On the Etymology of Nephritis: A Historical Appraisal of its Origins

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JASN 31: 1170–1173, 2020. doi: https://doi.org/10.1681/ASN.2019050510

But these are deeds which should not pass away.

And names that must not wither.[1]

For most of medical history the kidney was considered a glandular secretory organ subservient to nutrition for the elimination of excess "fluidities." When the kidney failed or as then considered "not strong enough," the accumulated excess fluidities (hydremia, hydremic plethora) were considered to collect in serous spaces as "hydrops, hydropsy, or dropsy," ancient terms popularized in the early 1700s. The principal renal ailments then considered were obstruction (dropsy of the kidney) and calculous disease (calculous nephritis), but it was studies on dropsy that led to the identification of the actual wider range of nephritic diseases. Interest in dropsy increased following the after of its treatment with foxglove by William Withering (1741–1799) in 1785. Subsequent reports documented the association of dropsy and heat coagulable urine with contacted kidneys, gout, diabetes, and scarlet fever.[2,3] Meanwhile, studies of calculous nephritis beginning in the 1760s led to the detection of urinary solutes (urea, uric acid, etc.) excreted by the kidney in addition to water.[4] In his well known book *Observations on the Nature and Cure of Dropsies*, published in 1813, John Blackall (1771–1860) of Exeter documented the association of dropsy with albuminous urine and attributed to the kidney a "selective power of separating from the blood whatever was hurtful to the body" as an explanation for the excretion of albuminous dropsical fluid and elevated blood urea levels of some cases, but failed to link dropsy to kidney disease.[5]

NEPHRITIS: A DISEASE WHOSE TIME HAD COME

It is in this state of the art and due acknowledgment of Blackall that Richard Bright (1789–1858) developed an interest in the kidney in dropsy in 1815, which would lead to his 1827 *Reports of Medical Cases*, wherein he described a causal relation of dropsy and heat coagulable urine with kidney disease, a momentous conclusion whose time had come.[6] Bright's transformative deduction is a classic example of the discovery process that Isaac Newton (1643–1727) had described in 1679 as, "If I have seen further, it is by standing on ye sholders of giants."

Subsequent recognition of the kidney as a site of disease was a product of the intellectual and technological changes of the times that followed. The 19th century was a transformative period in the evolution of medicine from its conjectural past into the scientific discipline it would become by the end of the century. The change begun with studies in morbid anatomy within which the systematic naming, description, and classification of diseases were done; a movement that started in the opening decades of the century in Paris before moving to England, and then on to Germany by midcentury, where it was enriched by studies in physiology, chemistry, and microscopy.[4,7]

The manner Bright reported his observations also reflects his changing times. It is in the 19th century that the publication of books and pamphlets began to be replaced by medical journals; there were barely ten medical journals in England at the beginning of the century, and about 479 new ones had been started by its end.[7] Bright's original 1827 report was published as a book; his subsequent major publication of two articles was in the inaugural volume of *Guy's Hospital Reports* in 1836. The second of his articles, titled "Tabular View of the Morbid Appearances Occurring in One Hundred Cases in Connection with Albuminous Urine," reflects the emerging approach to medical research using the new "numerical method" launched by the Paris physician Pierre Louis (1787–1872) in the 1820s, an early venture into quantification in medicine from which medical statistics would emerge by the close of the century.[8,9]

NEPHRITIS: AN INFLAMMATORY DISEASE

That was also the time that worldwide interest in "statistical nosology" was on the rise, a concept spearheaded in

Published online ahead of print. Publication date available at www.jasn.org.

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Table 1. Classification of kidney diseases in 1856

English	Latin	French	German
NEPHRITIS	Nephritis	*Néphrite*	*Nierenentzündung*
ISCHURIA	Ischuria	*Ischurie*	*Harnverhaltung*
Diuresis	Diuresis	*Diurèse*	*Unvermogen den Harn zu halten*
NEPHRIA (Bright's disease, albuminuria)	Nephria	*Néphrine*	*Brightsche Krankheit*
DIABETES	Diabetes	*Diabète*	*Harnruhr*
STONE (uric acid and c.)	Calculus	*Calcul*	*Stenkrankheit*
GRAVEL	Calculus	*Gravelle*	*Harngries*
Hematuria	Haematuria	*Hématurie*	*Blutharnen*
CYSTITIS	Cystitis	*Cystite*	*Blasenentzündung*
Disease of prostate gland	Morbus prostaticus	*Prostatite*	*Vorsteherdrüsen-krankheit*
CONTRACTURA URETHRAE	Contractura urethrae	*Uréthrosténie*	*Verengerung der Harnröhre*

Table of the nephritides from the 1856 "Report of the Nomenclature and Statistical Classification of Diseases for Statistical Returns" by William Farr (1807–1883). c, calculus.[10]

England by Willian Farr (1807–1883), widely considered a founder of medical statistics. In 1853, the First International Statistical Congress asked Farr to prepare a uniform nomenclature of the causes of death, a task he completed and published in 1857,[10] a forerunner of what would become the International Classification of Diseases. Two of the 30 notables Farr asked to review his list were Richard Bright and Robert Christison (1797–1892), the Edinburgh medicine professor and one of the first to confirm Bright's observations on kidney disease. Farr's list of renal diseases reflects the prevailing notion of Bright's disease as an inflammatory lesion of the kidney that is different from other nephritides (Table 1).[10] In Volume 2 of his landmark *Traité des Maladies des Reins*, published in 1840, the noted Paris physician Pierre Rayer (1793–1876) argued for naming the disease albuminous nephritis rather than *Morbus Brightii*, but Bright's disease prevailed and would remain in use into the 1950s.[11]

Bright had considered the lesions he observed to be "a decidedly inflammatory state of the kidney" and reported them as "nephritis," an ancient term meaning "pertaining to the kidney" that was reintroduced in the 1560s to denote "inflammation of the kidnies" observed in horses.[12,13] He classified the diseased kidney on the basis of gross appearance, color, and texture into three forms—a large, pale, yellowish-white kidney; a congested, red granular kidney; and a contracted, granular, hardened kidney—a classification that would prevail through the 1950s, albeit with a changing nosology (Table 2).[9]

Further progress in understanding Bright's disease was as much the result of scientific interest as that of ongoing technological developments, notably the microscope and the sphygmomanometer in the 19th century, and the electron microscope, immunofluorescence, and kidney biopsy in the 20th century.

Early microscopic observations had called attention to glomerular changes in Bright's disease. Bright himself had alluded to them in an 1842 letter as "one of the most interesting features of the morbid anatomy of this disease is to be found in the condition of the *corpora Malpighiana*," in connection to an ongoing study he had sponsored of the microscopic renal changes by his assistant Joseph Toynbee (1815–1866) published in 1846.[2,9] Malpighian bodies is also the term used by William Bowman (1816–1892) in the 1842 milestone report of his eponymous capsule. Reference to the glomerulus as the Malpighian corpuscle, tuft, or body continued until 1848, when Jones Quain (1796–1865), professor of anatomy at University College London, first referred to them as "These small red bodies, or

Table 2. The evolving nosology of nephritis

1827 Bright	1856 Virchow	1878 Charcot	1895 Allbutt	1914 Volhard and Fahr	1931 Addis and Oliver	1942 Ellis	1951 Smith
Large white kidney	Parenchymatous nephritis	Parenchymatous nephritis chronic > acute	Parenchymatous nephritis	Nephroses degenerative	Degenerative Bright's disease	Type 2 nephritis insidious, edema, recover/chronic	Nephrotic syndrome
Congested granular red kidney	Interstitial nephritis	Interstitial nephritis acute > chronic	Glomerular nephritis	Nephritis inflammatory hemorrhagic	Hemorrhagic Bright's disease	Type 1 nephritis acute, high BP hematuria, recover/chronic	Glomerulonephritis acute, chronic, subacute
Contracted kidney	Contracted kidney	Contracted kidney	Contracted kidney	Contracted kidney	Contracted kidney	Contracted kidney	Contracted kidney
? Vascular	Amyloid kidney	Amyloid kidney	Hyperpiesia hypertension	Sclerosis	Arteriosclerosis	Nephrosclerosis	Nephrosclerosis

The first row gives the last name of the author and the year of their contribution.

glomeruli, discovered by Malpighi" (Figure 1).[4,14]

NEPHRITIS: A MULTIDIMENSIONAL DISEASE

Although improved microscopy and tissue processing were instrumental in the progress that followed, it was the intellectual stimulus of the cell theory, espoused and promulgated by Rudolph Virchow (1821–1902) in his 1858 *Cellular Pathology*, that defined the progress that followed. Virchow classified kidney diseases into those of the renal parenchyma or tubules as "parenchymatous nephritis," those of the interstitium as "interstitial nephritis" that progressed to the atrophic end-stage kidney, and those of the vasculature or "amyloid kidney" (Figure 1, Table 2).[4] Importantly, it was students of Virchow who would characterize the details of the glomerulus, notably Edwin Klebs (1834–1913), who introduced the term "glomerulonephritis" in 1869 (Figure 1). The lesion Klebs described has been attributed to inflammatory exudation and leukocyte infiltration. However, Klebs' report is more consistent with what would be described in 1968 as IgA nephropathy or some other form of mesangial proliferative lesion. Klebs makes it clear that glomerulonephritis is a proliferation of the "connective tissue that binds the capillaries of the Malpighian tufts into complete balls," in essence, the mesangial cells that had been described recently by his Swedish colleague and Virchow trainee Axel Key (1832–1901) in 1865. Klebs classified his glomerulonephritis as different from Bright's nephritis and described it as, "One can designate glomerulo-nephritis as a form of interstitial nephritis in which the interstitial tissue of the glomerulus is involved exclusively".[4,15] Introduction of the term "glomerulitis" in 1885 as "inflammation of the glomeruli of Malpighi and their capsule" failed to replace Klebs' glomerulonephritis, which went on to gradually assume a broader meaning as any glomerular disease that ultimately was listed in the International Classification of Diseases as GN, alongside Klebs disease.

Preliminary reports of glomerular lesions notwithstanding, it was the tubular changes of parenchymatous nephritis that continued to attract attention, particularly those of tubular desquamation, epithelial cell proliferation, and fatty degeneration considered "lipoid" in nature. To distinguish them from the inflammatory lesions of nephritis, these were termed "nephrosis" by the Munich internist Friedrich Müller (1858–1941) in 1905, and the tubular lesions dubbed "lipoid nephrosis" in 1913 by the Berlin pathologist Fritz Munk (1879–1950), who also described the urinary anisotropic lipoid droplets of these cases. To represent their clinical and laboratory features rather than just their pathology, the New York internist Louis Leiter (1898–1986) introduced the term "nephrotic syndrome" in 1930 (Figure 1).[16,17]

For the noninflammatory lesions of interstitial nephritis, Lewellys Barker (1867–1943), successor to William Osler at Johns Hopkins, popularized the term "nephropathy," after the French term "*néphropathie*" that had been introduced in 1895 by the Paris internist Émile Achard (1860–1944) (Figure 1). This led to the use of "membranous nephropathy" for noninflammatory glomerular lesions, such as thickening of the glomerular basement membrane, in 1946 by the Minnesota pathologist Elexious T. Bell (1880–1963).[18] Identification of "acute interstitial nephritis" as a distinct entity in 1898 by the Harvard pathologist William Councilman (1854–1933) led to the recognition of interstitial nephritis as an entity different from GN and its gradual disappearance from the nosology of Bright's disease (Table 2).[4]

Introduction of the sphygmomanometer was fundamental in distinguishing the renal lesions of hypertension from those of Bright's disease. In his 1836 article, Bright had referred to the "hardness of the pulse" in patients with ventricular hypertrophy. Their associated microscopic lesions were described in 1872 as "arterio-capillary fibrosis" by the Guy's Hospital clinician William Gull (1816–1890) and London Hospital pathologist Henry Sutton

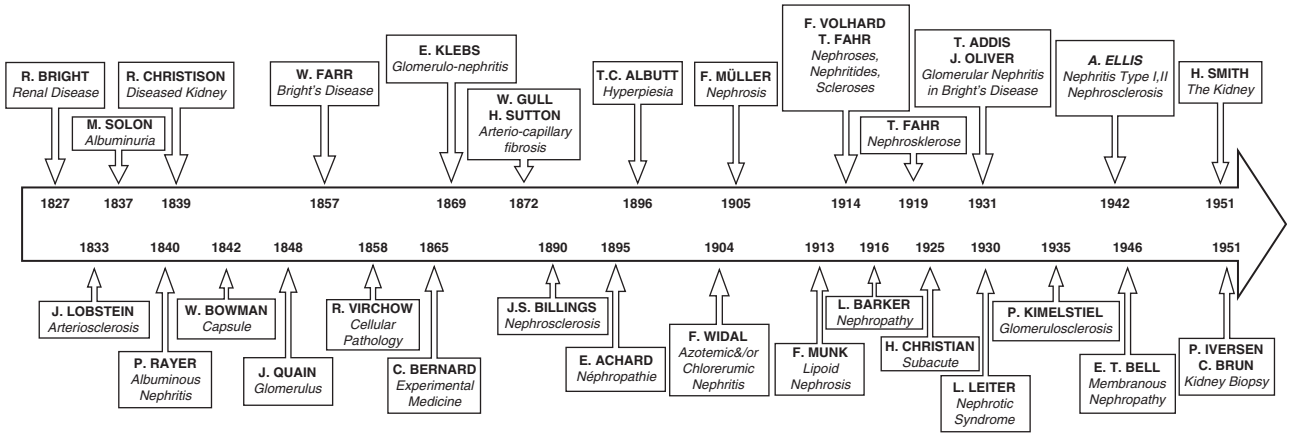

Figure 1. Timeline of the evolving terminology of nephritis. The name of authors are shown in capital, bold letters, and their contribution to nosology in italics.

(1837–1891). That the vascular lesions of high BP are independent of nephritis was elucidated by the Cambridge Professor of Physic T. Clifford Allbutt (1836–1925) in 1895. He termed the condition "hyperpiesia," today's essential hypertension.[19,20] This was a new entity classified as separate from Bright's disease, and was labeled "arteriosclerosis," a term introduced in 1833 by the Frenchman Jean Lobstein (1777–1835) for the thickened wall of arteries, implying their hardening (Figure 1). Ensuing reports of malignant hypertension further clarified the renal vascular lesions of hypertension, which in 1919 was termed "*nephrosklerose*," from the English "nephrosclerosis" that had been introduced in 1890 by John S. Billing (1838–1913), a London surgeon and a founder of the Index Medicus, for the nonspecific induration of the kidney (Figure 1). Over time, nephrosclerosis replaced the increasingly rare occurrence of amyloidosis as the principal vascular lesion of kidney disease (Table 2). The suffix for hardening (sclerosis) was applied to the glomerular capillaries as "glomerulosclerosis" by the Harvard pathologist Paul Kimmelstiel (1900–1970) in 1935.

Parallel functional studies elucidated the clinical features of nephritis. Notable among them are those by the German Herman Strauss (1866–1944) and particularly of the Frenchman Fernand Widal (1859–1929). Between 1903 and 1906, Widal demonstrated that changes in blood urea are induced by protein intake, that edema is caused by salt (measured as chloride) retention, and that prognosis depends on blood urea level. He classified kidney diseases as either associated with edema (*chlorérumique*) or azotemia (*azotémique*) or a combination of both (Figure 1).[21]

CONCLUSION

Continued attempts at classification of Bright's disease culminated in that of the German clinician Franz Volhard (1878–1950) and pathologist Theodor Fahr (1877–1945) in 1914 (Figure 1, Table 2).[22] Discontent with prevailing terminologies, in 1931 Stanford clinician Thomas Addis (1881–1949) and the New York University pathologist Jean Oliver (1889–1976) resurrected the label Bright's disease as a preferred inclusive term that covered the varied lesions being described.[23] Displeasure over the use of nephrosis, the terminology was further altered to type 1 and 2 nephritis by the Canadian-born University of London professor of medicine Arthur Ellis (1883–1966) in 1942 (Table 2).[24] What lay ahead with the advent of investigative nephrology is foretold in the 1951 milestone book of Homer Smith (1895–1962) *The Kidney in Health and Disease*.[25] Bright's disease is not mentioned in its 898 pages of text, nor is Richard Bright listed in its 2300 references.

DISCLOSURES

None.

FUNDING

None.

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