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EDITORIAL

Set Theory: Nephrology ∩ Urology

Each new patient encounter for me engenders 2 proclamations. The first is the formal introduction of name, and the second is to define who I am, a nephrologist, and who I am not, a urologist. The Guest Editors, Dr Hoenig, an adult nephrologist, and Dr Neu, a pediatric nephrologist, have placed us at the crossroads of Nephrology and Urology in this issue of *Advances in Chronic Kidney Disease*. Their intent and that of the invited authors of this review is for nephrologists to more fully acknowledge and comprehend what urologists do because some urological disorders affect the practice of Nephrology. It is important that nephrologists are knowledgeably prepared when urological problems that intersect with Nephrology come our way.

By virtue of the titular term "crossroads," the Guest Editors denote that Nephrology intersects the urological discipline at 1 or more places, that Nephrology and Urology represent a small community at such intersections, or that both parties are at a crucial point, particularly where a decision must be made. However, the "or" is not an exclusive one, and depending on the prevailing circumstances, any of the 3 denotations may apply in a given clinical scenario. Several examples of the crossroads of Nephrology and Urology follow.

With improved urological care of infants and children, the adult nephrologist must now appreciate congenital anomalies of the kidney and urinary tract (CAKUT) because these individuals will invariably enter one's clinical practice. CAKUT is an important and prevalent group of disorders. Among these are congenital obstructive uropathy, primary megaureter, ectopic ureter, duplicated ureter, fusion and ectopic abnormalities, and multicystic dysplasia and cystic disorders of children. Using standardized sonographic evaluation of 30,940 infants and fetuses, nearly 7% were considered major malformations and 35.8% mild morphogenetic errors. CAKUT constituted approximately one-quarter of identifiable, prenatal anomalies. Furthermore, CAKUT contributes to the development of ESRD in children in 30% to 50% of cases.[1]

Spina bifida patients may develop CKD. The combination of a dysfunctional bladder outlet is often compounded by secondary vesicoureteral reflux.[2] Repeated urinary tract infections, despite intermittent, clean bladder catheterization, may further complicate an already suboptimal scenario, with development of stones. Staghorn calculus disease (infection stones) may result from urease-producing organisms. Nephrologists who inherit spina bifida patients from pediatric urologists and nephrologists must rapidly learn the "tricks of the trade" when caring for these fragile patients. Treatment may include the application of anticholinergic medications, bladder catheterization, and prophylactic antibiotic administration. Urodynamic studies with which the nephrologist is generally unfamiliar may be required to guide therapy. One must also appreciate the dissociation between serum creatinine-based methods for determining kidney function. Low muscle mass in the lower extremities of spina bifida patients renders an overestimation of function. A cystatin C-based glomerular filtration rate is recommended.

Of course, the ultimate reduction of nephron number takes place when there is a congenitally absent kidney. The outcome of the solitary kidney is based on multiple factors, but obesity may be its most formidable stressor today. However, the determining factor for glomerulosclerosis in the single kidney of obese individuals may rest with the net elevation in single nephron glomerular filtration rate,[3] which is a function of total nephron number.[4] A reduction in total nephron number is correlated with an infant's "smallness" (ie, intrauterine growth retardation) for gestational age and African American ethnicity.[5] Fortunately, those born with 1 good kidney or those who donate one during kidney transplantation do well, even overweight.[6] Although most cases of CAKUT occur sporadically, in recent years, mutations in genes involved in kidney development have been associated with variable CAKUT phenotypes in humans.[7,8] One example is kidney agenesis with hydroureter, which has been ascribed to *Islet1* deletion.[9] Interestingly, the gene product of *Islet1*, Isl1, is a mammalian transcription factor important in limb and heart development. Its conditional deletion in a murine model produces kidney hypoplasia/aplasia and hydroureter. Ectopic branching of ureteric

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buds (limbs) led to ureterovesical obstruction, with consequent ureteral dilation. Apparently, the lack of Isl1 impairs bone morphogenetic protein-4 expression, the lack of which produces a CAKUT-like phenotype. Despite the identification of this and other genetic disorders, the etiopathogenesis of the vast majority of CAKUT remains unidentified.

Vigilance for worsening of CKD in patients with acquired obstructive syndromes is another area of opportunity where urologists can interact proactively with nephrologists. Obstruction may be insidious and silent, yet few patients are enrolled into screening programs. Bladder and/or ureteral pressure symptoms are unreliable barometers of the degree of kidney dysfunction, and objective measurements of kidney function are indispensable to the prevention of progression of CKD through tubular atrophy and tubulointerstitial inflammation and fibrosis from myofibroblastic production of extracellular matrix.[10] Biomarkers superior in performance to the serum creatinine and that portend trouble would be welcome, and there are some candidates in children. In children with posterior urethral valve-mediated obstructive uropathy, a case-control study identified several potential biomarkers. Cases displayed greater proteinuria, by urine protein-to-creatinine ratio, than controls by nearly 7-fold. Aquaporin-2 excretion was remarkably less in cases than controls and corresponds to the nephrogenic diabetes insipidus state of chronic obstruction. Urinary L1 cell adhesion molecule and transforming growth factor-β were greatly enhanced and correlated negatively with glomerular filtration as did proteinuria.

There must be education among nephrologists and urologists that antagonism of the renin-angiotensin system (RAS), which suppresses angiotensin II-mediated induction of transforming growth factor-β, is not contraindicated during stabilized obstructive uropathy. In fact, this treatment may retard an invariable progression to CKD in some individuals. To date, RAS blockade in the obstructive stages of kidney disease of children cannot be claimed superior to that of non-RAS blockade (see article by R. Chevalier in this issue).

Insofar as CKD patients with potential obstructive uropathy are concerned, especially elderly, African American men at risk for prostatic hyperplasia, RAS inhibition should be attempted. Not all patients will develop hyperkalemic kidney tubular acidosis. In fact, the majority will not develop severe hypobicarbonatemia and/or hyperkalemia. In the event that either occurs, a loop diuretic and/or bicarbonate therapy is warranted and permits continuation of RAS inhibition. A loop agent is the drug of choice in this circumstance, reversing acidosis by virtue of its chloruretic property.

Speaking of metabolic acidosis in the context of Urology should certainly excite any nephrologist. Reconstructive surgery, whereby a bowel segment is removed and used as a pseudo-bladder, is termed "augmentation cystoplasty." The procedure augments the bladder capacity of children and adults with inadequate bladder capacity, detrusor muscle compliance, or exstrophy-epispadias complex.[11] The first 2 problems may induce high pressure-related kidney damage. This procedure is increasingly used and has been performed for decades, and the original indication was the contracted bladder resulting from tuberculous cystitis. Today, neuropathic causes of diverse etiology are the reasons why patients undergo this procedure, which must be stringently followed by a rigorous campaign of clean, intermittent catheterization.[12] Cystoplasty may result in hyperchloremic metabolic acidosis, sometimes severe, and this complication is reminiscent of that which occurs with an ileal loop or ureterosigmoidostomy.[13] The pathogenesis of acidosis results from cation and bicarbonate loss with reciprocal gain of ammonium chloride. The clever use of a "gastric patch" may attenuate the degree of metabolic acidosis by secreting hydrochloric acid into the final urine and, hopefully, the slope of decline of kidney function.[14]

Nephrolithiasis, which affects 5% of the population and with a lifetime risk of nearly 10%,[15] remains a testable area within Nephrology training, and trainees are expected to gain competency in this diverse group of disorders within the 2 years of the standard training rubric. Yet few Nephrology trainees have witnessed any of the 3 principal, mechanical stone removal mechanisms: extracorporeal lithotripsy, mechanical extraction, or percutaneous nephrolithotomy. In addition, fellowship-based curriculum hours featuring kidney stones are generally few and far between. This reality appears odd when kidney stones are becoming more frequent and prevalent in the United States, year over year. Nephrologists must be able to treat and prevent stones, and this means that the access to Nephrology clinic must be nearly on-demand and target preventive strategies. Kidney stone clinics run by nephrologists exist but selectively, and this phenomenon may be attributed to an economic reality: procedures pay the bills. An opportunity exists here: collaborative clinics with Urology-backed nephrologists.

Significant cost savings could accrue with improved follow-up for kidney lithiasis. In 1984, the economic impact of stones in white male adults, aged 18 to 60 years, was gauged at $315 million. This conservative estimate included hospital (surgeries and room rates) and work force costs (lost work days). In 2000, total medical expenditures for stone disease were estimated at $2.1 billion.[16] Certainly, disease recurrence and the net cost of care may be reduced through collaboration between urologists and nephrologists. Overlaying of a sophisticated Markov model over a decision analytic model to determine cost-effectiveness of increasing fluid volume intake to more than 2 L daily provided eye-opening conclusions. Simply imbibing more water could reduce nephrolithiasis costs by as much as 25% in the nationalized, French health care system.[17] Another cost-saving measure rarely initiated by nephrologists is medical expulsive therapy. Medical expulsive therapy of distal ureteral stones by α_1-blockade may be initiated by internists and nephrologists and reduce hospitalizations and expensive imaging studies[18]—something the patients are clamoring for as exemplified in a recent story in the *Time* magazine.[19]

Hopefully, after completing this issue of *Advances in Chronic Kidney Disease*, the reader will more fully appreciate how urological disorders intersect with Nephrology. In set theory, when the elements of 2 different sets have like

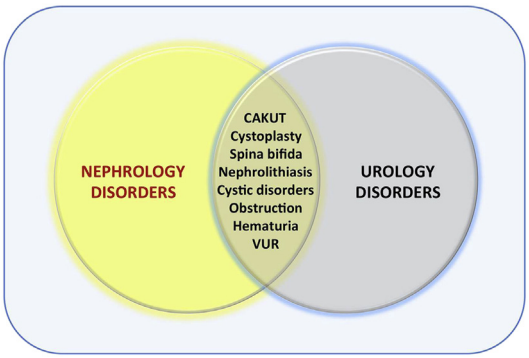

Figure 1. Nephrology ∩ Urology. The separate disciplines of Nephrology and Urology are represented as intersecting sets. The elements resulting from the intersection represent disorders that the nephrologist may encounter in clinical practice. CAKUT, congenital anomalies of the kidney and urinary tract; VUR, vesicoureteral reflux.

members, an intersection is born but possibly less clearly delineated than by a well-ordered, 2-set Venn diagram in which all elements are absolutely defined (Fig 1). Nonetheless, it is imperative that nephrologists engage urological intersections with high enthusiasm and seek to expand their volume within an enriched, collaborative care model based on a shared, foundational knowledge and abiding interest in delivering high-quality, cost-effective care.

> We live immersed in narrative, recounting and reassessing the meaning of our past actions, anticipating the outcome of our future projects, situating ourselves at the intersection of several stories not yet completed.—P.B.

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