10.5152/turkjnephrol.2023.22137392

Review

Turkish Journal of Nephrology

"Nephrology": An Inquiry of How It All Began and Evolved into a Discipline

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ABSTRACT

Although identified as the organ that produces urine by Galen in the second century, the kidney was considered a parenchymatous "structureless mass of veins" until the seventeenth century. After this, the pyramidal tubules were described by Fellini, and the glomeruli by Malpighi. The discovery of this "admirable structure of the kidney" then led to the introduction of the term "nephrology" in its Latin as "nephrologia" in 1672. It would be another 2 centuries before the capsule connecting the glomeruli to the tubules would be identified by Bowman and glomerular filtration described by Ludwig in 1842. The concurrent linking of albuminuria and dropsy with diseased kidneys by Richard Bright in 1827 provided the clinical catalyst for the expanding basic studies of the kidney that ensued. Ultrastructural studies of kidney form and function led to the introduction of the term "nephron" in 1924. As studies of the kidney in health and disease accrued, the need for specialists (*nephrologists*) in its study was formulated in the 1930s. All of these culminated in the First Congress of Nephrology organized by Jean Hamburger in France and the foundation of the International Society of Nephrology in 1960. And at the cost of being redundant, "*the rest is history*."

Keywords: Nephrology, nephron, nephrologist, chronic kidney disease, dialysis

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Received: September 7, 2022 **Accepted:** September 30, 2022

Publication Date: January 1, 2023

Cite this article as: Eknoyan G. "Nephrology": An inquiry of how it all began and evolved into a discipline. *Turk J Nephrol.* 2023;32(1):4-7.

INTRODUCTION

"Nephrology," as used in the title of the journal and as we understand it now, referring to the study and care of the kidney in health and disease, is a relatively new term. On the other hand, diseases of the kidney are ancient ailments whose study can be dated to prehistory when medical lore began to be gathered, was transmitted orally for millennia until it entered recorded history with the introduction of writing, flourished during the Greco-Roman period, went dormant, albeit nurtured, over the following centuries until the word "nephrology" entered the medical lexicon in 1752.[1] As listed in the medical dictionaries of the period, it was attributed to the Latin caption "nephrologia" that had been used in 1672 in a treatise on the "admirable structure of the kidneys" by Matthias Tiling (1634-1689), a professor of medicine at Ritlen, Germany. The treatise was reissued in 1709 under the title *Nephrologia Nova et Curiosa (A New and Curious Nephrology)* by Johann Helfrich Jüngen (1648-1726), a Frankfurt physician.[2-4] The definition of "nephrology" then evolved gradually to be more specific in its current meaning as denoting the scientific study of the kidney in health and disease in the closing decades of the nineteenth century. Still, it went relatively unused until the mid-twentieth century, when it resurfaced principally in French as "néphrologie" and then internationally as "nephrology" in the second half of the past century following the First Congress of Nephrology (*Premier Congrés de Néphrologie*) held in France, which led to the establishment of the International Society of Nephrology (ISN) in 1960, as shown in Figure 1.[5]

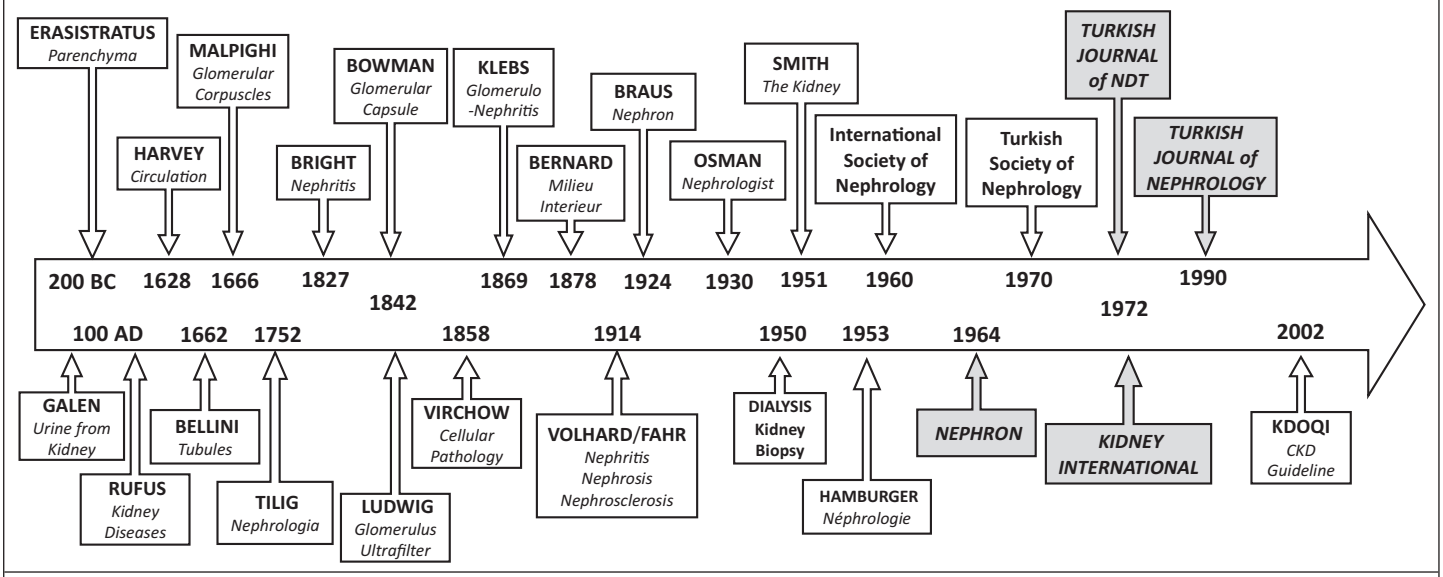

Figure 1. Timeline of the evolution of nephrology as a discipline. The name of the principal contributors is shown in bold capital letter and their contribution in smaller italic letter. Boxes highlighted in grey refer to institutions and journals. CKD, chronic kidney disease; KDOQI, Kidney Disease Outcomes Quality Initiative; NDT, nephrology, dialysis, transplantation.

In 1964, the ISN launched the first medical journal dedicated to kidney studies, *Nephron*. The term "nephron" is even of more recent vintage than that of nephrology, derived from the ancient Greek word for kidney, *nephrós*; it was introduced in German in 1924 by Hermann Braus (1868-1924) the then professor of anatomy at the University of Heidelberg.[1,5] It was popularized as the structural unit of the kidney in the microdissection studies of kidney form and function by another German anatomist Karl Peter (1870-1955) in Würzburg and subsequently by one of the founders of kidney morphology the American pathologist Jean R. Oliver (1889-1976) working at Stanford University and the Rockefeller Institute.[6,7]

The stated purpose of the journal *Nephron* in its inaugural issue was to serve as a link of "communication between *nephrologists* of all countries." The term "nephrologist" used therein is of even more recent vintage. The need for nephrology to become a specialty was voiced in the 1930s by Arthur Arnold Osman (1893-1972), appropriately a practicing physician at Guy's Hospital in London from whence Richard Bright (1789-1858) had described a century earlier his eponymous disease generally considered the beginning of clinical nephrology. Osman was the first to describe himself as a "nephrologist" in 1945 and went on to help found the first nephrology society in 1953, the Renal Association.[8] That was about the very same time that in France a founding pioneer of nephrology Jean Hamburger (1909-1992) began to popularize the term *néphrologie*, organized in 1960 the First Congress of Nephrology, and served as the first president of the ISN from 1960 to 1963.[9]

In 1972, the ISN broke its relationship with the publisher of its journal *Nephron* and launched its current official journal *Kidney International*, the same year that the Turkish Society of Nephrology founded in 1970 launched its official journal the *Turkish Journal of Nephrology Dialysis and Transplantation* that became the current *Turkish Journal of Nephrology* in 1990, as shown in the Figure 1.[9,10]

BEGINNINGS

Why was "nephrology" such a late discipline to emerge? The ancient Egyptians were aware of the kidney (*ggt, geget*) but not of its function.[11] They considered urine to be mysteriously separated in the circulation and inexplicably find its way to the bladder (*shepetyet*) from whence it was excreted. Their Asian counterparts in Mesopotamia were more descriptive of diseases of the urinary system but rather negligent of the kidney (*kalitu, kilia*).[12] It was in Greco-Roman medicine that the kidney (*nephrós*) was first defined as a structureless parenchymatous organ by the Alexandrian anatomist Erasistratus (304-250 BC) and then established as the source of urine by the experimental studies of Galen (129-216 AD).[1,13] Unfortunately, Galen erred in his physiology in considering the kidney blood flow as being a to-and-fro process from the liver, from which the inherent attractive forces of the kidney extracted excessive fluidities excreted as urine. Also, Galen perpetuated the structureless parenchymatous nature of the kidney of Erasistratus by describing it as "a structureless mass of veins." It was at about that same period that the first book on diseases of the kidney (*On Diseases of the Kidneys and Bladder*) was published at the close of the first century AD by Rufus of Ephesus (ca. 70-110 AD), as shown in Figure 1.[14] In the section on the kidneys, Rufus briefly discusses inflammation (infection), stones, hardening (sclerosis) of the kidneys, hematuria, and urinary diarrhea (diabetes).[14]

Thus, whereas diseases of the kidney had haunted humans since time immemorial, it was mainly as that of changes in urine (volume, color, and pain on urination) that they came to be perceived, observed, recorded, and perpetuated in the medical literature well into the nineteenth century, while the kidney as a site of disease was considered rare and generally treated with benign indifference.[15]

So, for 15 centuries after Galen and Rufus, the kidney continued to be considered an undifferentiated parenchymatous organ of purification with inherent attractive powers that served the nutritional needs of the body in eliminating excess fluidities. The first breakthrough came in the seventeenth century when William Harvey (1568-1657) described the systemic circulation of blood pumped by the heart in his milestone publication *Exercitatio Anatomica De Motu Cordis et Sanguinis in Animallibus* (*On the Motion of the Heart and Blood in Animals*) published in Frankfurt 1628. The second turning point came from the anatomical studies of Lorenzo Bellini (1643-1704) who in 1662 described the tubular structure of the kidney papilla and of Marcello Malpighi (1628-1694) who in 1666 described the glomeruli.[1,13] These were the landmark discoveries that prompted the text of Matthias Tiling in 1672 "on the admirable structure of the kidneys" referred to in the introduction that led to the introduction of the term "*nephrology*."[2]

However, it would be another 200 years before those early but fundamental observations bore full fruition when in 1842 William Bowman (1816-1892) in London described his eponymous capsule of Malpighi's glomeruli connecting them directly to the tubules, and in the same year, Carl Ludwig (1816-1895) in Marburg theorized the role of glomerular filtration based on physical forces.[16,17] Thus, the stage was set for the definition of kidney function as glomerular filtration and tubular secretion, crucial information that the physiologist Claude Bernard (1813-1878) in Paris used in 1858 to identify the kidney as central to maintaining the *milieu intérieur* (internal environment) necessary for animal life.[18] Thus, by the second half of the nineteenth century the kidney came to be considered a parenchymatous organ with glomerular filtering and tubular secretory properties that served a vital role in maintaining the internal body homeostasis essential for maintaining life in a hostile exterior environment, as shown in Figure 1.[19]

It is within these structural and functional elucidations of the kidney that a critical turning point in nephrology occurred in 1827 when Richard Bright (1789-1858) described his eponymous disease associating the presence of urinary albumin to kidney disease in edematous patients.[20] In keeping with prevailing notions, Bright considered his disease rare. In a textbook of medicine, he co-authored in 1839 with his Guy's Hospital colleague Thomas Addison (1793-1860), he describes nephritis or inflammation of the kidney as a rare disorder due to tuberculosis, calculous, or obstructive disease.[21]

MATURATION

What contributed to the subsequent prominence of kidney disease was Bright's introduction of the first clinical test of modern medicine, the detection of albuminuria. The simplicity of diagnosing kidney disease by the appearance of an albumin coagulate upon warming a urine sample in a teaspoon made its diagnosis readily accessible to every physician. As a result, kidney disease listed as "nephritis (all forms)" appears as number 6 among the top 10 leading causes of mortality in the United States in 1900. It would maintain a rank order of between 4 and 6 until 1932, when other causes of albuminuria such as diabetes mellitus, hypertension, and congestive heart failure came to be identified as a cause of albuminuria.[22]

It was in studies exploring Bright's disease that current disorders of the kidney now the subject matter of the journal became identified, clarified, classified, and expanded.[23] Technically it was due to advances in microscopy and tissue processing. Intellectually it was prompted by the discovery of the cell theory in 1839 and its adoption in explaining pathology by Rudolf Virchow (1821-1902) in his 1858 book *Cellular Pathology* which was regarded by many as the root of modern pathology. In his book, Virchow popularized the term nephritis while his students went on to detail the disease: Axel Key (1832-1901) who in 1865 described the cellular components of the glomerulus; Edwin Klebs (1834-1913) who in 1869 described and introduced the term glomerulonephritis; and Arnold Beer (1835-1880) who in 1859 identified interstitial kidney affections.[23] As a result, by the time World War I began, diseases of the kidney were authoritatively classified as glomerulonephritis, nephrosis, and nephrosclerosis by the clinician Franz Volhard (1872-1950) and the pathologist Theodor Fahr (1877-1945) working in Mannheim.[24] Those were the basic turning points that would fuel the need for a discipline dedicated to their study voiced by Osman in the 1930s and by Jean Hamburger in the 1950s referred to earlier.[5,8]

What stimulated the subsequent progress in the study of kidney function and disease was the introduction of kidney biopsy in 1951, which allowed for the study of the course of kidney diseases rather than that of their outcome observed at autopsy, as shown in the figure, and of technological advances such as micropuncture, membrane transport, and cell culture in the study of kidney function. Of greater clinical and public impact was the introduction of kidney replacement therapy by maintenance dialysis and transplantation beginning in the 1950s, which turned a theretofore fatal disease into a potentially treatable one by the second half of the twentieth century.[5,9,20] Hence the dramatic flourish in studies of the kidney in health and disease since their acknowledgment by a founder of nephrology, the physiologist Homer W. Smith (1895-1962) in his milestone text "*The Kidney: Structure and Function in Health and Disease*" in 1951.[25] That is in sharp contrast to the title of another milestone physiology book by Arthur R. Cushny (1866-1926) generally considered as the text which resolved kidney

function as that of filtration, reabsorption, and secretion that was titled "*The Secretion of Urine*."[26] Worse yet was that of the physiologist A. V. Wolf written at the same time and the same purpose as "*The Kidney*" by Homer Smith but titled "*The Urinary Function of the Kidney*"![27]

CONCLUSION

Thus, 1800 years after Galen identified the kidney as the source of urine, the kidney was no more the mere secretory organ that produced urine whose care had been relegated to had been surgeons specializing in the urogenital system that had led to the establishment of "*Urology*" as a certifiable specialty in 1902.[4] The kidney was now a vital homeostatic organ that was the domain of renal physiologists, morphologists, and clinicians collectively termed "nephrologists" that led to the establishment of "Nephrology" as a certifiable discipline in 1972.[5]

And it is thus that studies of the kidney burgeoned through the twentieth century. The next turning point came at the start of the twenty-first century when the Kidney Disease Outcomes Quality Initiative (KDOQI) of the National Kidney Foundation issued its guideline on "Chronic Kidney Disease: Evaluation, Classification and Stratification" in 2002.[28] This was a major milestone that provided a uniform approach for the evaluation of kidney function independent of its etiology that apart of its service to nephrologists achieved 2 monumental targets. First, it allowed for the determination of the prevalence of kidney disease as a major public health problem. Second, it served as a communication tool of nephrology for specialists (cardiologists, hepatologist, intensivists, pulmonologists, etc.) in other disciplines for their collaborative study and management thereby, broadening the scope of nephrology into its detection, prevention, and treatment well beyond the care of end-stage kidney disease it had been in the 1950s.

Peer-review: Externally peer-reviewed.

Declaration of Interests: The author declares that he has no competing interest.

Funding: The author declared that this study has received no financial support.

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