The kidney is capable of regulating systemic BP primarily because of its role in hormone release and fluid balance. Although it is clear that the kidney participates in the development of many forms of hypertension, direct evidence is often lacking. Studies that correlate renal function and BP offer only secondary evidence but have provided reproducible models. In a few models and in some patient populations, the kidney is more clearly identified as the source of hypertension. For example, increased release of renin from an obstructed renal artery disease leads to hypertension. Experimentally, this disease has been successfully modeled to study the effects of endogenous high levels of renin and angiotensin II that follows. However, other kidney-linked models of hypertension are not identified so easily.

Previous studies using kidney transplantation in rats began to identify the role but often not the mechanism of renal-dependent hypertension. Studies that transplanted kidneys from spontaneously hypertensive rats (SHR) to normotensive rats and conversely normotensive kidneys into SHR consistently revealed that the ambient BP follows the transplanted kidney.1–3 Subsequent studies also showed that the kidney determines the BP response to high salt intake in Dahl salt-sensitive rats4 and in renovascular hypertensive kidneys.5

Renal cross-transplantation studies of mice have now started to appear and add to our understanding of the role of the kidney in regulating BP. This technique in mice has the potential to identify the kidney source of various hypertensive genes. The challenge lies with the more complex surgery required in mice. However, Coffman and colleagues6 previously explored the role of the renin-angiotensin system on the regulation of BP in gene-deleted mice and in transplantation studies to separate the effects of the kidney versus nonrenal tissue. In a previous study, they transplanted kidneys from the hypotensive angiotensin II type 1a receptor-deficient mice into wild-type mice to show that BP again follows the transplanted kidney.

In this issue of JASN, Gurley et al.7 use the cross-transplantation method to study the role of the regulator of G protein signaling type 2 (RGS2) that is implicated in hypertension. There is growing evidence that G protein-coupled receptor (GPCR)-mediated control of vascular tone and BP is an important regulatory step in the development of hypertension. GPCRs are activated by several ligands, including angiotensin II. GAPs proteins modulate signaling by GPCRs and evidence now suggests the GAP RGS2 may be a key regulator of this process. Mice lacking RGS2 develop hypertension for unknown reasons.8 Gurley et al.7 now show that transplanting kidneys from hypertensive RGS2−/− mice increases BP in wild-type mice, demonstrating the dominant effect of the kidneys for this gene.

The clear results from this study are due to the elegant surgical skills of this group, who have perfected the ability to transplant kidneys in mice. This sets the stage for even more studies that should be able to associate the role of the kidney in the regulation of BP in several single gene-deleted models. This study does not define the mechanism by which RGS2 regulates BP or how its inhibition or absence causes hypertension. The specific ligands that interact with RGS2 are not explored either. The study does demonstrate that the effects of RGS2 in the kidney have more profound effects on BP than systemic effects of RGS2.

Of course, there remain difficulties with the interpretation of these and future studies. First, as the authors discuss, it is not clear how the kidney mediates hypertension and that both epithelial and vascular targets could be involved. Second, the absence of data on GFR makes this evaluation more difficult. However, the effects of GFR per se may have been factored out by the transplant controls. Regardless of these concerns with this method in mice, the BP results are compelling.

DISCLOSURES
None.

REFERENCES
Tubular Reabsorption of Albumin: It’s All About Cubilin

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The proximal tubule is a fascinating structure where 66% of the glomerular filtrate is returned to blood together with practically all glucose, amino acids, and vitamins. Our understanding of the mechanisms behind this efficient and nearly perfect transport is beginning to come into focus, mostly because of the discovery of cubilin, a protein that is required for an intact glomerular barrier.


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Several physiologic observations seem to refute the latter notion. In particular, Maunsbach 29, 30 in the mid-1960s found no significant uptake of intact albumin from cytosis, the megalin–cubilin complex delivers its ligands to lysosomes, where all proteins are degraded and the amino acids and vitamins are returned to the circulation.12 These studies have been highly relevant clinically for several reasons: First, they shed light on the nephrotoxicity and ototoxicity of aminoglycosides.13–15 Uptake of myoglobin and hemoglobin is also mediated by megalin.16,17 Furthermore, the megalin–cubilin complex is recycled in a process requiring chloride channel 5.18

In this issue of JASN, Amsellem et al.19 present new and exciting data on the importance of cubilin using a conditional Cre-LoxP mouse model, resulting in 90% inactivation of tubular cubilin in the kidney. The authors used a similar technique to inactivate megalin and were able to breed some mice that lacked both proteins and lived to adulthood. Amsellem et al. report that cubilin requires amnionless for expression at the brush border and vice versa; cubilin is essential for tubular uptake of albumin, and megalin is needed for the endocytosis of the cubilin–albumin complex; and several ligands known to have high affinity for cubilin, such as apo-A-I, CC16, and transferrin, are actually required for an intact barrier,20,21 although there are no endothelial null phenotypes to prove this unambiguously. The glomerular barrier is highly size and charge selective according to most physiologic measurements, a finding compatible with studies at the molecular level.20

Several important conclusions can be drawn from this study,19 but I focus on one: its relevance for tubular handling of albumin. Human kidneys filter every day 180 L of primary urine with a solute composition similar to plasma. Normally, the final urine contains <30 mg/d albumin. From a theoretical point of view, abnormal proteinuria could be due either to a defective glomerular barrier that increases the filtration of albumin or to reduced tubular uptake of filtered protein. For decades, it was assumed that the cause of proteinuria would be found in the glomerulus because nephritic and nephrotic syndromes are characterized clinically by histologic changes in that structure. Indeed, discoveries during the past decade of several previously unknown components of the glomerular filtration barrier support this view. Today, we know of several proteins in podocytes or glomerular basement membrane that, when mutated, give rise to proteinuria.20 In addition, the surface glyocalyx of glomerular endothelium may also be required for an intact barrier,20, 21 although there are no endothelial null phenotypes to prove this unambiguously. The glomerular barrier is highly size and charge selective according to most physiologic measurements, a finding compatible with studies at the molecular level.20

In contrast, other reports suggest that proteinuria in most kidney diseases is due to tubular defects, not glomerular.22–24 According to the latter point of view, the glomerular barrier is normally leaky, resulting in the filtration of >200 g/d albumin. Intact albumin is subsequently retrieved from the urine and returned to the blood according to this albumin-retrieval hypothesis.24

Several physiologic observations seem to refute the latter notion.20, 25–28 In particular, Maunsbach 29, 30 in the mid-1960s found no significant uptake of intact albumin from