Pyelonephritis: A Historical Reappraisal

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There is no human knowledge which cannot lose its scientific character when we forget the conditions under which it originated, the questions it answered and the function it was created to serve.1

As with most diseases of the kidney, pyelonephritis is an old ailment, which as a diagnosis, is a relatively new entity; it entered medical nosology in 1837, but it remained dormant until the 1950s when it was revived and for a brief interval, heralded as the leading cause of ESRD.

For most of its history, the kidney was considered a parenchymatous organ with glandular features accounting for its secretion of urine, in which the dense substance and tight capsule made it resistant to inflammation.2 Its principal afflications were considered calculous or obstructive diseases. That there may be some validity to the ancient notion of renal resistance to infection was documented in the 1950s in experimental models of pyelonephritis in which chronic infection could not be produced without inducing some form of renal injury, such as obstruction, massage, or trauma, to the kidney.3

A clearer description appears in the first book on renal diseases Diseases of the Kidney and Bladder by Rufus of Ephesus, which was published between late first and early second centuries AD. Rufus describes “Inflammation of the Kidneys” as “flank pain...at the beginning of the urine is thin and aqueous but as the disease progresses it becomes more reddish...it is then that suppuration of the kidneys, which in most cases is the culmination of the inflammation, becomes evident...fever is not regular but intermittent and accompanied by chills.”5 The “thin and aqueous” urine of Rufus may be taken as what would be described in the 1950s as the reduced capacity to concentrate urine maximally in pyelonephritis.3

Similar versions of renal inflammation appear in later texts, but for most of medical history, it was inflammation of specific urinary tract sites that attracted attention (urethritis, cystitis, and prostatitis), often to the exclusion of the kidney. Their treatment was assigned to surgeons specializing in the urogenital tract, a limitation that persisted well after pyelonephritis was defined in 1837 but remained glaringly absent from urologic dictionaries, classification of kidney diseases, and texts well into the first decades of the 20th century.6

PYELONEPHRITIS—AN OLD NAMELESS CLINICAL ENTITY

It is within this context that renal infection appears in the Hippocratic Corpus (circa fourth century BC) as “Another disease of the kidney...violent pain present as in preceding disease (calculous)...the pains increase greatly...when the kidney suppurates, swelling appears beside the spine.”4 What is described is likely pyonephrosis, for which the text recommends to “incise the patient at the site of the swelling, making an especially deep cut over the kidney” to drain the pus.4

PYELONEPHRITIS—A NAMED DIAGNOSTIC ENTITY

Medical interest in pyelonephritis traces back to the beginnings of nephrology with the publication of Reports of Medical Cases by Richard Bright7 (1789–1858) in 1827 linking dropsy and proteinuria to kidney disease. Bright7 considered his disease an inflammatory process or nephritis, a term denoting “inflammation of the kidneys” that dates back to 1567.7 This was an important conceptual evolution from the past when the kidney had been considered resistant to inflammation, a notion to which Bright still ascribed as he states, “Inflammation of one or both kidneys, as a purely idiopathic disease is less frequently met than with other phlegmasiae.”7 Although some of the patients studied by Bright7 are consistent with pyelonephritis, it was his French contemporary in Paris Pierre Rayer (1793–1867) who first coined the term pyelonephritis (pyélé-néphrite) in his Atlas des Maladies des Reins published in 1837 (Figure 1).8 In it, he states, “I have designated as pyelonephritis the reunion of the inflammation of the renal pelvis and calyces with inflammation of the two renal substances (cortex and medulla);...it is rare for it to begin in the kidney and then extend to the urinary tract...in these complex cases one encounters most of the changes in renal tissue previously described and illustrated under nephritis and pyelitis.”8 In his subsequent three-volume text on diseases of the kidneys, Traité des Maladies des Reins published between 1839 and 1841, Rayer addresses the issue in greater detail.9 Reflecting the preeminence of pyelitis, to which he dedicates the first 240 pages of volume 3, he devotes only four pages to that of pyelonephritis.
The pioneering studies of Louis Pasteur were fundamental to the foundation of bacteriology (Figure 2). The term “bacteriuria” was introduced in 1881. Low concentrations of bacteria were considered contaminants, and attempts at quantifying bacterial counts in catheterized urine were first made in 1941; however, it was in 1956 that Edward Kass (1917–1990) at the Mallory Institute of Pathology established the quantitative basis of bacterial counts for the diagnosis of significant urinary tract infection that could account for the development of pyelonephritis.3,15

Initially, renal infections were considered to be brought by way of the bloodstream (i.e., “hematogenous” or “descending” in origin). This was due to the then prevalent clinical models of renal infection: bacterial endocarditis and tuberculosis. Experimental and clinical studies soon revealed that “ascending” infection, as had been implied by Rayer, was the principal route of renal infection.3

That pyelonephritis may be due to invading organisms was a result of concurrent progress in bacteriology (Figure 2). The pioneering studies of Louis Pasteur (1822–1895) in Paris and Robert Koch (1843–1910) in Berlin had solved the mystery of contagious diseases and launched the study of bacteria in the 1860s.10 Actually, Pasteur was the first to report in 1862 that urine is normally sterile and an excellent culture medium for the study of microorganisms.11 Furthermore, in studies done with Joaquin Albarrán (1860–1918), then his assistant and later, Chief of Urology at Hôpital Necker, they described an organism (Bacillus pyogenes) responsible for urine infections.12 Later studies established that most cases of urinary bacteria were “gram-negative rods,” notably that of “Bacterium coli commune,” which was identified in 1885 by the German pediatrician Theodor Escherich (1857–1911). In 1959, the organism studied by Escherich was termed Escherichia coli in his honor.13 Also, Koch first isolated his Tuberkelvirus, later termed Mycobacterium tuberculosis, from the sputum and urine in 1882.14

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PYELONEPHRITIS—THE FIRST 100 YEARS

Progress would come from efforts at classifying Bright disease. Over time, the initial classification on the basis of gross appearance of the kidney (big white and little red) was refined by microscopic features (inflammatory, degenerative, or sclerotic), localized to structural components (glomerular, tubular, interstitial, or vascular), and linked to clinical correlates (nephritis, nephrosis, or nephrosclerosis). It is within the inflammatory nephritides that the lesion of interstitial nephritis was introduced in the 1880s and in the prevailing notion of toxicity at the time, attributed to that of bacterial toxins.16 In the process, the “pyelo” of pyelonephritis was forgotten, and the pathologic lesions of interstitial nephritis were taken as indicative of chronic or healed pyelonephritis (Figure 2). It is within this context that the potential detrimental effects of chronic pyelonephritis emerged in the German literature between the 1860s and 1930s, principally as a subject of pathologic interest.3 Their clinical features were exposed in 1933 by Warfield Longcope (1877–1953), then professor of medicine at Johns Hopkins Medical School, who described the course of progressive kidney failure with contracted kidneys due to pyelonephritis.17

These findings were confirmed and expanded by the subsequent 1939 milestone report of Soma Weiss (1898–1942) at Harvard and Frederic Parker (1890–1969) at the Mallory Institute of Pathology.18 In their account of 100 patients, they described the variable clinical and structural correlates of pyelonephritis as an acute, chronic active, healed, and healed but recurrent disease. Additionally, they highlighted the vascular lesions of pyelonephritis and their relation to coexistent hypertension that had not been emphasized previously. This initiated a wave of nephrectomies of unilaterally contracted kidneys for the relief of hypertension, the futility of which was exposed in 1956 to its proponents in the Journal of Urology by the renal physiologist Homer W. Smith (1895–1962), whose numerous seminal contributions to kidney function in health and disease were fundamental to the foundation of nephrology.19

PYELONEPHRITIS—NEPHROLOGY COMES OF AGE

Additional studies revealed that pyelonephritis was more common than it had been considered theretofore, with the number of cases detected at postmortem several folds greater than those patients diagnosed clinically. Additionally, unlike its acute form, chronic pyelonephritis usually was a low-grade, relatively asymptomatic infection with periods of remission and exacerbation, termed “inapparent” or “subclinical” pyelonephritis, that eventuated in chronic nephritis.3,20,21

This led to the proposal that, whereas clinically evident acute pyelonephritis is encountered in isolated and unrelated events, chronic pyelonephritis is actually a continuum that manifests itself as acute pyelonephritis (with or
without recurrent episodes) in infancy due to vesicoureteral reflux, in women due to “honeymoon cystitis” or “pyelitis of pregnancy,” and in men due to prostatitis. Between these episodic symptomatic phases, the disease could persist or smolder on as symptomless bacteriuria, eventually leading to chronic pyelonephritis: a disease that was then promulgated as the most common cause of kidney failure.3,20,21 Hence, the tantalizing possibility that CKD may be prevented by early detection and treatment of urinary tract infections prevailed in the late 1950s and early 1960s, just as nephrology was a budding specialty and kidney failure was identified as a treatable disease with RRT (Figure 2).

The virtual explosion of studies on pyelonephritis that followed in the 1960s and 1970s during the maturation of nephrology led to a re-evaluation of the facile conclusions about chronic pyelonephritis that had been derived therefrom including bacteriuria and postmortem studies.22–24 The accruing evidence derived from experimental and clinical studies revealed the following. (1) The tubular and interstitial morphologic changes that had been taken as diagnostic of chronic pyelonephritis could be due to a host of other causes that were being identified, such as analgesic nephropathy, Balkan nephritis, drug toxicity, sickle cell disease, and ischemia. (2) Technical developments, such as pyelograms, voiding cystograms, kidney biopsy, and functional tests, added considerable refinement to the clinical diagnosis of pyelonephritis that depended mainly on the presence of significant bacteriuria. (3) Long-term evaluation of individuals with bacteriuria, especially women, revealed that occasional urinary tract infections were fairly benign and in the absence of urinary tract abnormalities, did not eventuate in renal failure. (4) Data accrued from patients being initiated on dialysis revealed a paucity of cases that could be ascribed to pyelonephritis. (5) Epidemiologic studies on the basis of the refinements in the diagnosis of pyelonephritis revealed no difference in the prevalence of hypertension in those with bacteriuria compared with controls.22,24 These findings coupled with the availability of antibiotics to control bacteriuria put an end to the unjustified inflated role of chronic pyelonephritis as the principal cause of kidney failure that it had been pronounced. As a result, by the late 1970s and early 1980s, it was established that, although urinary tract infections can impair kidney function, it is a rare outcome in the absence of major predisposing factors, such as obstruction, calculus, reflux, neurogenic bladder dysfunction, or diabetes.24

Relevant to the story of pyelonephritis are the colloid casts of so-called thyroidization of the kidney that had been considered diagnostic of chronic pyelonephritis but are nonspecific, and they can occur with reflux of sterile urine as well as most other causes of chronic interstitial nephritis.3,23,24 They were shown to contain Tamm–Horsfall glycoprotein, which in 1987, was identified as uromodulin, a protein with a protective role against infection and antigenic potential in the immunopathogenesis of renal scarring in which genetic variants have been associated with increased risk of CKD.25

CONCLUSIONS

The history of pyelonephritis has been one of perceptive descriptions interspersed between periods of relative neglect (Figure 2). It began as an enigmatic inflammatory renal lesion, which centuries later, was attributed to bacterial infection and then, to organisms with pathogenicity and antibiotic sensitivity that could be assessed and treated. The brief claim that pyelonephritis may be the leading cause of kidney failure in the early 1960s was put to rest with the advent of nephrology as an investigative scientific discipline. Interest in pyelonephritis seems to be undergoing a revival, with new evidence on the role
uromodulin in CKD25 and its occurrence in transplant recipients, in whom it is a risk factor for graft loss and death.26

DISCLOSURES

None.

REFERENCES