The Development of Renal Pathology

Robert H. Heptinstall, MD

In his letter to the contributors of this special edition, the guest editor suggested that we focus on the years 1950 to 1990—the lifetime of the National Kidney Foundation—and that we draw heavily on our own experiences and reflections. The first is easy but, except to the very brash, the second presents problems because it would be all too easy to turn the article into a brochure of self-aggrandizement. Yet, in spite of these reservations, the suggestions have considerable merit and with due diffidence I shall adopt them.

Renal Pathology before 1950

To begin, it is of interest to look back and see what was known about renal pathology before 1950. Although published in 1914, Volhard and Fahr’s monograph “Die Brightsche Nierenkrankheit” still provided the cornerstone for our understanding of the pathology of glomerulonephritis, “nephrosis,” and hypertensive vascular disease. Considerable information on other aspects of renal pathology was available in Fahr’s chapter in the 1925 edition of Henke and Lubarsch’s, Handbuch der Speziellen Anatomie und Histologie, and the contributions of this remarkable pathologist (Fig 1) still constantly amaze me. In the United States, Bell’s textbook, Renal Diseases, first published in 1946, provided serious students of renal pathology with a wealth of information based on the author’s personal experience, and McManus’s book based on the application of the periodic acid–Schiff staining technique had just appeared.

Most of the published pathology was of a descriptive type and based on autopsy studies. For the main part it represented advanced disease, and with few exceptions little information was available on the early stages and on the evolutionary sequences. For this reason, glomerulonephritis in particular was poorly understood and the plethora of classifications was a manifestation of this. Important descriptions were also available on a variety of topics such as diabetes mellitus, collagen vascular disease, polycystic kidney, amyloid, stone formation, developmental defects, and many others.

While most pathologists relied on gross and light microscopic observations, some, like Oliver (Fig 2), took a different approach and used nephron dissection. In this way, the entire nephron could be reconstructed, the exact site of lesions located, and the heterogeneity of changes in chronic states demonstrated. With this unique approach, Oliver did much to stimulate ideas on functional behavior in chronic renal failure, and to determine the site of the lesion in “acute tubular necrosis.” It is a little known fact that he and Wilson in 1920 provided the first convincing demonstration of the production of experimental glomerulonephritis by the injection of anti-kidney antibody.

Important experimental studies, particularly on pathogenetic mechanisms of glomerulonephritis and vasculitis were begun in the pre-1950 era. These explored the possibility of immunologic processes being involved, and included both the serum sickness model and the effects of nephrotoxic antibody. The full impact of these had to await the introduction of immunohistologic methods, about which more will be said later. Notable among experimental studies on the kidney by pathologists were those of Harry Goldblatt on the genesis of hypertension. His work stresses the importance of careful observation in man, because the experiments were prompted by his noticing that hypertensive patients commonly showed narrowing of the renal vasculature at autopsy.

Thus, by the middle of the 20th century a great number of anatomical details had been accumulated and some crucial experiments performed. But in spite of this there was incredible confusion. This was brought home to me very forcibly in 1951, when on completion of training in pathology I was asked by George Pickering to look at a number of kidneys he had collected over the years. These had been removed surgically for what was considered to be unilateral chronic pyelonephritis in the expectation that the patients’ high blood pressure was caused by a renal lesion. I found that there were bilateral chronic pyelonephritis, one side more affected than the other.
pressures would be lowered. Knowing nothing about pyelonephritis, nor for that matter of any aspect of kidney pathology, I undertook some intensive reading. Apart from a few original articles, there was little written on pyelonephritis to succor the needy. The situation with glomerulonephritis was even worse, with a confusing profusion of different classifications and problems with terminology. The notation subacute was used for two conditions with vastly different clinical pictures, distinctions were drawn between subacute and subchronic, and the membranous form was equated with lipoid nephrosis. Nephrosis was a term used in many different senses and included toxic, lipoid, lower nephron, and even genuine varieties; happily there was no bogus form. Pity the young pathologist entering this arena!

There were of course good reasons for this state of affairs. Particularly in glomerulonephritis there were no clinical-pathologic correlations available on the evolution of the disease, and the widely held belief that the more chronic forms were inevitably preceded by an acute phase exerted a stultifying effect on progress. Ideas on pathogenesis—apart from the thought that an immunologic reaction might be involved—were infantile, and crucial experimental studies, which later made such great contributions to our understanding, had not yet been performed. A knowledge of pathogenesis in establishing pathologic diagnostic criteria cannot be overemphasized and the simplest example of this lies in chronic pyelonephritis. In 1950, and for several years later, controversy raged over the way in which the kidney became infected, and it was not until vesicoureteral reflux became accepted as the mechanism by which bacteria reached the kidney that pathologic diagnostic criteria could be defined with any accuracy.

RENAI PATHOLOGY AFTER 1950

The 1950s saw at least three major developments of far-reaching consequence, and it was fortunate that all happened within a few years of each other so that the effects were complementary. The first was the introduction in 1951 of the needle
biopsy of the kidney as a safe routine procedure by Iversen and Brun. The availability of renal tissue from living patients allowed an opportunity to see the early stages of disease and to follow evolution of the lesions by sequential biopsies. The renal biopsy also provided fresh material so that the other two developments, electron microscopy and immunohistology, could be used. More will be said of these later.

The use of the renal biopsy rapidly gained acceptance and by 1961 the various physicians taking part in a Ciba symposium were able to record that over 5,000 biopsies had been performed with little untoward effect. These early years of the biopsy were exciting times and it was indeed fortunate that there was such excellent collaboration between the clinician and pathologist. The original contributions were restricted to the use of the light microscope, but even with this limited approach much progress was made. Renal disease was seen at an early stage and sequential biopsies on a variety of conditions such as poststreptococcal glomerulonephritis and lupus nephritis were performed. The nephrotic syndrome could now be broken down into its constituent entities, and although before this time such causes as diabetes mellitus and amyloid were recognized, it now became possible to identify the panoply of conditions responsible. Importantly, it became possible to separate lipoid nephrosis (minimal change disease) from membranous glomerulonephritis using silver impregnation techniques. The entity of focal and segmental glomerular sclerosis was identified somewhat later, but in retrospect it should be noted that Fahr was quite familiar with the lesion, and even today there is no good explanation for the observation previously made by Rich (Fig 3), another of the pioneer renal pathologists, that the affected glomeruli were selectively situated in the juxtaglomerular cortex.

It also became possible to study poorly understood syndromes whose pathology was largely unknown, and the recognition of focal glomerulonephritis as one of the underlying lesions of recurrent hematuria, Schönlein-Henoch syndrome, etc, provides an example of this. I well remember the hostile reception given to the presentation Joekes and I made to the Renal Association on focal forms of glomerulonephritis, purely because it conflicted with contemporary thinking.

Fig 3. Arnold R. Rich demonstrating an autopsy to Louis Hamman, perhaps a case of Hamman-Rich syndrome. (Courtesy of Alan Mason Chesney Medical Archives, Johns Hopkins University School of Medicine.)

These early years of the biopsy were fascinating times and the Renal Association, which met monthly at the Ciba Foundation in London, provided a testing forum for presentation of new data. Not only were your views verbally assailed, but your physical well-being put in danger, for on one occasion I was quite literally thrown off the podium. Admittedly, I had long exceeded my time and the chairman of the session, R.A. McCance from Cambridge, was not one to be trifled with.

Even greater progress was made following the introduction of electron microscopy. Although the first commercial production of the electron microscope took place in 1939, it took until the 1950s for significant application of this instrument. The early studies were concerned mainly with describing anatomic features in laboratory animals, but soon there were accounts of human disease using tissue obtained by needle biopsy. Early observations, to mention only a few, included effacement of the foot processes in minimal change disease, the demonstration of deposits in different sites in glomerulonephritis and systemic lupus erythematosus (SLE), and thickening of the lamina densa in diabetes. With this technique the age-old controversy over the existence of an intercapillary
space (mesangium) with its own population of cells was resolved, and its illustration in the report of Latta et al\(^2\) must be one of the most reproduced pictures in the whole of renal pathology. Vast numbers of reports followed over the years and the quality of the pictures improved following the substitution of epoxy resins for methacrylate as the embedding medium. Unique and unsuspected features were revealed, such as splitting or layering of the glomerular basement membrane in Alport's syndrome\(^3\),\(^4\) and "fingerprints" in the deposits of SLE.\(^5\) New diseases such as dense deposit disease (type 2 membranoproliferative glomerulonephritis) were discovered,\(^6\) and a less tangible but most important contribution was the way in which it improved our interpretation of light microscopy as a result of better understanding of the structure of the capillary wall and the existence of the mesangium. The scanning electron microscope has not had such an impact on pathology, although it can dramatically demonstrate in panorama what is seen only casually with the transmission electron microscope.

Immunohistologic techniques have also had a big impact both on diagnostic pathology and on the elucidation of pathogenetic mechanisms in man and in experimentally induced models. Early application of the fluorescent antibody method to human material was made by various workers in the mid and late 1950s.\(^7\),\(^8\) These studies revealed the presence of \(\gamma\)-globulin in the glomeruli of various conditions, notably membranous glomerulonephritis and SLE, and were shortly followed by the demonstration of complement fixation in glomeruli from membranous glomerulonephritis.\(^9\) These and many subsequent observations on renal biopsy material, coupled with the immense amount of experimental work prompted by the pioneer studies of Dixon and Germuth, have firmly established the concept of immunologic injury in the pathogenesis of glomerulonephritis and allied disorders. Of great importance was the identification of antineutrophilic basement membrane antibody disease and its separation from the better established immune complex disease.\(^10\) As with electron microscopy, new conditions were uncovered by immunohistology; IgA nephritis\(^11\) and \(\kappa\)-light chain disease\(^12\) are good examples, while the demonstration by this technique of a missing antigen(s) in Alport's syndrome\(^13\) has prompted tremendous efforts in identifying and locating the so-called Goodpasture antigen. The scope of immunohistology was expanded with the development of monoclonal antibodies and the introduction of the immunoperoxidase method. Since this topic is the subject of a report by Dixon and Wilson in this issue, nothing more will be said of it.

While much of the progress in renal pathology has been in glomerulonephritis, considerable advances are apparent in other areas. Tubulointerstitial nephritis, of which little was known prior to 1950, is now a focus of great activity, particularly since monoclonal antibodies against subsets of lymphocytes and various experimental models are available as investigative tools. As mentioned earlier, one of its constituents, chronic pyelonephritis, is now a well-understood condition, and while the major contribution was made by the late John Hodson, a radiologist, we can console ourselves with the thought that a radiologist is really a gross pathologist working under a handicap. Considerable progress has been made in understanding lupus nephritis, amyloidosis, thrombotic microangiopathy (hemolytic uremic syndrome), toxemia of pregnancy, developmental defects, nonimmunologic glomerular injury, transplantation rejection, the pathology of acute renal failure, and a host of other conditions. It is gratifying that attention has at long last been directed to autosomal dominant polycystic disease, a potent cause of chronic renal failure.

Progress in clinical medicine has paradoxically created many problems for the pathologist. Whereas prior to 1950 chronic renal disease culminated in the death of the patient, life can nowadays be sustained by chronic dialysis or transplantation. The emergence of the acquired form of renal cystic disease is one of the consequences of chronic dialysis, and although much is known of the biology and pathology of transplant rejection, questions still remain. Adverse reactions to the increasing armamentarium of drugs administered by physicians bring their own problems and in particular contribute significantly to the pool of acute renal failure. Overindulgence in analgesics has been responsible for veritable outbreaks of papillary necrosis, and abuse of addictive drugs such as heroin produces its own pathology. The present acquired immunodeficiency syndrome (AIDS)}
demic is not without renal manifestations, and while we have some knowledge of the pathology of so-called human immunodeficiency virus-associated nephropathy, ideas of its pathogenesis remain embryonic.

RENAI PATHOLOGY TODAY

While much has been learned and many issues resolved, we still have old business to finish and new problems to face. At least we now have practicable nomenclature and classifications of most forms of renal disease so that pathologist and clinician can communicate with each other, even though we may not completely understand the cause of the particular condition and how it developed. In a general sense we know the likely outcome of most renal diseases, although in the individual case this may be difficult. As a result of many experimental studies, a vast amount is known about renal injury, both immunologic and nonimmunologic, but the application of much of this information to human disease is still awaited. Many techniques are now available and those of the molecular biologist are beginning to be applied. We can only hope that the second 40 years of the National Kidney Foundation will see as much progress as the first.

REFERENCES


