The title of this personal reminiscence of the changes in nephrology over the past 50 years is borrowed from As It Was…But Not Now: A Memoir by Joseph Merrill (born 1923), a past vice-president of Baylor College of Medicine, of his 60-year journey through medicine. That is just about the lifespan of nephrology.

For although diseases of the kidney are ancient, the discipline dedicated to their study, nephrology, is barely more than 50 years old. As recounted in this recollection of those events, the rudiments of what would become nephrology emerged in the time between the 2 World Wars from basic studies of normal kidney function and flourished after the integration of their methodologies into clinical medicine thereafter. Although shaped by studies of kidney function in the 1960s, it was the subsequent advent of dialysis that fueled the growth of nephrology well into the 21st century. Although to some extent this growth was a product of technical developments (micropuncture, dialysis, biopsy, etc), it was the paradigm shifts they engendered that brought about the revolutionary changes that stimulated the growth of nephrology from its formative years in the 1960s. Notable among those was the classification of chronic kidney disease on the basis of kidney function, calculated from serum creatinine level as estimated glomerular filtration rate, that has expanded nephrology’s interaction with and integration into other disciplines and begat the recent outpouring of epidemiologic and interventional studies, thereby establishing it as a leading discipline dedicated to improving outcomes for individuals with kidney disease worldwide.

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To a great extent, what catalyzed this change was the targeted research effort of World War II (WWII), which was goal directed and encouraged multidisciplinary investigation by applying the tools and methodologies of the basic sciences to resolving the clinical problems encountered in the battlefields. In the decades preceding WWII, studies of the kidney had been done by a growing number of physiologists, pathologists, and internists, often working independently, who may have been “nephrophiles,” but none considered themselves nephrologists, and several of whom were recruited to contribute to the war effort. One especially relevant example of this course of events is Alfred N. Richards (1876-1966), who between 1924 and 1941 developed a micropuncture technique of the renal glomerulus and made one of the most significant contributions to the understanding of kidney function.
function by isolating and demonstrating the protein-free glomerular filtrate and its electrolyte composition,7 work that he abandoned during the war to chair the Committee on Medical Research, one of the divisions of the Office of Scientific Research and Development chaired by the electrical engineer Vannevar Bush (1896-1974). What carried the interface between basic research and clinical medicine into the postwar era was the visionary leadership of the likes of Vannevar Bush and Alfred Richards, who convinced the federal government that targeted scientific research was a national asset deserving of financial support. This was a fundamental change that in the postwar period fostered academic departments dedicated to clinical investigation, where laboratories as well as physiology and chemistry methods were adopted and incorporated into the study of clinical disorders, a merging that would transform the conjunctural art of medicine into an evidence-based rigorous science.4

Serendipitously but propitiously for nephrology, the war effort’s targeted research on shock, hemorrhage, crush injury, blood transfusion, and fluid replacement and elimination were directly relevant to the elucidation of kidney function, whereas that of the independent development of dialysis machines in the early 1940s by Willem Kolff (1911-2009) in Holland, Nils Alwall (1904-1986) in Sweden, and Gordon Murray (1894-1976) in Canada would prove central to the treatment of kidney failure.2,9 Essentially, the seeds of nephrology were planted during WWII and then nurtured in the favorable environment of the immediate postwar “golden years” of research funding. As summed in 1951 by Homer W. Smith (1895-1962) in his landmark book The Kidney: Structure and Function in Health and Disease, this was when the kidney had a revolutionary metamorphosis from a “mere servant” of nutrition to a “master chemist” fundamental to the very process of life.10

FORMATIVE YEARS

It is in this environment and in one of the beneficiaries of these developments, the Department of Medicine, established in 1951 by Donald W. Seldin (born 1920) at the University of Texas Southwestern Medical School in Dallas, TX, that I began my training in kidney and electrolyte metabolism (viz not nephrology) in 1964. By then, clearance studies refined by Homer Smith were well established,10 micropuncture techniques introduced by Alfred Richards were being revived and refined,11,12 and samples analyzed by the chemical methods were compiled, developed, and perfected by John P. Peters (1887-1955) and Donald Van Slyke (1883-1981) in the several revisions of their benchmark 2-volume Quantitative Clinical Chemistry, first published in 1931.13

It was to learn micropuncture and electrolyte transport that I elected training in Dallas. How Floyd Rector (born 1929), then in charge of the laboratory, could foretell the limitations of my patience and dexterity to master micropuncture and assigned me to clearance studies remains a mystery, but is another measure of Floyd’s ingenuity. The clearance studies I was assigned to perform were directed at the elucidation of segmental tubular function in support of the results obtained from micropuncture studies, using the clearance of free water during volume expansion, diuretic administration, and urinary tract obstruction. That being 1964, the determination of electrolytes depended on a flame photometer, and of osmolalities, on a freezing point depression osmometer, laborious procedures that added several hours of tedious work at the end of the day’s experiment before one could leave the laboratory.1,4,15

Although clearance and micropuncture studies are now a relic of the past, 2 transforming technical developments that continue to affect the progress of nephrology occurred during my training. The first was the autoanalyzer, an early model of which was acquired by the laboratory. It was a major time saver that would periodically dysfunction, necessitating our reluctant fall back on the old standby flame photometer. At the practical level, autoanalyzers created a new need for nephrologists to interpret and manage the now easily detectable electrolyte abnormalities being reported by clinical laboratories.15 The second technical development was the availability of a noisy and clumsy punch card calculator that reduced the time spent on tedious calculations to less than an hour. Unfortunately, it provided only partial relief, limited by the number of punch cards allotted to each trainee, the huge demand for time on the machine necessitating scheduling for access to it, and ultimately the return of the machine to the manufacturer after the 2-month trial period. The role of subsequent generations of machines in facilitating calculations and that of the new programmable computer-based statistical analyses was beyond my imagination then. The impact of calculators on research in nephrology is self-evident in the extensive statistical validation of data that appear in the literature nowadays, even when little or none may be needed, and particularly in the “fast and furious” proliferating number of published epidemiologic and interventional studies based on analysis of information compiled by an increasing number of data banks.
In essence though, in the prevailing fashion of the time, my training in nephrology was in laboratory-based bench research. What clinical nephrology I learned was by attending early morning clinical rounds with Norman W. Carter (1925-1994), whenever time for the day’s scheduled experiment allowed before heading to the laboratory. As a trainee, I had limited exposure to dialysis. The hospital had a Baxter Travenol Twin Coil dialysis machine for use in cases of acute renal failure or poisoning. Notwithstanding that by then, Belding Scribner (1921-2003) had introduced his shunt and launched a maintenance dialysis program in Seattle, the general use of dialysis for chronic kidney failure was frowned upon by the renal establishment. Dialysis remained severely limited and was mainly restricted to cases of acute renal failure.\(^{10,11}\) I had the opportunity to observe the original Scribner Teflon shunt being bent and installed in 2 cases, but remained rather naive to the whole process of maintenance dialysis. Nevertheless, by the time I completed my training in 1966, nephrology was an established discipline and medical schools and training programs were actively recruiting clinical scientists in the field.

**BEGINNINGS**

My first job was at the University of Cincinnati Medical School in Cincinnati, OH, with the mission to start a dialysis program. My meager salary support was from the school’s Clinical Research Center, one of the then-popular National Institutes of Health (NIH)-supported centers for clinical studies. In preparation for my dialysis responsibilities, I visited Seattle. By then, their committee to select who received maintenance dialysis (later dubbed the “Life and Death Committee”) was history, but choices of who was dialyzed were still being made, albeit based on “medical criteria” and of a “first come, first served” basis imposed by limited funding for dialysis and available dialysis machines.\(^{8,9}\) Collecting soda bottle caps to purchase dialysis machines was a popular and noble public endeavor, but the funds for their regular use remained either very limited or unavailable. My first endeavor was to acquire a Baxter Travenol twin-coil dialysis machine and train a nurse in using it. Before this was accomplished, a case of acute renal failure was admitted to the Cincinnati General Hospital. The only available dialysis machine was an old Brigham-Kolff drum artificial kidney brought to Cincinnati by one of the early fellows of John P. Merrill (1917-1984), E. Gordon Margolin (born 1924), then chief of medicine at the adjoining Jewish Hospital in Cincinnati. As I recall, it took Gordon and a nurse most of the day to set up the machine and dialyze the patient into the night. I was a mere awed spectator of the whole process, charged with monitoring the patient’s blood pressure, and never handled the equipment.

Discharging my responsibilities to the Clinical Research Center entailed my first venture into clinical research to explore the bleeding tendency of uremia. In addition to measuring platelet function in uremic participants, the study entailed the ingestion of a high-protein diet while drinking urea in cranberry juice over a 12- to 24-hour period by 5 medical students and myself, after which our platelet function was measured. There were no institutional review boards then, and the study’s brief protocol was approved by the director of the Clinical Research Center. The results were presented at the American Society of Nephrology in 1968 and published, after minimal revision, in the March 29, 1969, issue of the *New England Journal of Medicine*.\(^{16}\) The straightforward design of the study, small number of participants studied, facility of its institutional approval, and its rapid acceptance for publication all reflect on the relative ease, simplicity, and rewards of renal research at the time, a feat that would be difficult, if not impossible, to duplicate today, when clinical studies have become so much more difficult, complicated, and demanding.

After 2 years in Cincinnati, I moved to what was then the Baylor University College of Medicine in Houston. My career then progressed in distinct but intertwined directions. One was basic research; the other, clinical investigation; and the third, dialysis. Although I continued bench research into the 1980s and clinical investigation well into the 21st century, my focus gradually shifted to that of kidney disease and its treatment with dialysis, which over time assumed an increasing part of my efforts and is the focus of the rest of this article. This is not to belittle the major contributions made to nephrology by renal pathology, kidney transplantation, immunology, genetics, and laboratory studies of the molecular biology of renal cells, transporters, and organelles. It is just that my involvement in most of them was rather limited, and in some, none at all. Moreover, my comments are limited to a great extent to areas in which I was directly involved and observed first hand. Also, this rather myopic view of changes in nephrology in the United States has been at the cost of excluding the equally important contributions being made from the United Kingdom, France, and other countries.

What brought dialysis to a personal level was the December 1988 earthquake in Armenia. As one of the few Armenian-speaking
nephrologists, I traveled to Armenia in January 1989 as part of the US relief effort. This was a first that brought nephrology back to its roots in WWII when acute renal failure due to crush injuries was recognized in the London bombings of 1941. It placed nephrology on worldwide front-page news for weeks after the earthquake. Following this, the International Society of Nephrology established a Renal Disaster Relief Task Force for planning response to future natural disasters, an endeavor that would get organized, be expanded, and go on to deliver renal relief in future disasters, and an early example of the broadening realm of nephrology.

**GROWTH**

Whereas nephrology was shaped by laboratory studies of kidney function in the 1960s, a period of conservative intellectual outlook on dialysis, it was the advent of maintenance dialysis that fueled its growth after the 1970s. In 1968, when I moved to Houston, maintenance dialysis remained restricted and its funding was still the big challenge. My first venture then was the organization of a Kidney Program for the Regional Medical Program of Texas. Regional Medical Programs were an extension of President Lyndon B. Johnson’s Great Society, meant to bring high-quality medical care to Americans. They became operational in 1966, but were short lived and ceased to be funded by 1974. The plans for a Texas Kidney Health Care Program were then directed principally to support medication costs for kidney transplant recipients. Funds to the Texas Kidney Health Care Program were then directed principally to support medication costs for kidney transplant recipients.

Essentially, by the early 1970s, dialysis had evolved from its rudimentary beginnings in the early 1950s as an experimental therapy to a short-term life-saving procedure in the 1960s, to become a long-term life-sustaining modality of treatment available to almost every citizen. That was when hospital-based dialysis centers moved into for-profit outpatient facilities and proliferated. The rush to save the lives of otherwise dying patients coupled with the financial rewards of the new outpatient dialysis centers outpaced the science of dialysis, resulting in the delivery of a treatment that was primarily empirical. It is not unexpected then that the complications of dialysis and the significant morbidity and mortality of dialyzed patients soon emerged as a serious public concern. The problem was magnified as the number of free-standing for-profit facilities increased and criteria for admission to dialysis liberalized. Some of those early complications were soon addressed and to some extent controlled (aluminum toxicity, hepatitis, water purity, and anemia), others linger on (mineral and bone disease, cardiovascular disease, and amyloidosis), whereas the major issue from the outset still awaiting resolution remains the adequacy of maintenance dialysis therapy.

The problem of dialysis adequacy was addressed by various agencies and institutions, all expressing the need for more scientific information. This led to the first randomized controlled trial in hemodialysis sponsored by the NIH, the National Cooperative Dialysis Study (NCDS), to evaluate the dose of dialysis on clinical outcomes. Published in 1981, this short (6 months), selective (young individuals), and limited (160 patients) study established a beneficial effect of a higher dialysis dose on morbidity. Importantly, secondary analysis of its data introduced 2 surrogate measures of dialysis adequacy still in use, the urea removal ratio and 

Kt/V (K, dialyzer urea clearance; t, time on dialysis; and V, body volume of urea). What followed were a series of observational reports on the effects of random and variable increases in dialysis dose on patient outcomes. Although the reported results varied, the common theme that emerged was that higher dialysis doses and use of more biocompatible membranes appeared to improve outcomes.

Also, the increasing costs of dialysis led to the exploration of conservative management strategies to delay the need for dialysis. The NIH then sponsored the Modification of Diet in Renal Disease (MDRD) Study to evaluate the effect of dietary protein restriction and strict blood pressure control on kidney disease progression. The arguable results of the trial notwithstanding, a major outcome of the study was the derivation of a formula to estimate glomerular filtration rate (GFR) from serum creatinine level. Validated and improved, this new predictive formula proved to be a clinically reliable index of kidney function in health and disease that would significantly affect the course of things to come.

Because of a changing patient population (older, diabetic, and hypertensive) and the introduction of biocompatible membranes of higher porosity, the NIH undertook its second hemodialysis randomized controlled trial in 1994, the Hemodialysis (HEMO) Study, to evaluate the effects of dose and membrane flux on clinical outcomes. HEMO Study results showed that hemodialysis patients treated thrice weekly did not
appear to benefit from the use of high-flux membranes or a dialysis dose greater than that recommended by published guidelines (urea removal ratio \( \geq 65\% \) or single-pool Kt/V \( \geq 1.2 \)).

The guidelines referred to were the response of the renal community to the disparities in the outcome of dialysis treatments. The National Kidney Foundation (NKF) had assembled a consensus conference in March 1994 on controversies in the quality of dialysis care. The principal recommendation made by the conferees was the need to develop clinical practice guidelines based on the best available evidence to assist dialysis teams in providing optimal care. As a result, in March 1995, the NKF launched DOQI (Dialysis Outcomes Quality Initiative). The areas selected for guideline development were the adequacy of hemodialysis and peritoneal dialysis dose, as well as vascular access and anemia, and these guidelines were published in the American Journal of Kidney Diseases in the September and October issues of 1997.26–28

What became evident in the process of developing the guidelines was what everyone was intuitively aware of but had not been clearly articulated; namely, the care of patients with kidney disease cannot start when dialysis therapy is initiated, but must be set in motion earlier when the complications of kidney disease begin to emerge. As a result, the focus, which before had been the care of patients with end-stage kidney disease, changed to that of individuals with kidney disease throughout the course of progressive loss of kidney function, when the increasing complications of kidney disease impose a cumulatively heavier disease burden on the patient presenting for dialysis. To reflect this broader outlook, DOQI became the KDOQI (Kidney Disease Outcomes Quality Improvement) initiative and entered a new phase of guideline development encompassing the entire spectrum of kidney disease, including measures for early intervention and prevention, which could postpone or even prevent the need for dialysis. To set the stage, the first guideline issued was the KDOQI Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification and Stratification (Fig 1).29,30 The proposed classification of chronic kidney disease (CKD) was based on estimated GFR (eGFR) calculated by the MDRD Study equation. As a result of this paradigm shift, the opportunity to improve outcomes changed from that of the thousands on maintenance dialysis therapy to the estimated (>10% of population) millions of individuals with CKD. The favorable response and rapid adoption of the new definition and classification of CKD worldwide by the nephrology community, as well as other medical disciplines and public health officials, was overwhelming. It was a transforming event that broadened the reach of nephrology well beyond its limited borders theretofore (Fig 2). Subsequently, the expressed need for a coordinated approach to guideline development led to the creation in 2003 of the KDIGO (Kidney Disease: Improving Global Outcomes) initiative.31 A major contribution of KDIGO has been continued improvements in CKD classification, a drive to improve the estimation and reporting of
eGFR, and the integration of the amount of proteinuria in the classification. Much like autoanalyzers had expanded the need for renal consultations in the 1960s, that of the now routinely reported eGFR by clinical laboratories has expanded nephrology consultations into the realm of every medical discipline.

CONCLUSION

As recounted in this selective recollection of nephrology in the past 50 years, the “kidney diseases” of the title of the American Journal of Kidney Diseases are old, but the discipline (nephrology) that the journal addresses is rather new and barely more than half a century old. The journal itself is just about 35 years old. Being fortunate enough to have observed and participated in the growth and maturation of the discipline has been a unique and most rewarding experience.

Although the growth of nephrology to some extent has been a product of technical developments (micropuncture, autoanalyzers, computers, dialysis machines, kidney biopsy, surgical transplantation, etc), it has been the conceptual changes and paradigm shifts they have engendered that in the terms of Thomas S. Kuhn (1922–1996) have actually brought the revolutionary changes in nephrology from its origins in kidney disease today is far superior than it has ever been before. The continued expansion of new information being generated on kidney structure and function in health and disease is both gratifying and overwhelming. It is bound to improve outcomes even further in the future.

One problem created by this otherwise fortunate acceleration of new information generated has been an overflow of published articles. Not only are there now more renal journals being launched yearly, but the principal ones have increased their pages and are using smaller type lettering to crowd more words into each page. Keeping abreast of this exponential growth has been rather difficult for some of us who have grown and matured (read aged) with the discipline. For my part, unable to keep up with the dizzying pace of this progress but determined on exploring new information on the kidney, I have gradually shifted my attention to the history of nephrology, a relatively unexplored territory in which contributions remain relatively easy, much as they were when I undertook my first clinical investigation on the bleeding tendency of uremia some 50 years ago. This has been a slippery undertaking given the increasing neglect and even disdain for the history of medicine in general and of nephrology in particular, but one that should help fulfill the Aristotelian wisdom expressed by a founding father of nephrology, Homer Smith, quoted in the opening of this article.

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REFERENCES


