

## Three Angiotensin Paradigms in One Patient

*Etiology of Hypertension, Glomerular Hemodynamics,  
and Long-Term Glomerular Protection*

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### 1. Introduction

This chapter on new methods of molecular biology applied to the investigation of the renin–angiotensin system (RAS) contains a description of a clinical case in its first section. There are two reasons for this. First, the case will illustrate the importance of increased understanding of the RAS, because of research by basic scientists, for clinical scientists, clinicians, and human health. Second, and more importantly, describing the applicability of scientific advances in the understanding of RAS to a particular patient is a fitting tribute to two remarkable clinician scientists, Irvin Page and Eduardo Braun Menendez, the co-discoverers of angiotensin II (Ang II) in the United States and Argentina, respectively (1,2). Their insurmountable curiosity was driven by a desire to help patients, at a time at which human hypertension was an untreatable and devastating problem.

### 2. The Etiological Role of Angiotensin II in a Case of Human Hypertension

#### 2.1. Initial Medical History

R. Y. is a 77-yr-old African-American man who developed hypertension at age 68. At the time of diagnosis, he already had evidence for vascular disease in the iliofemoral arteries (the symptom of intermittent claudication and the physical finding of bruits on these arteries). In addition to a family history positive for hypertension, coronary artery disease, and diabetes, the patient was a current smoker and was known to have high cholesterol. Approximately

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in 1993, his hypertension, previously well controlled with a simple medication regimen (prazosin and the diuretic combination HCTZ-amiloride), became refractory to treatment. A renal scan, before and after captopril showed normal uptake of the isotope by both kidneys, with captopril-induced bilateral slowing of excretion. His physician considered that this test was equivocal for diagnosis of renal artery stenosis and renovascular hypertension and decided not to perform an angiogram, considering this test too invasive in view of the perceived low diagnostic yield. The patient was, therefore, maintained on multiple antihypertensive medications, including the angiotensin-converting enzyme (ACE) inhibitor, benazepril, which only produced a modest reduction of blood pressure (BP) when added to other agents.

Two years later, the patient consulted us at the Hypertension Clinic of the University of Texas Medical Branch. His BP was elevated at 202/88 mmHg, his physical exam was characterized by the previously noted arterial bruits, which could now be heard from the epigastrium down to the level of the aortic bifurcation and in both flanks and lower abdominal quadrants. An echocardiogram disclosed left atrial enlargement and concentric left ventricular hypertrophy. The most important finding in his laboratory data was a deterioration of renal function (serum creatinine 206  $\mu\text{mol/L}$ ) without proteinuria in the urinalysis.

Serum creatinine values starting in 1975 were retrieved from old records. The plot of the inverse of serum creatinine over time (**Fig. 1**) demonstrated a clear change in slope (steeper downward) starting in early 1993. The refractoriness of the hypertension, the smoking and hypercholesterolemia, the presence of obvious peripheral vascular disease, and the deterioration of renal function, made it likely that the patient had developed renal artery stenosis with its two clinical manifestations, renovascular hypertension and ischemic nephropathy. An abdominal angiogram confirmed this suspicion, showing bilateral, severely stenotic renal arteries (both  $>90\%$ , **Fig. 2**), with systolic BP gradients across the stenoses of 130–140 mmHg.

## **2.2. Goldblatt Hypertension in Humans**

In the 1950s and 1960s, most clinicians thought of renovascular stenosis as a potentially reversible cause of hypertension in the young, because of one of the forms of congenital fibrous or fibromuscular dysplasia of the renal arteries (3). With the exception of progression to renal artery occlusion in the rare form of intimal hyperplasia, the clinical problem of these patients was exclusively that of potentially curable hypertension. Repercussion on renal function was either nil or modest. The marked improvement in survival of the elderly over the last four decades, particularly those with cardiovascular disease, has radically changed this issue. Atherosclerosis of the renal arteries is now the most common cause of renal artery stenosis (4). Its progression is such an important

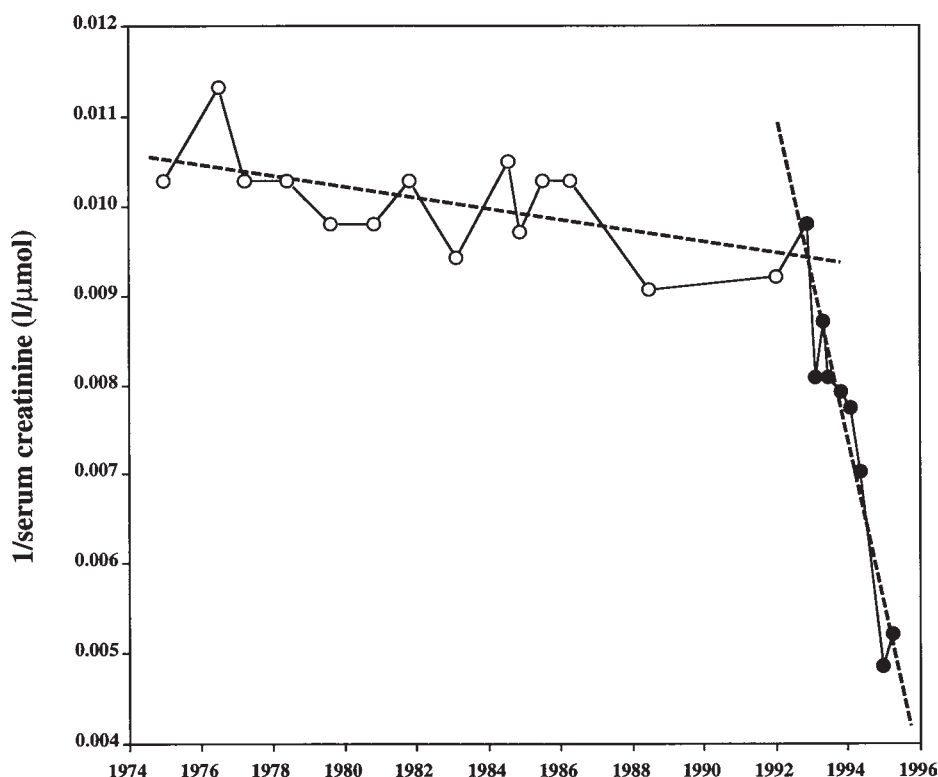


Fig. 1. Plot of the inverse of serum creatinine from 1974 until the time of the angiogram. The open symbols depict slow progression of renal dysfunction over the course of eighteen years, probably because of aging and essential hypertension. The closed circles indicate a 2-yr period of acceleration of renal dysfunction, presumably caused by superimposed, hemodynamically significant, bilateral renal artery stenoses (see discussion in text). The regression lines for both periods are shown. The choice of the cutoff point between the two periods was arbitrary, by inspection of the plot.

cause of renal dysfunction in the elderly that nephrologists have coined the specific term “ischemic nephropathy” to designate this entity (5) and differentiate it from renovascular hypertension, the other consequence of stenoses of the renal arteries.

Normal subjects start losing glomerular filtration rate (GFR) at about age 35 and at a rate of 1 mL/min/yr (6). The rate of loss of GFR with aging is increased in nonmalignant essential hypertension, because of arteriolar nephrosclerosis (7). This process exhibits large interindividual variability, probably due to differences in genetic susceptibility to renal disease (8,9). However, in uncomplicated essential hypertension, serum creatinine rarely reaches the levels we saw



Fig. 2. Aortogram depicting a markedly irregular atherosclerotic abdominal aorta and obvious stenoses of both renal arteries, extending from their origins for approximately 2 cm. Poststenotic dilatation of the renal arteries and involvement of the iliac arteries in the atherosclerotic process are also visible.

in our patient at his age. Furthermore, he had an abrupt change in the rate of loss of GFR (**Fig. 1**). This finding, if not explained by intercurrent illness, nephrotoxic medications, or acceleration of essential hypertension, must trigger the clinician's suspicion of atherosclerotic involvement of the renal arteries.

The Goldblatt experiment was a paradigmatic demonstration of the existence of a condition in which renin and angiotensin had a definite effect on regulation of BP. However, it was not until Gavras' seminal experiments in the 1970s that it was understood that the dependence of BP on renin in Goldblatt hypertension was contingent upon the existence of an uninvolved contralateral kidney, capable of undergoing pressure-induced natriuresis when exposed to the hypertension. Hence, in the rat with two kidneys and one clip (2K1C model), the clipped kidney secretes renin, producing BP elevation that leads to

pressure-induced natriuresis by the unclipped kidney. Maintenance of normal (or slightly contracted) plasma volume by this natriuresis perpetuates stimulation of renin secretion by the stenosed kidney. The resulting hypertension is, therefore, renin-dependent in sustained manner and pharmacologic blockade of the RAS reduces BP in its early and late stages (*10*). In contrast, in the rat with a clipped single kidney (1K1C), the entire renal mass is affected by hypoperfusion; therefore, pressure-induced natriuresis is impaired. Sodium retention and plasma volume expansion shut off the initial hypersecretion of renin produced by the clipping of the solitary renal artery. In its maintenance phase, this model becomes a sodium/volume-dependent form of Goldblatt hypertension which does not exhibit significant antihypertensive responses to antagonists of the RAS (*11*). In humans, occurrence of the “1K1C model” requires that atherosclerotic lesions of both renal arteries be not only present (which is common), but also hemodynamically significant on both sides (much less common) (*12*).

In our patient, several findings supported the diagnosis of hemodynamically significant bilateral renal artery stenoses before this was actually documented by the angiogram. First, the apparently “false” negative results of the renal scan. This test utilizes the fact that Ang II is predominantly a constrictor of the efferent glomerular arteriole (*13*). Pharmacologic blockade of the RAS will, therefore, increase “run-off” of blood flow to the distal nephron, with consequent decreases in glomerular capillary pressure and filtration fraction. In normal human beings, GFR is not decreased because of concomitant increase in renal blood flow. Renal artery stenosis precludes the increase in renal blood flow, therefore, the decrease in filtration fraction results in actual decrease of GFR. This is visualized as a captopril-induced decrease in the excretion of a radioisotopic compound in the scan. Hence, a “true positive” test depends on captopril-induced worsening of GFR in the affected kidney, as compared to the unaffected one. Bilateral hemodynamically significant lesions make this comparison unreliable and constitute a well-recognized cause of “false negatives” for this test (*14*).

Second, addition of an ACE inhibitor had very little effect on BP. This finding resembles the situation observed in the 1K1C model, hence, suggesting hemodynamically significant bilateral stenoses. It was noteworthy, however, that the poor response to benazepril was observed despite concomitant use of diuretics, a maneuver that may restore renin-dependency of the hypertension in the 1K1C rat by producing natriuresis (*11*).

Finally, a creatinine of 206  $\mu\text{mol/L}$  indicated that more than 50% of GFR had been compromised by the pathologic process. Even if one of the renal arteries were totally occluded, an explanation was needed to account for decreased GFR in the contralateral kidney. Hypertensive nephrosclerosis in

the kidney with a patent renal artery, i.e., exposed to the hypertension, could have been the explanation (15). However, the lack of an episode of accelerated hypertension to account for severe arteriolar disease of the nonstenosed kidney, and the other elements of the history made it very likely that the marked decrease in GFR was because of involvement of both renal arteries in the atherosclerotic process.

### **3. The Role of Angiotensin II in the Regulation of Glomerular Hemodynamics**

#### **3.1. Therapy and Initial Clinical Course**

Percutaneous transluminal balloon angioplasty was carried out on both renal arteries immediately after the diagnostic angiogram. The gradients across both stenoses were successfully abolished. The patient experienced a transient slight increase in creatinine (Fig. 3). This was attributed to dye-induced nephrotoxicity because there was no evidence (e.g., eosinophilia or eosinophiluria) for renal cholesterol embolism, the other relatively common complication of revascularization procedures on the renal arteries. Successful angioplasty decreased, but did not normalize BP completely. Approximately half the previous medications were needed to achieve a BP of 138/62 mmHg. At the time of addition of benazepril (which was required to successfully correct the hypertension), there was a striking increase in serum creatinine (Fig. 3).

#### **3.2. Glomerular Hemodynamics in Hypertension**

The characteristic histologic abnormality of nonmalignant essential hypertension is benign arteriolar nephrosclerosis, involving predominantly the afferent arteriole. In a kidney biopsy specimen, the distribution of this lesion is heterogeneous. Glomeruli with severe afferent arteriolar narrowing coexist with others minimally affected and still others without any lesion whatsoever (16). It has been hypothesized that this morphologic heterogeneity leads to functional heterogeneity of the RAS. According to this hypothesis, the ischemic hypoperfused glomeruli hypersecrete renin in an attempt to constrict the efferent arteriole for maintenance of GFR. In contrast, glomeruli with normal afferent arterioles sustain hypertensive hyperfiltration, leading to initial high-distal delivery of sodium to the macula densa, with suppression of renin secretion. The plasma renin activity resulting from the different secretion by these two populations of nephrons averages out to normal values. This results in inadequate compensation of reduced GFR in the ischemic glomeruli, and in inappropriate, excessive renin concentration reaching the hyperfiltering glomeruli.

In the ischemic glomeruli, persistent reduction of GFR with consequent reduction in distal delivery of sodium leads to antinatriuresis and sustained hypersecretion of renin by the macula densa/JGA. In the hyperfiltering glom-

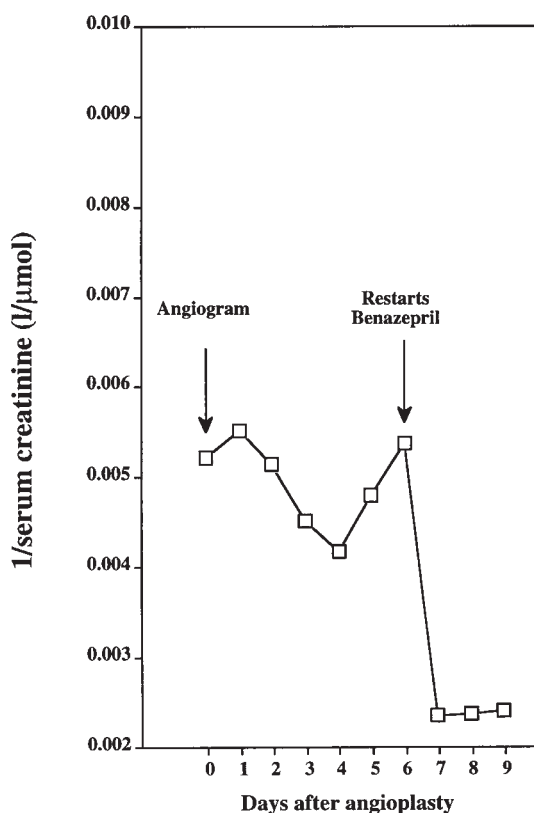


Fig. 3. Plot of the daily inverses of serum creatinine after the angiogram and after resumption of therapy with the ACE inhibitor benazepril (arrows). The angiogram produced a mild, 5-day deterioration of renal function, probably because of the contrast dye (*see text*). Administration of benazepril normalized blood pressure, but led to sudden marked deterioration of renal function. It is apparent from the graph that 1 and 2 days after this complication, there was evidence for minimal, but unequivocal, recovery of renal function. Therefore, benazepril was continued (*see text*).

eruli, tubulo-glomerular feedback, and the direct action of Ang II on sodium reabsorption at the proximal tubule also lead to antinatriuresis. These changes result in a sodium-retaining state that is inappropriate to the hypertension. Furthermore, this sodium-retaining state fails to completely suppress plasma renin activity, which is continuously driven by afferent arteriolar “stenoses” (17).

In addition to the anatomical abnormality of hypertensive nephrosclerosis (a combination of smooth muscle hypertrophy and fibrosis of the afferent arteriole), there is also superimposed afferent arteriolar vasoconstriction during severe hypertension (18), in part mediated by circulating vasoconstrictors and

also because of tubulo-glomerular feedback. As a consequence of this, autoregulation of renal blood flow is altered in hypertension and reduction of BP may lead to significant worsening of GFR. This is true for BP reduction of any magnitude, produced by any antihypertensive drug, but the severity of the phenomenon increases with the degree of preexisting BP elevation and involvement of the renal vasculature. For example, in accelerated or malignant hypertension, normalization of BP may lead to elevations of creatinine indistinguishable from those of acute renal failure. However, resetting of the autoregulatory curve by correction of the hypertension leads to a progressive decrease in serum creatinine over the ensuing 6–12 wk, until a plateau (indicating the degree of residual renal dysfunction because of “scarring” of the fibrinoid necrosis) is reached (19). Although the deterioration of GFR by BP reduction is independent of the type of agent utilized, efferent arteriolar dilatation by ACE inhibitors will tend to exaggerate it beyond what would be expected from BP reduction alone. An analogous mechanism explains the reports on ACE inhibitor-induced acute renal failure in bilateral renal artery stenosis, a situation in which both kidneys are unable to compensate for the decrease in filtration fraction with an increase in renal blood flow, not due to a problem with autoregulation, but to the stenoses of the main renal arteries themselves (20).

Our patient most likely had essential hypertension preceding the establishment of renal artery stenoses, as supported by lack of “cure” of the hypertension by the angioplasty. Therefore, he most likely had hypertensive nephrosclerosis preceding the period of hemodynamic “protection” of his glomeruli by the trans-stenotic gradients. Once the latter were abolished by the angioplasty, his compromised renal arterioles were exposed to a systemic BP that had been normalized by drugs. This most likely accounted for the period of nonoliguric acute renal failure that followed administration of benazepril. Although he had tolerated ACE inhibitors before the revascularization procedure (i.e., with bilateral renal artery stenoses), it is conceivable that part of his renal dysfunction was because of their use. The reason by which GFR was more profoundly altered during exposure of afferent arterioles to normal systemic pressure (i.e., abnormal autoregulation after angioplasty) than during the period of bilateral artery stenoses when the glomerular vessels were exposed to even lower (postgradient) pressures, remains unresolved, but may be linked to transient, concomitant, dye-induced tubulointerstitial damage.

## **4. The Role of Angiotensin II in the Long-Term Protection of Glomerular Function**

### **4.1. Long-Term Follow-Up and Outcomes**

In view of the fact that abrupt deterioration of renal function by use of benazepril and normalization of BP was expected, and because of confirma-



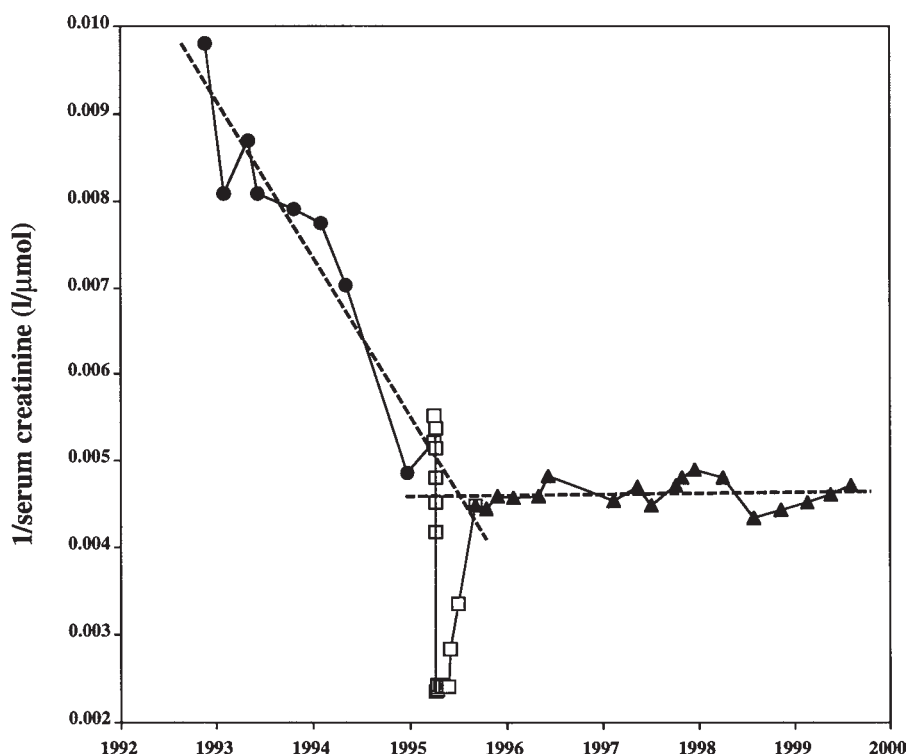


Fig. 4. Data from previous figures (filled circles = spontaneous progression of renal dysfunction before therapy, and open squares = detrimental effects of the angiogram and benazepril on renal function) are followed by the long-term course of renal function until the present (filled triangles). In addition to the arrest of the progression of renal dysfunction (abolition of the slope of  $1/\text{serum creatinine}$  over time), the graph depicts the point of intersection between the predicted (before intervention) and actual (long-term after intervention) regression lines, which occurred in early July 1995. This demonstrates that despite the complications of therapy, and soon after them, the patient's renal function was better than it would have been if left to its spontaneous progressive deterioration. This observation supports an aggressive approach to the management of ischemic nephropathy, as advocated by many.

tion of some improvement of serum creatinine over the next few days (**Fig. 3**), we did not decrease dosages or change antihypertensive medication. **Figure 4** shows that this led to progressive improvement of renal function, to the level before angioplasty. More importantly, the long-term progression of renal dysfunction was arrested, as shown by the zero (i.e., horizontal) slope adopted by the line depicting inverse of serum creatinine over time, once maximum improvement was achieved. The dotted line, extrapolating the previous slope

(i.e., loss of renal function before therapy) crosses the actual line in early July 1995, indicating that soon after the abrupt, but transient, deterioration of renal function by the angiogram and the ACE inhibitor, the patient was better off than he would have been left to his spontaneous course. This arrested progression of renal dysfunction has now lasted 4 yr. Thus, aggressive management of the problem, despite its risks (i.e., cholesterol embolism due to angioplasty, dye-induced nephrotoxicity, and ACE inhibitor-induced decompensation of glomerular hemodynamics), was well warranted and resulted in long-term benefit retarding the functional consequences of progressive hypertensive nephrosclerosis. The patient leads an active productive life and his BP remains well controlled on the benazepril-containing regimen. There has been no evidence for restenosis, a relatively frequent phenomenon after angioplasty, and one that has made primary stenting of the renal arteries the currently preferred method of treatment in many medical centers (21).

#### **4.2. Progression of Glomerular Dysfunction and Its Prevention in Experimental and Human Renal Disease**

It has long been known that glomerular damage of any cause, with significant loss of renal mass, leads to inexorable progression of renal dysfunction despite resolution of the initial etiologic factor. Hyperperfusion and increased pressure in the remnant, unaffected nephrons, are thought to have a major role in this progression. Among all experimental models in which this has been tested, perhaps the most important one is the rat with surgically induced renal mass reduction. In this model, hyperperfusion of the remnant glomeruli is produced by 5/6 nephrectomy; therefore, no other factor (e.g., inflammatory or metabolic) but redistribution of renal blood flow to a reduced remnant renal mass may be invoked in the causation of progressive renal dysfunction (17).

ACE inhibitors, by dilating preferentially the efferent arteriole and thus reducing intraglomerular pressure, slow down the progression of renal dysfunction in rats with reduced renal mass, independent of or beyond the effect that can be obtained by reducing arterial pressure with an agent that does not preferentially dilate the efferent arteriole (22). This observation has been replicated in many other experimental models of renal damage, where the noxious stimulus was of immunologic, metabolic, or hypertensive nature (23,24).

Investigation of the mechanisms by which glomerular hypertension ultimately leads to mesangial proliferation and glomerular sclerosis, the anatomic hallmarks of progression of renal dysfunction of any cause, led to the unraveling of another role for Ang II in the progression of renal disease. Hence, it became apparent that this peptide acts as a growth factor, with mitogenic effects resulting in glomerular endothelial and mesangial proliferation (25,26), and gene-stimulatory effects leading to fibroblast and mononuclear cell activation.

The latter effect leads to increased deposition of collagen I and III, fibronectin, vitronectin, and laminin (24), and other components of intercellular matrix. Multiple intracellular mediators for these actions of Ang II have been uncovered, such as TGF-beta (27), PDGF (28), nuclear factor-kappa B (29), and VEGF (30). Actions of Ang II or smaller angiotensin peptides on the coagulation cascade (e.g., stimulation of PAI-1) may also contribute via local thrombosis of the microcirculation (31). MAP kinase signal transduction pathways and overexpression of proto-oncogenes (32) participate in Ang II-stimulation of glomerular cell growth and proliferation.

All the actions of Ang II as a growth factor are mediated by its AT1 receptor and are, therefore, amenable to pharmacologic manipulation by means of either ACE inhibitors or the newer angiotensin AT1-receptor blockers (ARBs). In contrast to decreased generation of Ang II caused by ACE inhibitors, ARBs produce feedback increases in circulating Ang II, while blocking its actions on the AT1 receptor. Whether increased Ang II by ARBs confers an advantage to these agents by stimulation of the spared AT2 receptor (putatively involved in vasodilation and antiproliferation) is yet to be proved.

The theoretical advantages of pharmacologic interruption of the RAS in hypertensive or normotensive renal disease with threatened progression of renal dysfunction have been explored by clinical trials in humans. There is little doubt that ACE inhibitors retard the progression of renal disease in normotensive diabetic patients with microalbuminuria (33). A specific role for these agents in improving progression of renal disease in hypertensive diabetic patients is somewhat more controversial (34), perhaps because of the important independent role of systemic BP in determining the course of renal disease in these patients. In primary, severe (35) or mild (36) glomerulopathies, therapy with ACE inhibitors also slows the rate of progression of renal dysfunction. In contrast, there is not yet incontrovertible evidence for renal protection by pharmacological interruption of the RAS in hypertensive nephrosclerosis. Proof may emerge from ongoing trials such as the NIDDK-sponsored African American Study of Kidney Disease and Hypertension (AASK), which will compare the renal protective effects of different antihypertensive drug classes, or the industry-sponsored RENAAL, which assesses the effect of the ARB losartan on renal protection in hypertension. In the absence of a definitive clinical trial, but taking into consideration that the mechanisms involved in progression of renal damage seem to be common to all etiologies, we extrapolated the knowledge obtained in diabetic and other glomerulopathies to the aggressive approach we employed in our patient. The excellent result we obtained is hopefully a preview of the results to be obtained in the clinical trials testing for the effects of pharmacologic interruption of the RAS in human hypertensive nephrosclerosis.

## 5. Conclusion

Understanding of the role of the RAS in the causation of unilateral and bilateral renovascular hypertension in humans, knowledge about the role of Ang II as a regulator of acute glomerular hemodynamic changes, and information about the hemodynamic and tissue (growth factor) roles of Ang II in determining long-term progression of glomerular damage, allowed for the therapeutic decisions that led to a successful outcome in the complex hypertensive patient presented here.

A myriad of other patients are already deriving benefit from other aspects of research in the renin-angiotensin field. Examples include prolongation of survival in congestive heart failure and secondary prevention of coronary artery disease (37,38), and arrest or improvement in the progression of renal damage in diabetic (33) and nondiabetic glomerulopathies (35,36). Ongoing studies are also exploring effects of ACE inhibition on primary prevention of myocardial infarction (39), ARBs on regression of hypertensive left ventricular hypertrophy (40), and also ARBs on reduction of overall cardiovascular morbidity-mortality in unselected but complicated hypertensive patients (41). These studies, as well as the AASK study on progression of hypertensive nephrosclerosis in African Americans, may further extend the payoff of research in the field of RAS for the benefit of human cardiovascular disease prevention and therapy.

## References

1. Page, I. H. and Helmer, O. M. (1939) A crystalline pressor substance, angiotensin, resulting from reaction of renin and renin activator. *Proc. Soc. Clin. Invest.* **12**, 17.
2. Munoz, M. J., Braun-Menendez, E., Fasciolo, J. D., and Leloir, L. F. (1939) Hypertensin: the substance causing renal hypertension. *Nature* **144**, 980.
3. Maxwell, M. H., Bleifer, K. H., Franklin, S. S., and Varady, P. D. (1972) Cooperative study of renovascular hypertension: demographic analysis of the study. *JAMA* **220**, 1195-1204.
4. Working Group on Renovascular Hypertension. Detection, evaluation and treatment of renovascular hypertension. (1987) *Arch. Intern. Med.* **147**, 820-829.
5. Dean, R. H., Tribble, R. W., Hansen, K. J., O'Neil, E. A., Craven, T. E., and Redding, J. F. (1991) Evolution of renal insufficiency in ischemic nephropathy. *Ann. Surg.* **213**, 446-456.
6. Davies, D. F. and Shock, N. W. (1950) Age changes in glomerular filtration rate, effective renal plasma flow, and tubular excretory capacity in adult males. *J. Clin. Invest.* **29**, 496.
7. Lindeman, R. D., Tobin, J. D., and Shock, N. W. (1984) Association between blood pressure and the rate of decline in renal function with age. *Kidney Int.* **26**, 861-868.

8. Levy, S. B., Talner, L. B., Coel, M. N., Holle, R., and Stone, R. A. (1978) Renal vasculature in essential hypertension: racial differences. *Ann. Intern. Med.* **88**, 12–16.
9. Bell, E. T. (1953) Renal vascular disease in diabetes mellitus. *Diabetes* **2**, 376.
10. Gavras, H., Brunner, H. R., Thurston, H., and Laragh, J. H. (1975) Reciprocation of renin dependency with sodium volume dependency in renal hypertension. *Science* **188**, 1316–1317.
11. Gavras, H., Brunner, H. R., Vaughan, E. D., and Laragh, J. H. (1973) Angiotensin-sodium interaction in blood pressure maintenance of renal hypertensive and normotensive rats. *Science* **180**, 1369–1372.
12. Mann, S. J. and Pickering, T. G. (1992) Detection of renovascular hypertension: state of the art, 1992. *Ann. Intern. Med.* **117**, 845–853.
13. Myers, B. D., Deen, W. M., and Brenner, B. M. (1975) Effects of norepinephrine and angiotensin II on the determinants of glomerular ultrafiltration and proximal fluid reabsorption in the rat. *Circ. Res.* **37**, 101–110.
14. Mann, S. J., Pickering, T. G., Sos, T. A., Uzzo, R. G., Sarkar, S., Friend, K., et al. (1991) Captopril renography in the diagnosis of renal artery stenosis: accuracy and limitations. *Am. J. Med.* **90**, 30–40.
15. Tullis, M. J., Zierler, R. E., Caps, M. T., Bergelin, R. O., Cantwell-Gab, K., and Strandness, D. E., Jr. (1998) Clinical evidence of contralateral renal parenchymal injury in patients with unilateral atherosclerotic renal artery stenosis. *Ann. Vasc. Surg.* **12**, 122–127.
16. Castleman, B. and Smithwick, R. H. (1943) The relation of vascular disease to the hypertensive state based on a study of renal biopsies from one hundred hypertensive patients. *JAMA* **121**, 1256.
17. Brenner B. M., Meyer T. W., and Hostetter T. H. (1982) Dietary protein intake and the progressive nature of kidney disease: the role of hemodynamically mediated glomerular injury in the pathogenesis of progressive glomerular sclerosis in aging, renal ablation, and intrinsic renal disease. *New Engl. J. Med.* **307**, 652–659.
18. Hollenberg, N. K., Adams, D. F., Solomon, H., Chenitz, W. R., Burger, B. M., Abrams, H. L., et al. (1975) Renal vascular tone in essential and secondary hypertension: hemodynamic and angiographic responses to vasodilators. *Medicine* **54**, 29–44.
19. Lawton, W. J. (1982) The short-term course of renal function in malignant hypertensives with renal insufficiency. *Clin. Nephrol.* **17**, 277–283.
20. Textor, S. C., Novick, A. C., Tarazi, R. C., Klimas, V., Vidt, D. G., and Pohl, M. (1985) Critical perfusion pressure for renal function in patients with bilateral atherosclerotic renal vascular disease. *Ann. Intern. Med.* **102**, 308–314.
21. Tuttle, K. R., Chouinard, R. F., Webber, J. T., Dahlstrom, L. R., Short, R. A., Henneberry, K. J., et al. (1998) Treatment of atherosclerotic ostial renal artery stenosis with the intravascular stent. *Am. J. Kidney Dis.* **32**, 611–622.
22. Ots, M., Mackenzie, H. S., Troy, J. L., Rennke, H. G., and Brenner, B. M. (1998) Effects of combination therapy with enalapril and losartan on the rate of progression of renal injury in rats with 5/6 renal mass ablation. *J. Am. Soc. Nephrol.* **9**, 224–230.

23. Goyal, R. K., Satia, M. C., Bangaru, R. A., and Gandhi, T. P. (1998) Effect of long-term treatment with enalapril in streptozotocin diabetic and DOCA hypertensive rats. *J. Cardiovasc. Pharmacol.* **32**, 317–322.
24. Nakamura, T., Obata, J., Kimura, H., Ohno, S., Yoshida, Y., Kawachi, H., et al. (1999) Blocking angiotensin II ameliorates proteinuria and glomerular lesions in progressive mesangioproliferative glomerulonephritis. *Kidney Int.* **55**, 877–889.
25. Wolf, G., Ziyadeh, F. N., Zahner, G., and Stahl, R. A. (1996) Angiotensin II is mitogenic for cultured rat glomerular endothelial cells. *Hypertension* **27**, 897–905.
26. Weiss, R. H. and Ramirez, A. (1998) TGF-beta- and angiotensin-II-induced mesangial matrix protein secretion is mediated by protein kinase C. *Nephrol. Dialysis Transplant.* **13**, 2804–2813.
27. Ruiz-Ortega, M. and Egido, J. (1997) Angiotensin II modulates cell growth-related events and synthesis of matrix proteins in renal interstitial fibroblasts. *Kidney Int.* **52**, 1497–510.
28. Hanada, M., Saito, E., Kambe, T., Hagiwara, Y., and Kubo, T. (1999) Evidence for the involvement of platelet-derived growth factor in the angiotensin II-induced growth of rat vascular smooth muscle cells. *Biol. Pharm. Bull.* **22**, 137–141.
29. Ruiz-Ortega, M., Bustos, C., Hernandez-Presa, M. A., Lorenzo, O., Plaza, J. J., and Egido, J. (1998) Angiotensin II participates in mononuclear cell recruitment in experimental immune complex nephritis through nuclear factor-kappa B activation and monocyte chemoattractant protein-1 synthesis. *J. Immunol.* **161**, 430–439.
30. Gruden, G., Thomas, S., Burt, D., Zhou, W., Chusney, G., Gnudi, L., et al. (1999) Interaction of angiotensin II and mechanical stretch on vascular endothelial growth factor production by human mesangial cells. *J. Am. Soc. Nephrol.* **10**, 730–737.
31. Wilson, H. M., Haites, N. E., and Booth, N. A. (1997) Effect of angiotensin II on plasminogen activator inhibitor-1 production by cultured human mesangial cells. *Nephron* **77**, 197–204.
32. Hamaguchi, A., Kim, S., Yano, M., Yamanaka, S., and Iwao, H. (1998) Activation of glomerular mitogen-activated protein kinases in angiotensin II-mediated hypertension. *J. Am. Soc. Nephrol.* **9**, 372–380.
33. Ravid, M., Lang, R., Rachmani, R., and Lishner, M. (1996) Long-term renoprotective effect of angiotensin-converting enzyme inhibition in noninsulin-dependent diabetes mellitus: a 7-year follow-up study. *Arch. Intern. Med.* **156**, 286–289.
34. UK Prospective Diabetes Study Group. (1998) Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complication in type 2 diabetes: UKPDS 39. *Brit. Med. J.* **7160**, 713–720.
35. Ruggenti, P., Perna, A., Gherardi, G., Gaspari, F., Benini, R., and Remuzzi, G. [on behalf of Gruppo Italiano di Studi Epidemiologici in Nefrologia (GISEN)]. (1998) Renal function and requirement for dialysis in chronic nephropathy patients on long-term ramipril: REIN follow-up trial. *Lancet* **352**, 1252–1256.
36. Ruggenti, P., Perna, A., Gherardi, G., Garini, G., Zoccali, C., Salvadori, M., et al. (1999) Renoprotective properties of ACE-inhibition in non-diabetic nephropathies with non-nephrotic proteinuria. *Lancet* **354**, 359–364.

37. The SOLVD Investigators. (1991) Effect of enalapril on survival in patients with reduced left ventricular ejection fractions and congestive heart failure. *New Engl. J. Med.* **325**, 293–302.
38. Pfeffer, M. A., Braunwald, E., Moye, L. A., Basta, L., Brown, E. J., Jr., Cuddy, T. E., et al., on behalf of the SAVE Investigators. (1992) Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. *New Engl. J. Med.* **327**, 669–677.
39. Lees, R. S., Pitt, B., Chan, R. C., Holmvang, G., Dinsmore, R. E., Campbell, L. W., et al. (1996) Baseline clinical and angiographic data in the Quinapril Ischemic Event (QUIET) Trial. *Am. J. Cardiol.* **78**, 1011–1016.
40. Dahlof, B., Devereux, R. B., Julius, S., Kjeldsen, S. E., Beevers, G., de Faire, U., et al. [for the LIFE study group]. (1998) Characteristics of 9194 patients with left ventricular hypertrophy: the LIFE study. Losartan Intervention For Endpoint Reduction in Hypertension. *Hypertension* **32**, 989–997.
41. Mann, J. and Julius S. (1998) The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial of cardiovascular events in hypertension. Rationale and design. *Blood Pressure* **7**, 176–183.



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