Whether we like it or not, nephrologists around the world have been called to action. Our mission is to attenuate the growth of chronic kidney disease (CKD). Several conditions will need to gel for us to succeed. Although we now have a better understanding of its alarming incidence and prevalence within populations, however we choose to define it, better methods are needed to identify at risk and already affected individuals with progressive renal failure. Another major obstacle is the need for much more effective treatment strategies than are currently available. Furthermore, it has become clear the development of innovative new approaches to therapy will require a diverse armamentarium that together offers the best chance that renal progression can be halted and even forced to recede. It is time to strengthen alliances between academics and industry; among clinicians, clinical scientists, and basic scientists; and among nephrologists throughout each country (or, better yet, within several countries) to develop and test creative new treatment protocols in a way that is timely and that will enable us to provide our patients with evidence-based options. Our kidney patients who progress have a potentially malignant disease, one that certainly shortens life expectancy. We need only to look at our oncology colleagues who initiated such an approach many years ago with impressive improvement in survival for many cancers. At the same time, parallel efforts must be made to devise improved models of health care delivery so that that all affected individuals will have access to the most effective therapies.

This issue’s Frontiers in Nephrology presents five articles that cover much of the modern work in renal progression that is relevant to the clinician. In this modern era of disease prevention, growing interest has been drawn to the early identification of patients with persistent renal injury, and, increasingly, chronic renal disease has been identified as an epidemic. The temptation to describe ESRD as an epidemic can be argued from various positions, and the article by Kiberd speaks to qualifications on both sides of the issue. That is, are we in the midst of a true epidemic, or are we just getting better at detecting CKD in high-risk populations? Are consensus guidelines now more inclusive? Do the epidemiologic data speak for all patients or really apply to some ethnicities? Are indicators of cardiovascular damage, low birth weight, and diabetes just risk factors, or do they fulfill criteria for definition of primary renal diseases? Are the growing number of elderly patients in renal replacement programs just more accepting of dialysis and...
transplantation to prolong life than before? Nothing in the data sets with which we have to work adjusts easily for all of these issues.

Undoubtedly, the clinical staging of the transition toward ESRD has great bearing on health care planning, political dialogue, predictive outcomes, cost, and public attention to a critical health problem. Answers to these questions affect the goal of determining the efficacy of prevention treatment or replacement therapy. Such answers are complicated because most persistent renal disease is slowly progressive, not everyone is satisfied with the sensitivity and specificity of disease markers, and large at-risk populations are either frail or suffering from multiple systemic diseases. While disagreements will go on over the precision of our epidemiologic measures and the application of current treatment strategies, so does the hope that fundamental research will provide more clues for new therapeutic targets to combat the progression of CKD.

The pathologic correlate of clinical progression in patients with CKD is the relentless expansion of interstitial fibrosis. Renal fibrosis is an iterative product of hyperfiltration, persistent proteinuria, cellular inflammation, and the local release of morphogenic cytokines that disturb structure–function relationships among nephrons. It is increasingly clear that as more is known of the mechanisms that contribute to CKD, the more these fragments can be ordered into a unified theory of renal progression.

Some of the most important advances in pathophysiology today are evolving from the early and persistent role of proteinuria, the renin-angiotensin-aldosterone system, and fibroblast biology in the expression of interstitial nephritis that leads to renal fibrogenesis. The complexity of these subjects is increasingly being reduced to the dimensions of cell biochemistry and signaling, disciplines that offer some hope for new therapeutic targets that attenuate molecular mechanisms of disease. Bone morphogenic protein-7, hepatocyte growth factor, inhibitors of TGF-β and PDGF, anti-proteases, and regulators of NF-κB all someday may have an adjunctive role with angiotensin-converting enzyme inhibi-
tors, angiotensin receptor blockers, and aldosterone antagonists in modulating renal progression.

The role of proteinuria in renal progression and its interface with chemokine and complement activation, macrophage accumulation, and NF-κB signaling are reviewed by Abbate et al. Their synthetic discussion points strongly to a number of molecules that are ripe for therapeutic modulation. Reduction of proteinuria and podocyte retention is iteratively related to the attenuation of the downstream cytokine bath that is responsible for the inflammation producing subsequent interstitial nephritis. Eddy and Fogo discuss the rapidly expanding field of plasminogen activator inhibitor-1 (PAI-1) and its accelerating affect on protease activation, inflammation, and fibrogenesis. Controlling PAI-1 activity has an antifibrotic effect on the kidney, and it is of some interest that drugs that modulate angiotensin II activity also reduce PAI-1. Only time will tell, but new, specific anti–PAI-1 agents that are in the pipeline may have a useful role someday in managing fibrotic risk. In a comprehensive review, Rüster and Wolf describe current thoughts on the role of the renin-angiotensin-aldosterone system in renal progression. Angiotensin II, aside from its hemodynamic effects, has a morphogenic role in activating glomerular and tubular cells, chemokines, and cytokines such as TGF-β. Angiotensin II has a high concentration effect from local production, but there are other, new peptides, such as angiotensin 1–7, that may modulate renal cell signaling in ways that can be turned into regulatory advantage; with more study, only time will tell. Last, Strutz et al. take a timely look at progress that has been made in understanding the local origins of fibroblast development and activation through epithelial-mesenchymal transition. Evidence that the push to fibroblast formation and activation is in a dynamic state with forces that maintain epithelial phenotype suggests that altering the mix of profibrogenic cytokines may offer new therapeutic approaches to controlling persistent fibrogenesis.

This issue’s Frontiers in Nephrology brings us current with important fields of research that hold much potential for intervention in the clinic. Fifteen years ago, such progress was unimaginable. New technology and clever experimental design by many scientists and clinicians around the world have brought us a long way through a difficult area that is rich in opportunity, and the continued efforts in this regard are a credit to the public and private support of research that helps the patients whom we serve.