

Remembrance of things past

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It is a distinct honor for me to author this editorial for the closing issue of the 25th anniversary of the *Portuguese Journal of Nephrology and Hypertension*. When my dear friend Fernando Carrera, the Editor-in-Chief of the *Journal*, invited me to submit the editorial he suggested that I write on “life after nephrology”, with the intent of addressing what senior nephrologists do after retirement. I wrote back expressing concern on taking on such a task as, albeit a senior, I remain active in teaching nephrology while diligently pursuing the advice of Aristotle (382-322 BC), adopted by a founding figure of Nephrology, Homer Smith (1895-1962), in justifying the writing of his “*Man and His Gods*”¹, that “He who sees everything grow from the beginning will have the best view of them”. Essentially, I have been devoting more time and effort to exploring and writing on the history of nephrology. It is in this line of my current renal activities then that I selected the subject of this essay, which contrary to its proposed intent is actually directed to junior nephrologists lest they forget how it all began.

The topic I have selected to address has been on my mind for some time: “Given the vital functions of the kidney as we have come to know them, why was nephrology such a late medical discipline to emerge?” As for the reference to remembrance in the title, 2011 in addition to being the silver anniversary of the *Journal* also is the 50th anniversary of the formal registration of our discipline as the “*Société Internationale de Nephrologie*” in the

“*Préfecture de Police*” of Paris², as well as that of my graduation from medical school. As such, to paraphrase the title of Dean Acheson’s (1893-1971) Pulitzer Prize winning memoir³, I was “present at the creation” though unaware of it then, and trained in the field as it was beginning to define and identify itself. Therefore, in addition to a historical examination of why nephrology was a late discipline to emerge, this is in part a personal reminiscence whose title is based on that of the famous memoirist Marcel Proust’s “*Remembrance of Things Past*”⁴.

Reference to Marcel Proust (1871-1922) to recall and explore the emergence of nephrology as a discipline is most appropriate for several reasons. He was the son and brother of two eminent Parisian physicians. His father, the Academician Adrien Proust (1834-1903), was a well published pathologist and epidemiologist, while his brother, Robert Proust (1873-1935), was a famous urologist and member of the *Faculté de Médecine* of Paris^{5,6}. Proust himself was fascinated by medicine, which permeates his voluminous reminiscence of things past⁵⁻⁹. He was especially attached to his mother who had renal calculi, suffered from “nephritis”, and died of uremia in September 1905¹⁰. Proust recreates her agony in the third volume of his semi-autobiographical series in the illness and death of the protagonist’s grandmother, Bergotte, who suffered from nephrolithiasis for which several doctors are consulted to relieve her pains and sudden fever attacks. As part of her management she is prescribed water treatments, as was Proust’s mother at Evian-les-Bains, the very location where the founding Congress of Nephrology convened in 1960². In her

final illness, when Bergotte sustains a stroke the pronouncement of the consultant is recounted by Proust as: “There is no hope for your grandmother. The stroke was brought on by uremia. Uremia in itself is not inevitably fatal, but this seems a hopeless case to me. I don’t need to tell you that I hope I am mistaken.”¹¹ To a great extent that sums up the state of understanding of kidney disease and its outcome well into the first part of the past century. This was all to change with the emergence of nephrology as a discipline and the introduction of dialysis and transplantation in the second half of the century. But this is getting ahead in a story that should start at the beginning.

■ BEGINNINGS

The progressive intellectual liberation which began in the Renaissance, begat the Scientific Revolution, matured in the Enlightenment and launched the modern era of medicine, also defined the nature of kidney disease and its management¹². Throughout it all, the kidney was regarded as an accessory to the “oeconomy” of nutrition and relegated to excreting the excess water ingested with food. It was not considered to be the subject of many diseases, although rarely susceptible to inflammation, occasionally to ulceration, and usually to obstruction due to calculi. “Nephritis”, a term introduced in the 16th century to describe non-purulent inflammation of the kidneys, was classified as being idiopathic or symptomatic. The rare idiopathic form was usually clinically silent and discovered at autopsy; the more common symptomatic form was associated with hematuria, renal or ureteral colic, fever and gastrointestinal symptoms. By far the most common cause of the symptomatic form was obstruction due to calculi, which became a major subject of study, investigation, and treatment^{13,14}. It is not unexpected then that urology emerged, evolved, and assumed the care of kidney diseases long before the very term “nephrology” entered medical parlance in the 19th century². In fact, the first clinical textbooks on diseases of the kidney that began to be published in the sixteenth century were urological texts. Two such classics mentioned in historical reviews are “*Tratado Nuevamente Impresso de Todas las Enfermedades de los Riñones, vejiga y Carnosidades de la Verga y Urina*” by Francisco

Diaz (1527-1590) published in 1588, and “*Tractatus de Affectibus Renum et Vesicae*” by Jean de Vanda (1563-1617) published in 1617¹⁵.

The lineage of nephrology is generally traced to Richard Bright (1789-1858), who described his eponymous disease of albuminuric dropsical cases of end-stage kidney failure in 1827. Shortly thereafter, Pierre Rayer (1793-1867) published his three-volume monumental “*Traité des Maladies des Reins*” in 1840¹⁶⁻¹⁸. Two years later, William Bowman (1816-1892) reported what is likely one of the more important contributions to the elucidation of kidney function, the connection of the glomerulus to the tubule¹⁹. Essentially, by the middle of the 19th century kidney disease was defined, the details of its functional and structural changes recorded, but the specialty went unborn, and patients continued to seek urological care for the management of their hematuria, proteinuria and uremia. A condition that prevailed throughout most of the past century and continues to be encountered in certain regions of the world to this day. In fact, the initial studies to determine the amount of kidney necessary to maintain life were undertaken by urologists in an experimental model of progressive surgical reduction in renal mass to produce uremia in dogs²⁰. This was the very model then used in the 1950s to study and explain the pathophysiology of chronic Bright’s disease²¹. It is not unexpected then, that in the U.S., urology became one of the first certifiable medical specialties in 1935, but it would be 1972 before nephrology would achieve the status of a certifiable specialty.

■ EVOLUTION

During the century and one half that followed the aborted efforts of the mid-19th century to launch the formal study of kidney disease as a specialty, there was progress in the characterization of the morbid and clinical features of Bright’s disease, but its therapy remained almost static and its outcome fatal, the fate that befell Marcel Proust’s mother in 1905. Although by the time Proust died in 1922, the controversy over glomerular filtration followed by tubular reabsorption and secretion that had preoccupied physiologists was nearing resolution after 1917 when Arthur R. Cushny (1866-1926), a pharmacologist interested in diuresis,

published his monograph "*The secretion of the urine*"^{17,22}. Concerning Cushny and relevant to the emergence of nephrology is that he had been recruited to the University of Michigan by John J. Abel (1857-1938) and succeeded him as the chair of pharmacology there when Abel left for Johns Hopkins, where in 1913 he developed the first artificial kidney²³.

However, the road to elucidating kidney function was slow and tedious. The intricacies of tubular function acquired over the millennia of evolution proved to be more challenging and complicated than envisioned by Cushny²⁴. It is only after the Second World War (WW II) that the study of kidney function and disease finally emerged and flourished after the first meeting of the International Congress of Nephrology in Evian, France in 1960^{2,18}. In the interim, studies of kidney function in health and disease were made by an increasing number of physiologists, pathologists, and internists who actually worked and contributed to several other fields of medicine; none of whom considered himself a nephrologist. This had certainly been true of Richard Bright, whose important contributions to kidney disease was but one of his many other contributions to gastroenterology, neurology and hematology, and of Pierre Rayer who is better known for his contributions to dermatology¹⁷. It is perhaps best illustrated in the career of Bowman, whose elegant and substantive observations on the nephron were not enough to keep him interested in continuing his renal studies, which he abandoned to pursue the practice of ophthalmology¹⁹.

It was the conceptual and technical advances during the years around WW II that were to change the theretofore fragmented course of renal studies. Amongst those were the clearance and micropuncture studies of Homer Smith, Alfred N. Richards (1876-1966), James T. Shannon (1904-1994), Carl Gottschalk (1922-1997), and Karl Ulrich (1925-2010) to name just a few of the pioneers in the early studies of kidney function^{25,26}. Another was the introduction of kidney biopsy, for the structural and immunologic investigation of the kidney in health and disease²⁷. The consequent incremental increase in information led to attempts at integrating the accruing knowledge and hence to the first International Congress of Nephrology in 1960 convened at the initiative of Jean Hamburger (1909-1992)². It is in this intellectually fertile ground that renal replacement therapy made

its entry and catalyzed the subsequent exponential growth of nephrology in the 1970s¹⁸.

Those early days of the budding discipline were before there were journals dedicated to nephrology, which were actually resisted by several lead academicians who felt that maintaining an interest in all of scientific medicine rather than focus on the kidney or any other internal medicine sub-specialty was important. Thus it was that the new information on the kidney was initially transmitted in general medical journals. One example that reflects this trend in the dissemination of new renal information is the *American Journal of Medicine*, which in 1958 and 1964 published two issues dedicated to renal topics^{28,29}. The 1958 issue was titled "Symposium on Renal Physiology" and the 1964 issue "Symposium on the Kidney". The subtle changes in the respective titles, deletion of 'physiology' and use of 'kidney' instead of 'renal', are pertinent to the growing pains and coming changes in these formative years of nephrology. Especially relevant is the 1964 issue, which included an article on the management of chronic renal failure by John P. Merrill (1917-1984), emphasizing its conservative management but concluding with the potential role of dialysis and transplantation in the care of "selected" cases of end-stage kidney failure. A point that the editor of the issue, Robert Berliner (1915-2002), deemed necessary of further emphasis in his Foreword, "In these days when popular media, as well as the medical literature, is full of enthusiastic reports on organ transplantation and artificial mechanisms for the maintenance of patients with renal insufficiency, it is reassuring to find Dr. Merrill giving so much space and attention to the conservative management of renal insufficiency... While there is cautious optimism about the future of such procedures, I would interpret Dr. Merrill's view as indicating that in the current state of knowledge a little function from the patient's own kidneys is, on the average, a better basis for survival than most of the transplants so far."

Especially and ironically relevant to the sequence of events going on at the time is that Belding Scribner (1921-2003) is a co-author of an article titled "Non-ionic diffusion and the excretion of weak acids and bases" in the 1958 issue on renal physiology³⁰. By sharp contrast he is not a contributor to the 1964 issue on kidney disease and referenced only once by Merrill, despite the fact that his shunt had been introduced in 1960, he had established the first

out-patient dialysis facility (Seattle Artificial Kidney Center) in 1962, and by 1964 was sustaining the life of 47 patients on maintenance dialysis^{18,31}. For these accomplishments Scribner was the recipient of the 2002 Albert Lasker Clinical Medical Research Award together with Willem Kolff (1911-2009) who had devised and introduced the artificial kidney. As far as I am aware, none of the contributors of the 1964 symposium were considered for the Lasker award and for sure none of them received it.

Apart from the early social, scientific and financial limitations plaguing renal replacement therapy in the 1960s³², the confusion in terminology of chronic kidney disease that affected the subsequent course of nephrology was already evident. Where Merrill uses “chronic renal failure”, Berliner uses “renal insufficiency”. And, for a scientist famous for his precision and exactitude, Berliner uses an adjective, ‘a little’ kidney function without mention of what actually ‘little’ implies. These side remarks notwithstanding, Merrill and Berliner were some of the giants who shaped the nephrology that was to come, and for their many contributions have been dubbed as “the father of nephrology as a specialty” and “the dean of renal physiology”, respectively.

It was in this rather conservative intellectual environment that nephrology emerged and flourished in the last quarter of the past century. Further, the diversity of approaches (physiology, pathology, biochemistry) used to study kidney disease tended to obscure focus on the disease that Richard Bright had identified. On-going investigations progressed somewhat independently, and at times at cross purposes or even in opposition to one another. This was aggravated by the increasing availability of maintenance dialysis that fueled the growth of nephrology but at the same time created an empiric approach to kidney disease after it had reached the end stage described by Bright in his post-mortem studies^{18,33}. The establishment of the International Society of Nephrology followed by that of regional nephrology societies gradually pulled these efforts together and integrated them by the end of the past century³⁴. But it was a return to the roots of nephrology in the beginning of the 21st century that was to re-focus attention on chronic kidney disease not as a fatal condition requiring replacement therapy but as a public health problem of a condition that is common, harmful, easy to diagnose and treatable³⁵.

RETURN TO THE ROOTS

Regrettably, the diversity of scientific approaches that followed the emergence of nephrology tended to obscure the basic contribution of Richard Bright linking albuminuria with kidney disease, with or without dropsy. The detection of albumin in the urine which had been equated with a diagnosis of “nephritis” in the early decades of the 20th century was lost by mid-century. Pertinent in this regard is a review of the listing of “nephritis” in the epidemiologic data collected on the leading causes of death in the United States³⁶. As shown in Figure 1, whereas in the 1900 ranking of the leading causes of death in the U.S. nephritis was the 6th; in 1940 it had gone up to 4th; but by 1960 it had disappeared from the list of the top ten. Thus at the very time that interest in the study of the kidney and its diseases was on the rise, that of its importance as a public health issue was fading. This was gradually remedied by the 1980s and thereafter, especially when the Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines on Chronic Kidney Disease: evaluation, classification and stratification were published in 2002³⁷. The paradigm shift introduced by these guidelines is a milestone in the evolution of nephrology that reverted to its roots as the chronic kidney disease (CKD) that Richard Bright had defined but now refined and polished by lessons learned over the previous four decades³⁸. As a result, kidney disease is now back in the top ten leading causes of death in the U.S. (Fig. 1). Its future fate remains to be revealed.

Rank Order of “Nephritis” in Leading Causes of Death in the U.S.

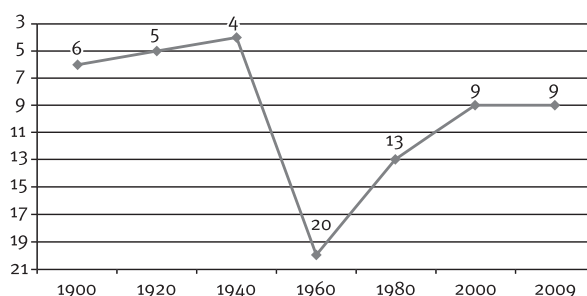


Figure 1

Rank order of death from chronic kidney disease in the United States from 1900 to 2009, classified as “nephritis” by the Center for Disease Control. The numbers indicate the rank order of nephritis as a cause of death. Data from reference 34.

That said, another notable development in the evolution of nephrology has been the exponential information overload being generated. The pattern began in the 1960s has continued and been magnified by the specialty journals that have appeared since then. As shown in Table 1, over the years since their inauguration, the number of pages in the leading journals in the field has doubled for some (JASN), quadrupled (Kidney Int) and quintupled (NDT) for others. A trend to refrain from this relentless expansion seems to be emerging in the comparison of the pages for each of them between the issue of January 2010 and June 2011 (Table 1). But then, each of those journals has spawned new publications (*Nature Review Nephrology*, *Advances in Chronic Kidney Disease*, *NDT plus*, and *Clinical JASN*), each spurring and spreading additional information. The only journal to have maintained a steady balance in the midst of this extravaganza has been the *Portuguese Journal of Nephrology and Hypertension* (Table 1). Although it too has undergone drastic changes in content and in transition into English since 2007. The foresight of its founders of the coming changes in nephrology is evident on the cover of its inaugural issue (Fig. 2). It shows the heart contained within the kidney. Recall that this was prior to the full appreciation of the high cardiovascular mortality of CKD patients, and well before the term “cardiorenal syndrome” had entered medical parlance.

With expansion of the discipline and the escalation of publications in nephrology came rigorous scrutiny

Table 1

Journals dedicated to nephrology showing the trend of their increased pagination since their respective inauguration.

Information Overload in Nephrology

YEAR	JOURNAL	Inaugural Issue # of Pages	January 2010 # of Pages	June 2011 # of Pages
1964	Nephron	72	219 (Dec. 2002 issue)†	---†
1972	Kidney Int	65	246	233
1981	AJKD	51	182	161
1986	NDT	63	336	309
1987	PJNH	60	60	62
1990	JASN	123	229	193

AJKD, American Journal of Kidney Diseases; Kidney Int, Kidney International; NDT, Nephrology Dialysis Transplantation; PJNH, Portuguese Journal of Nephrology and Hypertension; JASN, Journal of the American Society of Nephrology. † As of January 2003 Nephron has been divided into three separately edited sections, Clinical Practice, Experimental Nephrology and Physiology.



Figure 2

Cover of the inaugural issue of the *Portuguese Journal of Nephrology of Nephrology* then published in Portuguese and titled *Revista Portuguesa de Nefrologia e Hipertensão*.

of the increasing number of technical, therapeutic and interventional studies. A need for guidelines became evident as refinements in quantification and statistical analysis paralleled the expanding literature in medicine in general and in nephrology in particular³⁹. It began with the need to provide measurable precision for the expanding number of technical and interventional procedures being introduced, and consequent systematic analysis and meta-analysis that had set the stage for evidence-based medicine. The need to transfer this new analytical information into clinical practice prompted the emergence of guidelines in nephrology in the 1990s. Originally directed at dialysis, they have expanded into all aspects of nephrology practice and went global in 2003 with the founding of the Kidney Disease: Improving Global Outcomes (KDIGO) initiative⁴⁰.

CONCLUSION

Once considered an organ rarely afflicted by disease and an accessory one for the mere riddance of excess water, it is now evident that kidney disease is common and harmful and that the intricate offices of its functional unit, the nephron, are essential in a host of vital functions necessary to maintain homeostasis. As a result, the care of kidney disease which had been relegated to urologists now requires specialization in a discipline that is barely half a century old. During that relatively short span of time, much has changed in our knowledge, practice and care of kidney disease. The principal beneficiaries of it all have been patients with CKD for whom earlier diagnosis and care are now available, especially for those with end-stage kidney failure whose once fatal disease is now a treatable one. The contributions and ground breaking advances in kidney transplantation to this progress were not detailed in this essay in order to maintain its focus on nephrology.

Having started this editorial with a paraphrase from Dean Acheson, it is proper to end it with one in the conclusion of his memoirs, "the whole structure and order of the world that we had inherited is gone"³, as is that of nephrology since it emerged in the 1960s. Marcel Proust would have agreed and recorded that most of the changes have been for the better. And especially for his dear mother who could have been treated with lithotripsy, kept alive on dialysis or even transplanted with a kidney donated by him.

Conflict of Interest statement. The author declares that he has no conflicts of any financial interests whatsoever.

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