A rare disease is defined by the federal government as any condition that affects fewer than 200,000 people in the United States. Rare diseases can be distinguished from neglected diseases, such as malaria, hookworm, or Chagas disease, in that neglected diseases receive less attention because although common they are uncommonly found in this country. As so defined, there are >6000 rare diseases affecting >25 million individuals in the United States or approximately 7% of the population. Renal diseases are well represented on this list and include >100 disorders of transport, development, metabolism, and inflammation. The study and clinical management of patients with these diseases have been the focus many investigative efforts. In many instances these studies have yielded fundamental insights into renal physiology and pathophysiology.

The development of therapeutics for patients with rare diseases presents several unique challenges. Because the patient populations are small, the phenotype and natural history of an individual disorder are often difficult to define. Many genetic disorders demonstrate a poor correlation between genotype and phenotype, and thus defining an appropriate clinical outcome may also be problematic. If a potential treatment is identified, the limited number of study subjects may render a standard clinical trial design inappropriate. Finally, the significant cost of developing novel therapeutics makes many of these diseases unattractive targets for most pharmaceutical and biotech companies. Nevertheless, these hurdles should not be viewed as insurmountable because there are compelling social and ethical reasons to address the needs of patients with these diseases.

Many rare diseases result from inherited or acquired mutations that result in protein misfolding. These missense mutations may cause impairment of the catalytic activity, pH-dependent protein stability, disruption of protein–protein interactions required for enzyme regulation, improper trafficking to organelles, accelerated degradation of the newly translated protein, or protein aggregation (1). Fabry disease and nephrogenic diabetes insipidus are two well-studied renal diseases that are associated with protein misfolding. In the former case the degradative enzyme α-galactosidase A is often translocated but exhibits low catalytic activity (2). In the latter case, both aquaporin and the V2 receptor have been shown to be misfolded and inefficiently trafficked to the plasma membrane (3,4).

In recent years investigators have sought to develop small molecules as potential therapeutics for rare diseases based on targeted mechanisms as opposed to using available drugs to provide symptomatic relief. For example, globotriaosylceramide accumulation in Fabry disease may be amenable to inhibition of glycosphingolipid synthesis (5). Several groups have recognized that the reduced folding efficiency of mutant proteins can be partially overcome by the use of small molecule ligands that bind to mutant proteins to improve the energetics of the misfolded proteins. Many studies, including some on diabetes insipidus, have employed the use of chemical chaperones, typically glycerol or dimethylsulfomide (DMSO) for conformationally defective proteins (6). More recently, “pharmacochaperones” have been experimentally employed as potentially useful agents for disorders such as Fabry disease (7). The utility of these agents is often counterintuitive because in many cases these are active site inhibitors of the targeted proteins.

In this issue of JASN, Bernier and colleagues have elegantly studied the use of a nonpeptide V1a antagonist in X-linked diabetes insipidus (8). They demonstrate that two different vasopressin receptor antagonists are capable of rescuing the cell surface expression and function of misfolded V2 receptors. They further report that, in five patients representing three types of missense mutations, the V1a receptor antagonist significantly decreased urine volume and water intake in association with a rise in urine osmolality. Although the urine output remained substantially elevated in these patients, this study is noteworthy in the use of an agent that partially restores the function of the mutant V2 receptor.

This study nicely confirms the promise of using pharmacochaperones as a therapeutic strategy. Several hurdles will need to be overcome before the nephrology community can seriously entertain the more general application of pharmacochaperones. Many of these challenges are intuitively obvious. First, a more systematic understanding of which rare renal diseases are characterized by protein misfolding will be necessary. Nonsense mutations resulting in the absence of translated proteins are obviously not amenable to this approach. Second, more efficient means for genotyping patients and a priori predicting which mutations are amenable to chaperone therapy will be important steps in the practical application of this strategy.
Third, advances in the in silico identification of protein ligands and platforms for rapidly screening identified compounds will render the discovery of new small molecule chaperones more tractable. Fourth, better means for phenotyping individual patients and registries for establishing the natural histories of these disorders will be critical if any future clinical trials are to be contemplated. At present very few rare renal diseases have international registries that follow patients.

Why should nephrologists care about understanding and treating rare renal diseases? After all, compared with hypertension and diabetes mellitus, a single rare disease of the kidney can hardly be considered to be a public health challenge. Although collectively rare renal diseases affect a significant number of individuals, there is one compelling reason why they deserve our attention. Rare diseases are currently the best model we have for approaching the future challenges of individualized medicine. Very common disorders such as diabetes mellitus and hypertension and less common ones such as focal segmental glomerulosclerosis are continually being redefined as new insights into pathogenesis are discovered. Though historically viewed as single diseases, these are in actuality clinical syndromes that are more appropriately understood as a collection of less common, mechanistically definable diseases sharing common clinical phenotypes. The challenge of approaching these newly redefined disorders and rare diseases is fundamentally the same. The challenge includes understanding the pathogenesis and natural history of these diseases, in addition to the development of mechanism based therapeutics. Undoubtedly, significant effort will be expended in addressing these goals in years to come.

References