in French of a summary less than 1 page long.3 This report, now cited time and again all over the world, was entitled “Les dépôts intercapillaires d’IgA-IgG,”2 and the coauthor was Nicole Hinglais, an expert electron microscopist.

At the time Berger reported his seminal observations, he was working as a pathologist in Paris at Hôpital Necker and also was Professor at the Université René Descartes. In the late 1960s, kidney biopsy was an increasingly used technique for investigating kidney disease, and the nephrologists with whom Berger worked at Hôpital Necker and Hôpital Tenon in Paris were among the leaders in this new wave of work.

A classification of glomerulonephritis (GN) had been developed based on the various pathologic appearances on specimens obtained using kidney biopsy, but in the mid-1960s, it was based largely on morphologic characteristics seen on light microscopy. The new technique of immunofluorescence microscopy, undertaken with fresh kidney biopsy material to identify the presence of immunoglobulins and complement components, was still regarded as experimental. Berger applied the technique to kidney biopsy specimens and recognized that there was a group of patients, not previously well defined, in whom the dominant finding was IgA deposition in the glomerular mesangium. Electron microscopy showed mesangial electron-dense deposits corresponding to the mesangial IgA. Light microscopic findings were variable, but typically included mesangial hypercellularity, which usually was focal and segmental, but sometimes diffuse. Interpreting his findings in the light of clinical information, he realized that these typically were young adults with low-grade proteinuria and microscopic hematuria and most often with recurrent episodes of macroscopic
hematuria coinciding with upper respiratory tract infection. Within a short time, Berger made further key observations. First, he identified that similar mesangial IgA deposits also typified the GN associated with Henoch-Schönlein purpura, which morphologically often was indistinguishable from IgAN. Second, he showed that mesangial IgA deposits recurred frequently in kidneys transplanted into patients who had developed end-stage renal disease due to IgAN. Third, Berger also published a major description of the secondary form of IgAN associated with alcoholic liver disease.

It might be tempting to belittle Berger’s observations with the apparent wisdom of hindsight. After all, he merely applied a new technique and got an interesting answer, the sort of thing in modern scientific vernacular we might term a “fishing expedition.” But what he picked out of his net was enduring and remarkably important.

Berger (Fig 1) was a charming and modest man. Liliane Striker (née Morel-Maroger) has published an affectionate memoir from her experience as a young research fellow in Berger’s laboratory in Hôpital Necker in the 1960s in which she describes the excitement of those early days when Berger identified IgAN. She also vividly tells of Berger’s great skills not only as a researcher, but as a teacher and diagnostician.

What’s in a Name: IgAN or Berger disease?

Many titles have been used for IgAN during the last 40 years. Berger followed his original descriptive phrase, “dépôts intercapillaires d’IgA-IgG,” by using the term “nephropathy with mesangial IgA-IgG deposits.” However, this soon was replaced by a number of other terms, including IgAN, mesangial IgA disease, mesangial IgA GN, and IgA-IgG nephropathy; of these, IgAN has proved the most enduring. In 1973, the term Berger disease was proposed first by Levy et al in Paris, although this term subsequently sometimes was restricted to patients who had recurrent episodes of visible hematuria.

Because Berger’s observations were so innovative and influential, why has the term Berger disease gradually fallen out of use? Perhaps this simply is because eponymous titles for diseases are becoming less fashionable. However, much more importantly, it seems that Berger himself preferred not to see his name attached to the disease he first described, an object lesson in due modesty that adds to Berger’s justified reputation as a great figure in the history of glomerular disease.

EARLY HISTORY OF IgAN

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Progress Before Berger

Classifications of Nephritis, 1820-1970

The 1968 report of Berger and Hinglais was more than...
just a novel observation, it introduced a new level of descriptive classification into the study of GN and highlighted the confusions of the time about the classification of glomerular disease, which even now await full resolution. To understand fully this report’s importance requires a long look back.

From the time of Richard Bright’s remarkable book in 1827, ideas about nephritis were dominated by the combination of clinical observation and macroscopic and microscopic observation of kidney tissue obtained at autopsy. There was an uneasy tension between this level of description and clinical observation from the start: very early, it was noted that in one clinical setting (say dropsy and proteinuria), a number of different appearances could be seen in the kidney. These appearances initially were described in the 1840s as either a fatty kidney with normal or nearly normal glomeruli or, in contrast, a form in which the presence of cells and tubular destruction predominated. Debate about the relationship between these 2 forms and their relationship to scarred granular kidneys dominated renal pathology up to and beyond the First World War.

Pathologists naturally believed that their level of description was more fundamental than clinical classifications and that the underlying “diseases” were expressed primarily in morphologic terms. A further, apparently more fundamental, layer of description was introduced as the cause of some of the appearances was teased out: “poststreptococcal nephritis” was the first, in the 1880s. Then the idea of time came to influence classification: “acute” and “chronic” forms, for example, the “Dauerstadium” (dormancy) of nephritis, coined by Volhard and Fahr, and the “chronic latent nephritis” of Addis. As ideas of immunology developed, immunologic terms came into use. Thus, in the 1960s, “(chronic) hypocomplementemic nephritis” made its appearance and by analogy from studies of experimental nephritis in animals, different patterns of deposition of immune reactants, such as complement and immunoglobulin, were seen: the “lumpy bumpy” and “linear” deposits that Germuth and Rodriguez and Dixon correlated to different routes of immunopathogenesis. Finally, from the 1950s onward, terms based on results of the new effective treatments, such as corticosteroid-sensitive and corticosteroid-resistant nephrotic syndrome, appeared.

How then should GN be classified: by morphologic characteristics, by clinical presentation, by cause, by tempo, or by treatment response? The result of all this was great confusion for pathologists, physicians, and, not least, patients. A further major breakthrough in the 1950s was the advent of kidney biopsy, which allowed the study of early disease and began to show the plasticity of renal histologic appearances.

Such was the context of Berger’s seminal observations on IgA deposition.

Background of IgAN: An Intersection of Paths

To place IgAN in context, we must trace the evolution of 3 layers of description in GN: the clinical syndrome of recurrent hematuria, the histologic appearance of focal or mesangial nephritis, and the immunohistochemical identification of IgA deposition (Fig 2).

Recurrent and persistent hematuria. During the latter half of the 19th century, urine microscopy produced data as good as any today, including observations of acanthocytes in renal bleeding. About the same time, patients with recurrent attacks of macroscopic hematuria were described who had microscopic hematuria between attacks. However, the study of GN at that time was dominated by the focus on the presence and quantity of proteinuria. Although hematuria and proteinuria had been known to coexist in urine since Wells in 1808, the presence or absence of hematuria in GN was not widely discussed until the 1920s, when Thomas Addis described the quantitative excretion of formed elements in urine, including red blood cells, as a measure of the activity and/or progression of kidney diseases. The “Addis count” was performed widely as a surrogate until kidney biopsy became available 30 years later.

Focal nephritis. The first reports to draw wide attention to focal segmental nephritis were in the early 1920s. At first, focal nephritis was noted in patients with endocarditis and thus described as “embolic,” a term that erroneously persisted for decades. Then, in 1926, Baehr described 14 young adults without endocarditis, but
with recurrent macroscopic hematuria, many of whom did well and some of whom had focal segmental nephritis. In the report by Arthur Ellis\textsuperscript{17} discussing the work of the team led by his clinical associate, Clifford Wilson, at the London Hospital in the 1940s, patients also were described who today would be given the diagnosis clinically of IgAN, despite which Wilson opposed the idea of focal nephritis when it resurfaces in kidney biopsy specimens a decade later.

It was not until the advent of kidney biopsy in the 1950s that focal nephritis really came to attention. In 1957, Bates, Jennings, and Earle,\textsuperscript{18} as part of a study of acute nephritis, noted immediate postpharyngitic macroscopic hematuria with proteinuria in 10 young soldiers with normal serum complement concentrations and normal antistreptolysin O titers. Biopsy specimens showed red blood cells in tubules and generally mild and often focal segmental nephritis. However, it was the report of Heptinstall and Joekes\textsuperscript{19} in London published 2 years later that showed the range of clinical features associated with focal segmental nephritis; only 3 of their 31 patients in 1960 showed recurrent hematuria as a presentation, many having Henoch-Schönlein purpura or lupus nephritis. Ross\textsuperscript{20} at the London Hospital in 1960 identified a group of patients with long-term relapsing hematuria. Two articles in 1965 also described similar cases in childhood.\textsuperscript{21,22} Thus, by the 1960s, focal segmental GN was a recognized subgroup of proliferative GN.

Finally, during the late 1950s, electron microscopy first was applied to kidney biopsy material, and in 1962, Galle and Berger\textsuperscript{23} noted “intercapillary” electron-dense material, presumed by analogy from animal work, to be deposits of circulating immune complexes in biopsy specimens showing predominantly mesangial nephritis.

IgA deposition within glomeruli. Fluorescent-labeled specific antibodies first were used to detect and trace proteins in the early 1950s, but until the mid-1960s, very few laboratories offered this technique, and the antisera used often were of poor specificity. By 1963, antibodies were available commercially against IgG, IgA, and IgM, but the few laboratories studying immunofluorescence in kidney biopsy specimens at that time mostly used only anti-IgG reagents because this was thought to be the predominant immunoglobulin class involved in the immunopathogenesis of nephritis. For example, Bodian et al\textsuperscript{21} from Great Ormond Street Hospital, London, in 1965 reported biopsies from children with recurrent hematuria using immunofluorescent techniques for the first time, but only antisera against whole immunoglobulin and IgG were used and thus an opportunity to identify IgAN surely was missed. Then in 1968 came the report by Berger and Hinglais\textsuperscript{2} of predominant IgA mesangial deposi-
tion in kidney biopsy specimens, although they emphasized that it usually was associated with some IgG. Comparative quantification was unsatisfactory, but in these patients, the IgA reagent “outshone” the IgG reagent strongly. Berger had trained with the pathologist Deborah Doniach in London, where he got the idea of applying fluorescent techniques to kidney disease as she had to liver problems. Berger and his colleagues also had the advantage of a pure anti-IgA antibody prepared by immunologist Maxime Seligmann, who had described anti-DNA antibodies for the first time a decade previously.

Emergence of IgAN as a Recognized Entity

The world of nephrology remained a little skeptical about IgAN as a discrete entity. Other reports from Paris emerged from Druet et al.24 and Morel-Maroger et al.,25 so that for a short time the disease seemed to be confined to France. Then in 1972 and 1973, reports from outside France appeared, including series from the groups of Maintz (the Netherlands), McEnery (United States), Davies (United Kingdom), Ueda (Japan), and Woodroffe (Australia).26-30 Quickly, the finding of predominant mesangial IgA in hematuric patients with mesangial or focal nephritis was realized to be common worldwide. Nevertheless, only a dozen reports were published on the subject up to 1975, when a UK opinion leader wrote that “it seems debatable whether the use of terms such as ‘mesangial IgA disease’ and ‘IgA nephropathy’ is warranted.”31(p614) There still were only a few dozen reports during the late 1970s; this slow progress occurred in part because immunofluorescence techniques were far from universally available in renal pathology laboratories even during the early 1970s, when workers still needed to fluorosceinate their own antibodies before use. However, after this, interest expanded rapidly and more than 600 reports appeared from 1981 to 1988.

Nevertheless, by 1975, the salient features of IgAN were established: a condition with moderate mesangial proliferative glomerular changes, often focal and segmental; associated with hematuria, often macroscopic; and associated with increased serum IgA concentration. Clinical evolution often was stable or slow, but renal failure, increasing proteinuria, and hypertension occurred eventually in some patients. When such patients underwent transplant, Berger showed in 1975 that IgA rapidly recurred in the transplanted kidney in about half the recipients, but that not all transplants failed as a result.4

With the advent of these methods to identify and classify glomerular disease, the focus could move to the study of pathogenesis, clinical course, and treatment.

THE INTERNATIONAL IgA NEPHROPATHY NETWORK

A key element in the more rapid progress of our understanding of IgAN from the 1980s onward was a series of international symposia devoted exclusively to IgAN. At the second of these symposia, organized in Bari, Italy, an informal “IgA Club” was established, which started as little more than a diffuse alliance of colleagues and friends with a shared interest in the field. The main initial output of the club was the series of international symposia held every 2 or 3 years (Table 1). These small meetings, typically no more than 100-150 registrants, served as an effective forum for the exchange of ideas and new findings, increasingly expanding to involve not only nephrologists, but also renal pathologists, immunologists, biochemists, cell biologists, and geneticists. Restyling itself the International IgA Nephropathy Network in 2000 (www.igan-world.org), it increasingly has formed the basis for substantial collaborative research efforts. Most notable to date has been the development, working with the Renal Pathology Society (and supported by the International Society of Nephrology), of a novel evidence-based approach to clinicopathologic classification resulting in the Oxford classification of IgAN published in 2009.38 The network remains without formality, but now is serving as a basis for emerging validation studies for the Oxford classification. It is hoped that the network also will facilitate the collaborative efforts that are needed to maximize progress in understanding the complex genetics of IgAN and will provide a focus for mounting treatment trials of sufficient power to give credible answers to continuing uncertainties in the treatment of IgAN.
PROGRESS AND CHALLENGES IN OUR UNDERSTANDING OF IgAN

A review of the programs and proceedings for those 12 international symposia since 1983 (Table 1) confirms that the preoccupations of those who study IgAN and the research challenges have been consistent, and that progress in our knowledge and understanding unsurprisingly has been incremental rather than spectacular. Progress to date and the major unresolved issues are briefly summarized here, but continue to be reviewed in greater detail elsewhere.39

Epidemiology and Genetics

A picture has steadily emerged of global variations in the prevalence of IgAN, apparently based on ancestry. Differences in attitude about the use of kidney biopsy in patients with minor urine abnormalities are no more than a partial explanation for these differences. There is no doubt now that there is a higher prevalence in East Asians compared with Europeans and an even lower prevalence in those of African origin. Perhaps more remarkable and still unexplained is the difference in sex distribution: IgAN is markedly male predominant in Europeans and equal in males and females in Asia.

Genetic explanations for these differences have been slow to emerge. Case-control association studies of candidate genes have continued to disappoint, rarely producing replicable results. The 3 large kindreds of IgAN that have been studied in some detail have each been associated with different regions of the genome and to date have not yielded plausible candidates. However, the first genome-wide analysis of IgAN performed in Europeans40 has opened a new era in genetic analysis of IgAN, and with other large cohorts of differing ancestry under analysis and partnership opportunities for meta-analysis, there soon may be significant progress in this field.

Clinical and Pathologic Characteristics

Our clinical and pathologic view of IgAN has in many ways improved little since the lucid original descriptions of Berger and his contemporaries. It is notable that one archetypal feature, the onset of visible hematuria within 24 hours of mucosal infection, still defies a convincing pathogenic explanation.

Although there has been steady progress in understanding the natural history of IgAN, especially from registry stud-
ies, our ability to prognosticate with great accuracy for an individual patient is still somewhat limited, and this has inhibited therapeutic progress by preventing the efficient design of clinical trials that focus on the highest risk patients.

None of the various attempts to classify the pathologic features has gained widespread approval, but the recent evidence-based Oxford classification of IgAN now has identified pathologic features that still add to the prediction of outcome even when clinical features at presentation and during follow-up are known. This needs further validation in a broader range of patients, including those of different ancestry, but this may prove to be an important step forward.

**Relationship With Henoch-Schönlein Purpura Nephritis**

The precise pathogenic relationship between IgAN and Henoch-Schönlein purpura nephritis is poorly defined. Although glomerular histopathologic characteristics are similar and some of the emerging pathogenic concepts (eg, alteration in IgA glycosylation, described next) appear to be shared, there are differences in age of onset, tempo, and outlook for the glomerular disease in Henoch-Schönlein purpura. Also, the reasons that some patients have systemic vasculitis (Henoch-Schönlein purpura) while others have a lesion restricted to the kidney (IgAN) are unclear.

**Pathogenesis of Mesangial IgA Deposition and Injury**

It perhaps is in our understanding of the pathogenesis of mesangial IgA deposition and subsequent glomerular injury that progress has been most encouraging, although not unexpectedly, questions continue to emerge.

**Characterizing Mesangial IgA**

Analysis of the deposited IgA gradually has become more sophisticated, reaching our present understanding that mesangial IgA is predominantly polymeric IgA with reduced O-linked glycosylation of the hinge region that connects the antigen-binding fragment of the immunoglobulin molecule with the Fc region.

**A Mucosal or Systemic Defect?**

Despite the clinical association of mucosal infection with clinically overt IgAN, evidence has emerged suggesting that mesangial IgA may originate not from the mucosal immune system, but from the bone marrow, and the possibility that this is a consequence of derangement of the normal mucosa-marrow axis in the IgA immune system.

**The Role of Complement**

Early assumptions that IgA is a poor activator of complement have been challenged, and a role for glomerular secretory IgA in local complement activation has emerged.

**IgA Glycosylation**

Perhaps the most striking change in thinking about IgAN stemmed from observations starting in the mid-1990s that altered hinge region O-linked glycosylation of IgA1 is a cardinal feature of serum and mesangial IgA in IgAN. The changed molecular behavior associated with altered hinge glycosylation may contribute to the inflammatory and fibrotic processes that are the hallmark of the glomerular injury that follows mesangial IgA deposition in many, but not all, patients with IgAN. The basis for the altered glycosylation is still debated, with conflicting data implying either an inherited or acquired defect in relevant glycosylation enzymes or disruption in the mucosa-marrow axis, resulting in changes in glycosylation patterns of IgA1 synthesized in different compartments of the IgA immune system.

**Treatment Trials**

“IgA-specific” treatment for IgAN made an early start. In 1980, a randomized controlled trial of phenytoin had been reported by Clarkson et al based on the rationale that long-term use of phenytoin is associated with a decrease in serum IgA levels. Although by contemporary standards, the study was underpowered and lacked the duration of follow-up necessary to be sure a long-term benefit had not been missed, it nevertheless led the way by pointing to the possibility of targeting mechanisms of disease initiation rather than “downstream” inflammatory events. Progress has been slow because the mechanisms that lead to IgA deposition have turned out to be more complex than was imagined in the 1970s, and practical treatment
options with surrogate markers of early success have not yet emerged.

Instead, the published treatment trials for IgAN have investigated strategies that are not disease specific, including corticosteroids and other immunosuppressive agents, and blockade of the renin-angiotensin system. Despite the prevalence of IgAN, it proved surprisingly difficult to mount effective trials with sufficient power. However, after the trial of corticosteroids by Pozzi et al.,42 there has been progress during the last decade in the number and quality of published trials, although there still is no consensus about definitive treatment strategies.

Transplant

Berger reported in 1975 the recurrence of IgAN after kidney transplant, but proper assessment of its true prevalence took another 20 years to emerge. Early clinically silent recurrence almost certainly is underestimated because transplant biopsy frequently is restricted to investigation of episodes of decreased transplant function and often relies on light microscopy only. However, the picture gradually has emerged that recurrence is very common, with at least 50%-60% having IgA deposits by 5 years after transplant, although apparently this is not universal.

Recurrent IgAN after transplant provides a fertile but underused opportunity to further our understanding of the pathogenesis of IgAN. It is the one clinical opportunity to observe the evolution of IgAN ab initio and ask some intriguing questions. Why does IgAN recur in many, but not all, patients? Does this hint at different entities, in one of which immunosuppressive therapy initiated before the onset of disease prevents disease, whereas in another it does not? Why does recurrent IgAN often seem to follow the same tempo in the transplanted kidney as it did in the native kidneys?

IgAN: PATTERN OR DISEASE?

More than 40 years have passed since the seminal observations of Berger and Hinglais2 in 1968, and the study of IgAN still carries with it several of the same paradoxes that began to emerge in the early years of the scientific symposia devoted to its study.

The entity we call IgAN remains a pragmatic way to categorize the most common pattern of mesangial proliferative GN and defines an entity that to date makes sense for practicing nephrologists. However, how can it be considered a single disease in light of the many variations in clinical and pathologic presentation and progression, geographic and sex variations in its prevalence, and variations in risk of transplant recurrence? Will we in due course be required to acknowledge our naiveté, both clinical and scientific, and recognize different entities with different cause and pathogenesis and with genetic and other identifiable risk factors for progression and transplant recurrence that require distinctive therapeutic approaches?

The emergence of IgAN served to highlight the conundrum that continues to afflict our classification of GN. On the one hand, classification had grown from morphologic patterns through application of light microscopy to the early kidney biopsy specimens without the benefit of testing for immune deposits (using immunofluorescence or immunoperoxidase) and without the ultrastructural information provided by electron microscopy. Even when immunofluorescence or electron microscopy provided additional discriminatory information, classification was still being dominated by the light microscopic appearance (eg, membranous nephropathy, membranoproliferative GN, and focal segmental glomerulosclerosis). However, in IgAN, we define an entity by very consistent and characteristic diffuse mesangial IgA deposition regardless of the light microscope appearances that can cover the whole gamut of light microscopic change, including normality, diffuse or segmental hypercellularity, progressive segmental or diffuse glomerulosclerosis, and, occasionally, severe rapidly progressive crescentic GN.

We also are classifying IgAN with no regard for the other clinical criteria (eg, disease tempo, cause, and response to treatment) that may mark distinct entities within the gamut of IgAN.

Given the fluidity of these approaches to classification, it perhaps is not surprising that the definition of an entity called
IgAN produced some initial skepticism.

More sophisticated skepticism is based on the observation in clinical and autopsy studies that many people have mesangial IgA with no evidence of glomerular injury on light microscopy. Hence, some have suggested that the deposited IgA is a “coincidental bystander” commonly found in patients who develop mesangial proliferative GN and who have other reasons for marked clinicopathologic heterogeneity. The counterargument that the deposited IgA is pathogenic is based on the very strong association between mesangial proliferative GN and mesangial IgA deposition. More than 90% of patients with mesangial proliferative GN will have mesangial IgA deposits, and similar light microscopic patterns with no IgA (sometimes called “pure” mesangial proliferative GN) are distinctly unusual.

Slowly emerging evidence of a pathogenic role for IgA in a variety of in vitro and in vivo studies during the years has weakened the innocent bystander argument that the IgA represents coincidence rather than cause. The final justification for the term IgAN eventually may come from experimental evidence that IgA extracted from human kidneys transmits the disease.

While we still look at IgAN “through a glass darkly,” there is no doubt that over 40 years our vision has increased.

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REFERENCES


43. 1 Corinthians 13:12 (*Holy Bible, King James Version*).