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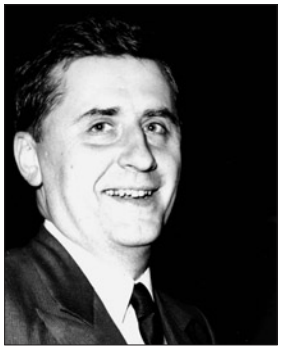

Jean Berger
1930–2011

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The passing of Jean Berger on 22 May 2011 marks the end of an era. He was the renal pathologist who first described IgA nephropathy, and whose seminal work coincided with the burgeoning of renal biopsy as a ground-breaking investigative tool in kidney disease.

Jean Berger was born on 17 September 1930. He became *Interne des Hôpitaux de Paris* (the equivalent of residency) in 1954. Working in the Department of Nephrology headed by Professor Jean Hamburger at the Necker-Enfants Malades Hospital in Paris, he became interested in pathology. He qualified as a specialist in medicine in 1960, writing a thesis entitled, "Contribution of the renal biopsy to the pathological knowledge of the kidney diseases."

Renal biopsy had initially emerged in the early 1950s as an innovative tool for the understanding and classification of glomerular diseases on the basis of morphology defined by light microscopy. Then, during the late 1950s, electron microscopy was first applied to kidney biopsy material. Berger, working with Pierre Galle, an electron microscopist, described "fibrinoid intercapillary deposits" in patients with chronic glomerulonephritis, a first step toward his future description of IgA nephropathy. They also made the first description of dense deposits within the glomerular basal membranes.

At the same time, Berger had trained with the pathologist Deborah Doniach in London in order to apply fluorescent techniques to the kidney. Fluorescently labeled antibodies were first used to detect proteins in the early 1950s, but until the mid-1960s very few laboratories offered this technique, and the antisera were often of poor specificity. By 1963, antibodies were available commercially, but laboratories studying immunofluorescence in kidney biopsies mostly used only anti-IgG reagents, as IgG was thought to be the predominant immunoglobulin class involved in the immunopathogenesis of nephritis. Berger was helped by Professor Bernard Antoine, an immunologist working at Necker-Enfants Malades Hospital, who developed the methodology for immunofluorescence. They tested commercial sera and labeled them with fluorescein; anti-IgA specificity was confirmed with an anti-IgA serum produced by Professor Maxime Seligmann (who had made the first description of anti-DNA antibodies).

Berger had developed a fruitful partnership with two other pathologists. Nicole Hinglais was in charge of light and electron microscopy in the pathology department of Hamburger's nephrology clinic (she would later discover the characteristic ultrastructural lesions of the glomerular basement membrane in Alport syndrome). The immunofluorescence technique was performed in the laboratory of Dr. Halina Yaneva. Liliane Striker (née Morel-Maroger) has published a memoir from her own experience as a research fellow in the 1960s, in which she describes the excitement of those days when Berger identified the new nephropathy that was to bear his name.

In 1967, at a session of the Actualités Néphrologiques de l'Hôpital Necker, Berger presented a panorama of renal lesions based on their immunofluorescence pattern. Among these findings, he had identified glomerular IgA deposits in a few patients with chronic glomerulonephritis or Henoch–Schönlein purpura. An oral report to the Société de Néphrologie in Paris in the winter of 1968 was followed by the publication in French of a summary less than one page long.[1] This report, now cited time and again all over the world, was entitled "Les dépôts intercapillaires d'IgA-IgG." It concerned 25 patients presenting with recurrent hematuria and with focal and segmental lesions by light microscopy, in whom the IgA reagent 'outshone' the IgG reagent strongly. As Professor Stewart Cameron has reminded us, biopsies of children with recurrent hematuria and focal glomerulonephritis had already been studied by immunofluorescence, but only with the use of antisera against IgG.

Berger extended his observations the following year,[2] describing a nephropathy characterized by the presence of mesangial IgA–IgG deposits in 55 patients with a range of light microscopy appearances, most commonly focal glomerulonephritis. All patients had moderate proteinuria and persistent microscopic hematuria, and 22 "had one or several bouts of gross hematuria which usually occurred during a sore throat." He remarked, "The

course of the disease appeared to be remarkably slow," but in one patient renal transplantation was needed, and biopsy of the transplant showed recurrent IgA deposits. IgA deposits were also identified in lupus and Henoch–Schönlein purpura nephritis.

There was at first some reluctance to give credence to Berger's observations by acknowledging IgA nephropathy as a distinct clinicopathological entity. For a short time it was thought that the disease was confined to France, but the finding of predominant mesangial IgA in patients with mesangial or focal glomerulonephritis was soon realized to be common worldwide. Berger and his colleagues at the Necker-Enfants Malades Hospital went on to show that mesangial IgA deposits recurred frequently in transplanted kidneys,[3] noting that graft function was usually not impaired, and therefore that "the high incidence of recurrence was not a contraindication to transplantation." Studying alcoholic liver disease, they showed the high frequency of glomerular IgA deposits previously noted by others in a few cases.

Jean Berger made further epidemiological observations. He reported that in France IgA nephropathy accounted for 20–25% of cases of primary glomerulonephritis and was an important cause of terminal renal disease, accounting at that time for 15% of cases of glomerulonephritis requiring renal transplantation. He was interested by the high frequency of IgA nephropathy in many parts of the world and was especially puzzled by the high frequency of IgA mesangiopathic glomerulonephritis in the Zuni Indians.

Berger's later work was devoted to understanding the pathogenesis of the disease. He reported that inadvertently grafted kidney with IgA deposits reversed after transplantation,[4] concluding from this case as well as from recurrence of IgA deposits after transplantation that circulating rather than local kidney abnormalities were responsible for the disease. Working in collaboration with Necker hospital immunonephrologists, he characterized abnormalities in deposited IgA eluted from biopsies, an important step in the identification of a major pathogenic factor of the disease.

Different names have been used for IgA nephropathy over the past 40 years. In 1972 the term 'Berger's disease' was first proposed for IgA nephropathy by a French group, although subsequently this term was sometimes restricted to those patients who had recurrent episodes of visible hematuria.

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 that in modern scientific vernacular we might term a 'fishing expedition.' But Berger's original 1968–1969 reports were more than just a novel observation; they introduced a new level of descriptive classification into the study of glomerulonephritis, and highlighted the confusion of the time about the classification of glomerular diseases, which even now awaits full resolution. Should glomerulonephritis be classified by morphology on light microscopy, by the pattern of immune deposits defined by immunofluorescence or electron microscopy, or by clinical presentation, or by etiology? The presence of IgA deposits remains to date the only means to diagnose IgA nephropathy, now recognized to be the most common glomerulonephritis.

Jean Berger had a high opinion of his work, but was a vigorous critic of others'. He was a relentless reader of the kidney literature, endowed with an excellent memory, and had a perpetually enquiring mind. One of his last sentences published stated that "Despite this effort, the pathogenesis of IgA nephropathy remains mysterious. It is clear that there is something wrong with IgA in these patients, but the precise defect has not been uncovered, and no treatment has proved to be effective." These words define the challenges that remain ahead for nephrologists worldwide.

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