Introduction

The kidney contains all the components of the renin-angiotensin system. Therefore, the renin-angiotensin system can be regarded as both a circulating hormonal system (endocrine) and a local intrarenal system (auto-crine, paracrine) [1–3]. Presumably, renin and angiotensin II can be excreted into the vascular, tubular, and interstitial compartments of the kidney, and angiotensin II, both from the circulation and from local intrarenal production, can act on the kidney. Angiotensin II has multiple renal actions [4,5], including regulation and redistribution of renal blood flow (RBF); differential vasoconstrictor effects on the efferent and afferent arterioles of the glomerulus; contraction of the mesangium; regulation of vasa recta blood flow, with effects on renal concentrating ability; suppression of renin synthesis and release; and an influence on sodium transport in the proximal tubule. Angiotensin II receptors at many of these sites have been documented in animal kidneys [6].

Thus, it is not surprising that angiotensin-converting enzyme (ACE) inhibitors have been shown to have profound effects on the renal function. In normotensive subjects and in patients with essential hypertension, RBF and glomerular filtration rate (GFR) are well maintained after administration of ACE inhibitors [7]. Moreover, in some cases of angiotensin-induced renal vasoconstriction, RBF actually may increase. However, soon after ACE inhibitors were introduced into clinical practice, reports appeared that they produced acute renal failure [8]. It is now known that patients at risk of developing acute renal failure in response to ACE inhibition include those with bilateral renal artery stenosis or stenosis in a solitary native or transplanted kidney. Patients with low, fixed RBF, particularly those who are volume/sodium depleted from excessive diuretic therapy, may also develop increased plasma creatinine concentrations. The incidence of such acute increases in plasma creatinine in these patients is not yet established. Hollenberg [9] has indicated that the incidence may be as low as 2.6%. In a study of patients with renovascular hypertension and unilateral or bilateral renal artery stenosis, our group [10] reported acute renal failure in 19% of the patients who were treated with ACE inhibitors. However, acute renal failure occurred only in patients with bilateral stenosis, or in those with a single kidney, in whom the incidence rose to 32%.

The mechanism for acute renal failure has been studied in experimental animal models [11,12]. When a renal artery stenosis is applied in dogs, RBF and GFR gradually return toward normal. This occurs because of a rise in systemic blood pressure (BP) and, more importantly, by differential vasoconstriction of the efferent glomerular arteriole, which maintains intraglomerular pressure and hence GFR. Administering ACE inhibitors to these animals prevents the GFR from
returning toward normal; however, the simultaneous intrarenal infusion of angiotensin II will restore GFR. Thus, it seems likely that the renal function in patients with fixed RBF is angiotensin dependent and that blocking angiotensin II’s constriction of the efferent glomerular arterioles with ACE inhibitors is the cause of the deterioration in renal function. Results of recent studies in animals and humans suggest that a decrease in GFR with maintenance of RBF occurs in any kidney with a fixed RBF [13]. Thus, in patients with unilateral renal artery stenosis and renovascular hypertension, isotopic renograms demonstrate decreased renal uptake of Tc diethylenetriamine penta-ace-tic acid on the stenotic side following a single dose of captopril [10,14]. This is reversible, as is the acute rise in plasma creatinine that accompanies administration of ACE inhibitors to patients with renovascular hypertension. This change in the isotopic renogram following captopril administration, together with the rise in plasma renin, can be used diagnostically to confirm renovascular hypertension [15].

Clinical Benefits
Paradoxically, ACE inhibitors may also be renopro-tective. In both severe and malignant hypertension, treatment with ACE inhibitors is often associated with long-term improvement of renal function. In scleroderma renal hypertensive crisis, ACE inhibitors reverse acute renal failure [16]. Evidence increasingly indicates that the administration of ACE inhibitors in experimental states of progressive renal failure slows the progression of the renal failure [17]. This is seen in both the remnant-kidney model of progressive renal failure [18] and, more importantly, in experimental diabetic nephropathy [17]. Several groups have reported that the administration of ACE inhibitors maintains GFR, reduces proteinuria, and prevents the structural abnormalities of diabetic nephropathy. There is also suggestive evidence that ACE inhibitors may improve renal function and reduce microalbuminuria in both hypertensive and normotensive diabetic patients with early incipient diabetic nephropathy [19–21]. ACE inhibitors can, therefore, be regarded as renoprotective due to their actions of reducing BP, maintaining RBF and GFR, reducing glomerular hypertension, altering mesangial function, and preventing pathologic structural changes. The contributors to this symposium discuss many of the above issues. In particular, the articles address some of the wider indirect actions of angiotensin and ACE inhibitors on renal function and examine the interactions of the renin-angiotensin system and other hormonal systems within the kidney.
Finally, these reports detail the usefulness and effectiveness of ACE inhibitors in treating patients with severe hypertension, renovascular and renal hypertension, and diabetic nephropathy.

References