On the contributions of Fernand Widal to the classification of chronic kidney disease

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ABSTRACT
Fernand Widal (1862-1929) was a French scientist who worked at a defining period in the scientification of medicine when the basic sciences were being applied to clinical medicine. In the medical fashion of the time his early studies were centered on infectious diseases. He is best known for the diagnostic test that bears his name, the Widal agglutination test for the diagnosis of typhoid fever reported in 1896. Much like other investigators of the period he worked in several areas (shock, asthma, immunization, hemoglobinuria), ultimately focusing on the kidney during 1903-1906. He demonstrated that changes in blood non-protein nitrogen (NPN) level are induced by modification of protein intake, that edema is due to salt retention (from measurements of chloride), and that the prognosis of kidney disease is based on NPN levels. He staged the course of CKD on the gradual retention of NPN, which at 0.5-1 gm/L had a guarded prognosis (*azotémie d'alarme*); at 1-2 gm/L heralded death in 2 years (*azotémie grave*); at >2 gm/L had a fatal outcome worse than cancer; and at 5 gm/L death was imminent (*azotémie fatale*). He classified kidney disease as either associated with edema (*chlorérumique*), with elevated NPN (*azotémique*) or both. He recommended reduced intake of salt in edematous subjects and of protein in azotemics. One of his assistants in these studies was a grandson of Louis Pasteur, Pasteur Vallery-Radot (1886-1970), who maintained his interest in kidney disease and as professor of medicine in charge of Broussais hospital trained Jean Hamburger (1909-1992) and Gabriel Richet (1916-2014), the future founders of French nephrology and the International Society of Nephrology.

KEYWORDS: Fernand Widal, edema, salt, CKD classification, nephritis

Introduction

It was in the closing decades of the 19th century that medicine began its metamorphosis from the empirical profession it had been theretofore to the scientific discipline it would become by the end of the 20th century (1, 2). The ground rules driving that changeover were laid in 1865 by Claude Bernard (1813-1878) in his iconic "*Introduction to the Study of Experimental Medicine*" as: testable hypotheses that lend themselves to experimental verification (3). It was also then that the etiology of diseases due to specific causes began to be explored driven by the studies of Louis Pasteur (1822-1895), subsequently formulated as the 'germ theory' of disease by Jakob Henle (1809-1885) and Robert Koch (1843-1910) (4). The story of this transformational change has been told mainly in terms of the contributions of selected individuals shaded by overtones of hero worship and portrayed along nationalistic lines. In actuality, the progress made was more of an integrated, interrelated, and interdependent evolution of science in general, and medicine in particular, that was as much a product of its changing times (industrial, political, cultural, social) as it was that of the work of countless committed but forgotten investigators that made it happen (1, 5). However, as much as the final product was the work of many, research then was in fact mostly an individual was as much a product of its changing times (industrial, political, cultural, social) as it was that of the work of countless committed but forgotten investigators that made it happen (1, 5). However, as much as the final product was the work of many, research then was in fact mostly an individual endeavor in which most labored, some excelled, others were lucky in the laboratory, and a few gifted ones who could synthesize and present their contributions better than others. It is the work of the latter whose ideas have survived and names dominate the narrative of how it all happened, while that of many others is mentioned only in passing, and that of most is totally forgotten. This article pays tribute to the seminal contributions of a clinical scientist of that period to the development of nephrology who is mentioned only in passing but deserves better recognition.

The changes in medicine during this transformative period were driven mostly by attempts to change the practice of medicine into a clinical science by incorporating the tools and methods of the basic sciences into the clinic. As a result, what had been theretofore a descriptive discipline of observations at the bedside and at postmortem now became enhanced by clinical studies magnified by new tools (thermometer, stethoscope, microscope, ophthalmoscope, etc), enriched by laboratory data obtained on body fluids and tissue biopsies, and verified by experimental studies (1, 5). The movement is generally considered to have started in post-revolution France, nurtured in Germany after its unification, and enriched by contributions from England. Indeed it was in Paris hospitals that the movement germinated when, concurrent with the building of the future City of Lights by Baron Haussman (1809-1891), Paris hospitals were enlarged, renovated and modernized (6, 7). In the process they acquired conference rooms, lecture theaters and laboratories to accommodate the curricular changes taking place in the teaching of medicine that had centered on classroom recitations into one of seminars, bedside teaching rounds, demonstrated lectures and increasingly a laboratory based hospital experience (6-8). Medical students after their lectures at the faculty of medicine now rushed from hospital to hospital to attend the rounds and lectures of star performers such as Jean-Marie Charcot (1825-1893) at the Salpêtrière, as well as to that of the other flourishing hospitals around town each with its own star performer and famous professor (6-9).

The principal progress made was in three medical domains. First, the quest to explain the 'vital' properties of organs that

led to the study of their function at the bedside where disease was considered an experiment in nature that provided insight into normal function (10). Second, the study of bacteriology that blossomed because of its potential to overcome the major fatal diseases of the time (typhoid, cholera, malaria, tuberculosis) (11). Third, the emerging methods for the chemical analysis of body fluids in the laboratory. As a result, by the end of the 19th century microbiology and physiology were the two principal basic sciences being applied to the study of humans. Where the former opened the door for the conquest of the big killers, the latter established the new science of pathophysiology, both enriched by the new analytical methods of chemistry (12-14). This was a major shift from the descriptive morphological approach to medicine that had dominated medical progress theretofore into a totally new investigative phase termed laboratory and experimental medicine (1); a move qualified in 1919 as "the birth of new medicine" by Clifford Allbutt (1832-1925) then Regius Professor of Physic at Cambridge, himself a product of Paris hospital medicine. The major impact of these changes notwithstanding the dichotomy of the basic sciences and clinical medicine persisted well after the First World War. It was only after World War II that the 'new medicine' of Allbutt would sustain its exponential growth in the second half of the 20th century (15).

The kidney

It was during this period that the functions of the kidney began to be examined, diseases of the kidney studied, and the vital role of the kidney in maintaining Bernard's "*milieu interieur*" explored (1). By then, Richard Bright (1789-1858) had already described his eponymous end-stage disease of the kidneys characterized by albuminuria and dropsy; William Bowman (1813-1892) had shown the continuity of the tubules with the glomerular capillary space surrounded by the capsule named after him; and Carl Ludwig (1813-1892) had argued convincingly for a role of glomerular capillary ultrafiltration (1, 15). Still and well into the late 1920s, the kidney continued to be considered a secretory organ subservient to the nutritional functions of the gastrointestinal tract while debate on the role of glomerular filtration and tubular function continued to rage. How the kidneys handled urea and salts was considered to be related to the 'permeability' of the kidney to these and other excretory substances, with disease causing a reduction in the 'efficiency' of the kidney in its excretory function leading to the monikers of "*insuffisance rénale*" in French, "'*Niereninsuffizienz*" in German and "*renal insufficiency*" in English, terms still in use by some (1, 15, 17).

During the early stages of this transformative period studies of the kidney were undertaken by an increasing number of physiologists, pathologists, internists and surgeons with widely varied medical interests in addition to that of the kidney, none of whom would have considered themself a nephrologist. Ironically, it was then that nephrology was founded. In fact, it was then that the term nephrology first appears in medical terminology in the 1842 Medical Dictionary compiled by Robley Dunglison (1798-1869), the personal physician of Thomas Jefferson, considered a "Father of American Physiology". It was also then that microscopic examination of the kidneys in Bright's disease led to its consideration as an inflammatory lesion termed 'nephritis' and classified principally as either a large white kidney termed "parenchymatous nephritis" or a smaller contracted kidney termed "interstitial nephritis" (1, 9). The term "nephrosis", introduced in 1905 would not be clarified and fully espoused until the 1930s (18).

The metabolic studies on patients at the various stages of 'nephritis' initiated by Robert Christisson (1797-1882) and Samuel Wilks (1824-1912) in England, were now expanded by those of a number of investigators such as Charles Achard (1860-1944) and Léon Ambard (1876-1962) in France, Sándor Korányi (1860-1944) in Hungary, Franz Wolhard (1872-1950) and Theodur Fahr (1877-1945) in Germany, and Leonard Rountree (1883-1959) and John Geraghty (1877-1945) in the U.S., to name just a few (16, 17). Notable amongst them are the studies of Fernand Widal (1862-1929) in France and Hermann Strauss (1864-1944) in Germany who almost simultaneously but independently were instrumental in establishing the separate associations of blood urea nitrogen levels to the manifestations of the uremic syndrome and that of sodium chloride retention to the production of edema (16, 19, 20). This article presents the more seminal and broader contributions of Fernand Widal.

Fernand Widal

George Fernand Isidore Widal (Figure 1) was born on March 9, 1862 in Dellys, Algeria (50 miles east of Algiers) where his father was serving as medical inspector of the French army stationed there. He studied medicine at the *Faculté de Médecine* in Paris. A hard working, intelligent and driven student of medicine Widal rose rapidly to prominence. In 1884 he was accepted as an *Interne des Hôpitaux* at the Hotel-Dieu under Victor Cornil (1837-1908), where he completed his medical thesis and earned his doctorate in 1889. In 1892 he was appointed *Médecin des Hôpitaux de Paris*, in 1894 *Professeur Agrégé*, in 1911 Professor of Internal Pathology, which he inherited from his past professor Paul George Dieulafoy (1839-1911), and in 1913 Professor of Clinical Medicine (16-21).

Figure 1 - Fernand Widal (1862-1929).

His initial studies centered in infectious diseases (21, 27, 28). As an intern he was exposed to two students of Louis Pasteur, Emile Roux (1856-1938) and André Chantemesse (1851-1949) who served as the advisor of his medical thesis on puerperal fever. He is best known for the diagnostic test of typhoid fever developed in 1896 that bears his name, a simple agglutination test requiring a culture of the bacillus and a drop of the patient's serum that rapidly distinguishes typhoid fever from other infectious diseases. His fame was earned from his bedside teachings and studies at the *Hôpital Cochin* where he was appointed and served for the final 25 years of his life, becoming ultimately its Chief of Service. As a teacher, he is said to have been a firm advocate of the idea that science should be applied to the practice of medicine. His lectures were said to have been lucid but brief and delivered without notes (21-28).

As a member and subsequently vice-president of the *Société de Biologie*, most of his communications were made at its

meetings and published in its journal, *Comptes Rendus et Mémoires de la Société de Biologie* in which Claude Bernard had published his '*Introduction to Experimental Medicine*' in 1865 (24) (28). The society had been founded in 1848 by Claude Bernard and his colleagues, with its first president Pierre Rayer (1793-1867), upon whose death Claude Bernard served as president through 1878 (9).

Much like the clinical investigators of the time, Widal was a man of many interests who explored several areas of medicine. Having started in the study of infectious diseases, he next focused on the cytodiagnosis of pleural fluids that he classified as due to tuberculosis, sepsis, or mechanical due to cardiac or Bright's disease, presented to the *Société de Biologie* in 1900. It is about then that he embarked on his initial studies of the kidney, focusing on them from 1903 to 1906. For the rest of his life he returned to the study of various infections, worked on anaphylactic shock and paroxysmal hemoglobinuria, studied cerebrospinal fluid composition, and helped develop a typhoid vaccine. For his numerous contributions to medicine, Widal was the recipient of many honors including the *Grand Croix de la Légion d'honneur* in 1917 and admission to the *Académie des sciences* in 1919 (21, 22, 24, 28).

Widal suffered from gout and died from a cerebral hemorrhage on January 14, 1929 at the age of 67. He was buried in Montmartre Cemetery, where his eulogy was delivered by André Lemierre (1875-1956), one of his interns at Cochin hospital and co-author of most of Widal's studies on the kidney.

Contributions to nephrology

The most important work of Widal is said to have been on nephritis (29). A claim best supported by his being one of the two medalists at the first centenary of Bright in 1927 celebrated at Guy's Hospital in London (30). For his contributions to the kidney he is best known for his studies on edema and its treatment with salt restriction (Figure 2).

Figure 2 - A contemporary cartoon of the changes in a patient before and after the salt restricted diet of Professor Fernand Widal, shown in the middle as 'the apostle of dechloruration' proudly declaring 'I gave desalinated him'. In the background is the amount of salt removed from the patient.

Rarely mentioned and generally unknown are his contributions to the differentiation of various forms of nephritis, studies on blood urea nitrogen changes at different levels of dietary protein intake, the classification of chronic nephritis from the level of blood urea nitrogen, and most importantly his role in training the next generation of French clinical scientists some of whom would go on to establish the discipline of nephrology in the 1960s. To highlight some of his renal contributions:

- *Edema, its cause and treatment*. Widal's interest in edema was prompted 1902 from observation of changes in weight in two of his patients at the Cochin hospital (16). This prompted his subsequent metabolic studies of patients with nephritis in collaboration with Adolphe Javal (1873-1944), a chemist, and later with his intern André Lemierre. In June 1903 at two separate sessions (31, 32), one chaired in part by William Osler (1873-1919) (32), he reported to the *Société Médicales des Hôpitaux de Paris* his studies on four patients with 'interstitial nephritis' and three with 'parenchymatous nephritis' during periods of varied salt intake. One patient, a 72 year old woman with parenchymatous nephritis, was studied over the course of 3 months during 9 different periods of salt intake, ranging from 1.5 to 20.5 gm/day (32). This is the one case of his many other reports that he presented in a chart and an accompanying table providing data that has been reproduced in most papers on Widal as well as in his own subsequent publications (Figure 3). As shown in the figure there was a direct relationship between edema as reflected in the weight of the patient and her salt intake. Of note, the differential between measured urinary salt excretion and that of its intake showing the changes in balance that reached a steady state by the end of each dietary variation studied.

The role of salt in edema was being reported by other investigators, notably Hermann Strauss in Berlin but also other French investigators (Charles Achard, Léon Ambard) whom he acknowledges in his writings (19, 20). That the principal role of salt retention would go on underestimated is due in part to its attribution to the accompanying water retention because of "local tissue changes that induce them to suck up water" (33), and even in his own use of the terms "*hydration*" and "*maladies hydropigènes*" (34, 35). To his credit his article was translated and published in English in 1904 in the inaugural issue of International Clinics, of which Osler was a contributing editor (34); his treatment was popularized and characterized as 'desalination' in the press (Figure 2); and highlighted as such by Marcel Proust (1871-1922) in his classic "*Remembrance of Things Past*" (36).

- *Relation of albuminuria to salt intake*. Notable in this report are the changes in albuminuria that paralleled the changes in salt intake, from 12 gm/day at high dietary intake of salt (20.5 gm/day) and their reduction to 0.72 gm/day after salt restriction (1.5 gm/day) (32). In his later textbook on the treatment of edema in Bright's disease he highlights this observation noting that its occurrence is variable and not observed in all albuminuric cases (35). This was another important observation that would go forgotten until the advent of the renin-angiotensin inhibitors and not deservedly credited to him in the literature.
- *Different manifestations of nephritis*. In the same report presented in 1903 were included four patients with interstitial nephritis who despite reduced kidney function as reflected in their elevated levels of blood urea nitrogen levels were able to maintain salt balance without weight changes or water retention.
- *Mechanism of urea retention*. Prompted by the differential handling of salt by different patients and the absence of salt retention in all uremic patients, the following year he reported on the changes in blood urea levels during

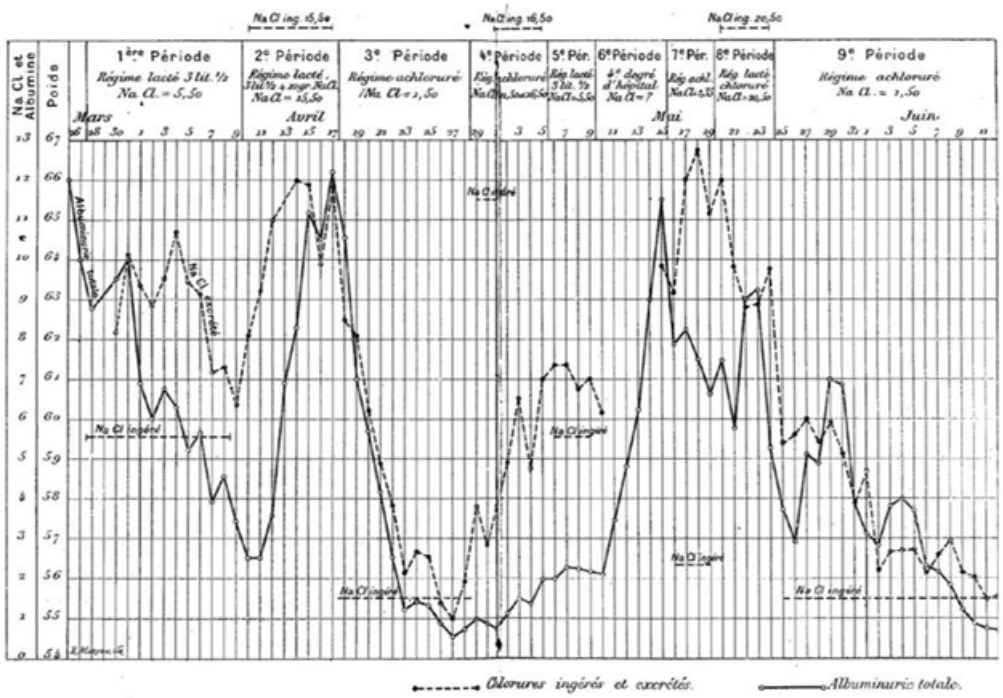

Figure 3 - The chart of a 72 years old woman with 'parenchymatous' nephritis showing the changes in weight (light solid line), sodium chloride excretion (hyphenated line) and albuminuria (heavy solid line) at different levels of salt intake (Reproduced from reference #32).

variations in protein intake (37). As shown in Figure 4, the changes in blood urea paralleled the changes in protein intake and occurred without any water retention as deducted from the stable weight of the subjects. In an accompanying article he reports on the reduced urinary urea excretion compared to its intake that follows increased protein intake returning to balance once the blood urea level stabilizes, with the reverse occurring when dietary protein intake is reduced. This (protein intake – proteinoid excretion) he terms '*indice de retention uréique*' or index of urea retention (38).

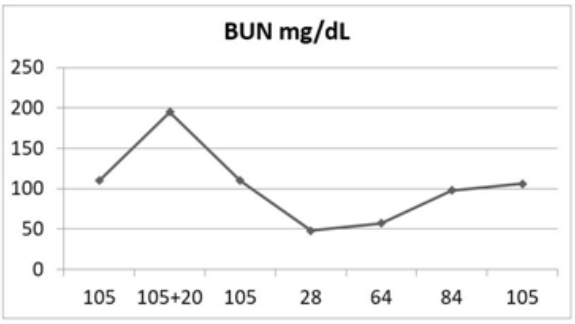

Figure 4 - Changes in blood urea level of a patient with nephritis at various levels of dietary protein intake. The numbers at the bottom represent the protein intake in gm/day; the +20 reflects the baseline protein intake of 105 gm/day plus 20 gm of urea drunk in solution (Chart constructed from data provided in reference #37).

- *Classification of nephritis*. On the basis of the observed differences in the renal handling of urea and salt Widal proposed the clinical classification of nephritis as: 1) associated with edema (*chlorurémique*); 2) associated with elevated blood urea (*azotémique*); and 3) mixed where edema and azotemia are both present. Further, he comments on the course of the disease in individual patients from one form to the other and their more common co-existence in the advanced stages of the disease (39).
- *Prognostic classification of chronic nephritis*. Having observed that the living organism could not tolerate a concentration of urea greater than 500 mg/dL of blood for any length of time; and that there was a direct correlation of the blood urea level, uremic symptoms and the outcome of nephritis Widal classified the stages of nephritis depending on the chronic level of their blood urea nitrogen. Essentially, a persistent blood urea level from 50-100 mg/dL signaled concern in which the prognosis should be guarded (*azotémie d'alarme*) and the patient monitored regularly for the possible progression of the disease; from 100 to 200 mg/dL heralded that death would follow within two years (*azotémie grave*); while at levels of 200 to 300 gm/dL a fatal outcome would ensue within less than a year; and at 400 to 500 mg/dL or higher death was imminent (*azotémie fatale*). Moreover, he documented that the index of Ambard (calculated from the levels of blood and urine urea) while useful in the detection of reduction of renal function (*insuffisance rénale*) in those with borderline elevations of blood urea (>50 mg/dL), it was the actual level of blood urea nitrogen rather than the Ambard index that determined the course of the disease thereafter (39, 40).

The lasting impact of Widal on nephrology

Widal's studies on kidney disease represent early translational research at its best. In bringing the laboratory to the bedside, Widal freed kidney disease from the post-mortem anatomical criteria of Virchow and his followers to that of a clinically assessed functional evaluation that allowed for their prognostication. This was a prescient approach to the classification of kidney disease based on renal function that would not be achieved until 2002. Until then it continued to be known by the broader non-specific terms of 'renal insufficiency' or 'renal failure' that regrettably continue to be used by some.

Regrettably, Widal's work has been criticized as "extreme keenness in many directions; but can hardly be credited with

any ordered researches", a harsh, cruel and unjust posthumous evaluation that was immediately rebutted by others (29, 41). One shortcoming of Widal is his failure to include tables and graphs in his articles, which are all narratives of his meticulously documented balance studies that make it hard to follow to the casual reader.

Widal's greater contribution may be the inspiration of his many trainees at the Cochin Hospital who were to go on to prominence by shaping the future of French medicine. Notable amongst those is Pasteur Vallery-Radot (1886-1970), grandson of Louis Pasteur, much of whose research continued to focus on diseases of the kidney and who went on to become the chief of service of *Hôpital Broussais*. It was one of his interns, Gabriel Richet (1916-2014), and his assistant, Jean Hamburger (1909-1992), at the Broussais who in turn would go on to establish nephrology at *Hôpital Necker* and launch the International Society of Nephrology in 1961 (42, 43).

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