Aldosterone activates the epithelial sodium channel (ENaC) in principal cells of the collecting duct to regulate salt excretion, extracellular volume, and BP. Seminal studies by Hostetter and colleagues demonstrated that aldosterone also contributes to glomerular sclerosis in a remnant kidney model. Treatment of rats with aldosterone and salt induces an inflammatory response, characterized by perivascular leukocyte infiltration and increased expression of the NF-κB target gene plasminogen activator inhibitor 1 (PAI-1) in mesangial cells in part through in vivo proteolytic cleavage of its α subunit. It is possible that, during low salt intake, increased inflammation puts a break on sodium reabsorption. The same group previously reported that prolonged activation of NF-κB by LPS decreases expression of SGK1 and activity of the ENaC–α subunit, as well as basal, glucocorticoid, and mineralocorticoid-stimulated sodium transport in cultured principal cells. Bens et al also reported that LPS reduced amiloride-sensitive ion fluxes in cultured cortical collecting duct cells. In addition, increased expression of the NF-κB target gene plasminogen activator inhibitor 1 (PAI-1) during low salt intake could decrease activation of ENaC by decreasing plasmin-mediated proteolytic cleavage of its κ subunit.

Although Leroy et al. found that low salt intake increases MR-dependent activation of NF-κB in the collecting duct, it is well established that high salt intake enables the proinflammatory and profibrotic effects of aldosterone in the kidney in whole-animal studies. High salt intake paradoxically activates renal MR in obese hypertensive rats, resulting in increased translocation of the MR to the nucleus, increased expression of SGK1, and increased NF-κB activity. Although the cell specificity of this effect is not known, MR antagonism decreases renal NF-κB expression and glomerular podocyte injury in parallel during high salt intake. Taken together with the observation that low salt intake increases MR-dependent inflammation in the cortical collecting duct, it is possible that salt intake modulates the site and proinflammatory effect of aldosterone in the kidney. Increased oxidant stress also contributes to salt-induced activation of renal MR, in that the antioxidant tempol prevents the effect. Likewise, aldosterone increases PAI-1 expression in mesangial cells in part through increased oxidative stress and TGF-β. It would be interesting to know whether increased oxidative stress contributes to the MR-dependent activation of NF-κB in the cortical collecting duct during low salt intake.

Aldosterone or MR activation causes both tubulointerstitial fibrosis and glomerulosclerosis in animal models. Thus, the MR antagonists spironolactone and eplerenone decrease interstitial inflammation and glomerular injury in rats with radia-
tion injury, unilateral ureteral obstruction, diabetes, and aldosterone infusion. MR inhibition even reverses preexisting glomerulosclerosis in a five-sixths nephrectomy model. The extent to which increased expression of NF-κB-targeted genes contribute to aldosterone-induced renal injury may be deduced from studies in genetically deficient mice. Obese (db/db) mice genetically deficient in MCP-1 are protected against proteinuria, inflammation, and glomerulosclerosis; whether MCP-1 deficiency protects against aldosterone-induced renal injury per se has not been reported, but obesity is associated with increased circulating aldosterone concentrations. PAI-1–deficient mice are also protected from aldosterone/salt-induced glomerulosclerosis; in contrast, PAI-1 deficiency does not protect against interstitial inflammation in response to aldosterone and salt treatment.

What implications do these studies have for the treatment of patients? Activation of the renin-angiotensin-aldosterone system increases whereas MR antagonism decreases circulating IL-6 and PAI-1 concentrations in humans. Whether MR activation decreases renal cytokine or PAI-1 expression in humans is unclear. It is known, however, that spironolactone decreases urinary excretion of F2-isoprostanes, markers of oxidative stress, and MCP-1, through a BP-independent mechanism in patients with type 2 diabetes. More important, MR antagonism decreases proteinuria and progression of renal disease in patients with hypertension or diabetes.

Our understanding of the pathophysiologic role of aldosterone has progressed during the past 15 yr, and the clinical use of MR antagonists has seen resurgence. We often contrast the proinflammatory/profibrotic effects of aldosterone in nonepithelial cells to the classic physiologic role of aldosterone in promoting epithelial sodium transport. The studies of Leroy et al. suggest that, in the kidney, these two effects are more intimately linked than previously appreciated.