parameter more easily affected by the avoidance of myograph-assisted technique) was the determining factor in the increased M:L ratio values.

Nevertheless, the reduction observed in the M:L ratio was about 15%, reasonably close to the reduction of about 20% observed in other studies.[3] Unfortunately, the baseline (before-treatment) M:L ratio was significantly higher in the losartan-treated group than in the amlodipine-treated group (see Table 2 in Gómez-Garre *et al.*[5]), and although it may be argued that the differences between losartan and amlodipine are even more remarkable because the former was applied to patients with more severe cases, comparison of the effects of two treatments on a given variable is difficult when the starting characteristics of the variable are not similar.

As noted by the authors[5], CTGF, TGFβ, and collagen IV expressions were not reduced by losartan treatment; rather, this drug prevented the increase observed with amlodipine treatment. Interestingly, the expression of collagen III was reduced by both treatment schedules.

The villain role of amlodipine is, at least to me, somewhat unexpected, as *in vitro* studies have shown that amlodipine inhibits proliferation of vascular smooth muscle cells,[8] downregulates expression of collagens, and increases collagenase type IV activity.[9] Inasmuch as the spontaneous evolution of cytokine expression in the resistance arterioles of patients with well-controlled mild essential hypertension is unknown (it would be unethical to withhold antihypertensive treatment for 1 year), the conclusion that losartan prevented, or that amlodipine caused, an increment in cytokine expression is open to question. Nevertheless, this important study discloses discordant effects of two well-accepted treatments of essential hypertension on the structural changes of resistance arterioles. Taken together with previously reported investigations and recent clinical studies,[10] these results would speak in favor of the use of AT_1 receptor blockers in this condition and underline the need of further studies to define the effects of antihypertensive drugs on arterial remodeling.

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ACE inhibition and glomerular repair: restructuring or regeneration?

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In this issue of *Kidney International*, Andrea Remuzzi *et al.* convincingly demonstrate glomerular repair in spontaneous renal disease by ACE inhibition. These findings provoke questions about how ACE inhibition (or AT1R blockade) can on the one hand actually repair some diseased kidneys while on the other interfering with normal renal development or the recovery of other diseased kidneys.

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Suppression of angiotensin formation by angiotensin-converting enzyme (ACE) inhibitors or blockade of the angiotensin II receptor type 1 (AT1R) can induce regression of injury in patients with non-diabetic or diabetic proteinuric nephropathy.[1] Regression of glomerular injury by ACE inhibition or AT1R blockade has also been shown in rodents, both in spontaneous models of renal disease such as in aging and in the Munich Wistar Frömter (MWF) rat,[2] and in diverse experimental models including puromycin aminonucleoside nephropathy, chronic nitric oxide synthase inhibition, and five-sixths nephrectomy.[3] In this issue, Dr. Andrea Remuzzi and his colleagues go one step further and convincingly demonstrate glomerular repair.[4]

Remuzzi *et al.* found that the extent of glomerular damage in MWF rats at 60 weeks of age, after 10 weeks of ACE

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inhibition starting at 50 weeks of age, was significantly less than that in 50-week-old MWF rats. Proteinuria fell and renal function remained constant. Presumably, arterial pressure also fell to normal levels during ACE inhibition,[2] although this was not confirmed in the old rats in the present study. Age-matched MWF rats showed progressive proteinuria and increased serum creatinine over this 10-week period, and, at 60 weeks, much more glomerulosclerosis expressed as volume of the tuft. Complete analysis of individual tufts led to the conclusion that in this model ACE inhibition truly appears to effect glomerular repair. This contrasts with our findings in fawn-hooded hypertensive (FHH) rats, in which withdrawal of ACE inhibition revealed that further development of previously established glomerular damage could not be prevented despite lowering of glomerular capillary pressure.[5]

Interestingly, glomerular repair in MWF rats happens without any decrease in glomerular tuft volume, despite the fact that systemic arterial and glomerular capillary pressures are known to fall in this model during ACE inhibition.[2] This is at variance with the fall in mean glomerular tuft volume observed in rats with subtotal nephrectomy (SNX) in which ACE inhibition was initiated after 8 weeks.[3] In the latter study, by Adamczak *et al.*, tuft volume was lower after 12 weeks of SNX in combination with ACE inhibition for the last 4 weeks, than after 8 weeks of SNX. However, tuft volume after SNX and late ACE inhibition remained higher than in sham controls,[3] despite the fact that ACE inhibition is known to reduce glomerular capillary pressure in this model. Thus, ACE inhibition can support regression of glomerular damage both with and without effects on glomerular tuft volume.

Remuzzi *et al.*[4] used elegant three-dimensional reconstruction of individual glomerular capillary tufts based on serial sections of 15 to 20 glomeruli per rat with a total of 100 glomeruli per group. In these aged MWF rats, this striking technique revealed that after 10 weeks of ACE inhibition, at 60 weeks of age, more than 20% of glomeruli were completely free of sclerosis, whereas at 50 weeks of age practically no glomeruli had been free of some degree of sclerosis. This observation strongly suggests that space previously occupied by glomerulosclerosis was now occupied by new capillary tissue. The question is: How does this happen?

The three-dimensional reconstruction technique does not provide information on glomerular components at the cellular level. This prohibits insight into repair mechanisms. The authors document a reduction in glomerular staining of TGFβ and α-smooth muscle actin, which suggests that ACE inhibition reduced glomerular matrix. Indeed, it is well known that angiotensin acts as a mitogen on mesangial cells. However, repair restricted to the mesangial compartment cannot fully explain tuft repair. There may also be effects on podocyte number, but their quantitative contribution is unknown in situations where injury is reversible. Improved endothelial-cell function and enhanced angiogenesis might explain a beneficial effect of ACE inhibition; however, whether such an effect of ACE inhibition[6] may be extrapolated to the glomerular endothelium or glomerular capillary repair (angiogenesis) is unknown.

ACE inhibitors may also affect progenitor cells of the bone marrow. In various experimental models, bone marrow progenitor cells have been shown to differentiate into glomerular endothelial cells, mesangial cells,[7] and podocytes and to contribute to glomerular repair. Angiotensin II has been shown to accelerate endothelial progenitor cell senescence via increased oxidative stress.[8] Both ACE inhibition and AT1R blockade enhanced the number of regenerative endothelial progenitor cells in patients at increased cardiovascular risk.[9]

Effects of AT1R blockade and ACE inhibition on vascular structure in the kidney, either on locally residing cells (angiogenesis) or on progenitor cells (vasculogenesis), are not restricted to the glomerulus. In the developing kidney, loss of signaling by angiotensin gives rise to vascular hypertrophy. This has been observed in mice lacking angiotensinogen, ACE, or AT1Rs, and in normotensive and hypertensive rats after ACE inhibition or AT1R blockade.[10] It is interesting in this regard that, in mice with selective ablation of renin-expressing juxtaglomerular cells, no abnormalities in renal arteriolar dimensions were observed, which contrasts with findings in all of the other mice with angiotensinogen, ACE or AT1R gene deletion.[11] Thus, inhibition of the actions of angiotensin has been associated with vascular hypertrophy. Because renin levels will be high under these conditions, renin may be a primary factor in the pathogenesis of this hypertrophy. There appear to be direct interactions between renin and vascular endothelial growth factor in glomerular angiogenesis and renal arteriogenesis.[12] Similar vascular changes were observed in the kidneys of Fischer donor rats after transplantation into Lewis recipient rats treated with ACE inhibition or AT1R blockade.[13] Thus, angiotensin II appears to be crucial not only in embryonic renal development but also in certain phases of adult renal repair. Interestingly, specific adult repair mechanisms mimic, to some extent, the development of the glomerular tuft during ontogeny. Indeed, angiotensin II infusion accelerated renal repair in the early phase of experimental glomerulonephritis.[14]

The complexity of repair is illustrated by the finding of a marked, progressive increase in the number of glomerular capillaries and endothelial cells in parallel with glomerular hypertrophy in the SNX model, without much change in capillary density per unit volume of tuft, or in endothelial-cell number per capillary. This suggests that, at least in SNX, increased endothelial-cell numbers and hence capillary hyperplasia parallel glomerular injury. This process appeared to be reversed by ACE inhibition.[3] Thus, new questions are spawned by these studies on glomerular repair: Is the local mitotic index reduced, or is there less recruitment of bone marrow-derived stem cells? How does ACE inhibition under certain conditions increase but under others decrease glomerular endothelial-cell number? Such a

dichotomy has recently been observed in other vascular beds with ACE inhibition in type 1 diabetic mice.[15] Perhaps, in glomerular injury, inhibition of endothelial-cell contact — or, in renal development, incomplete establishment of a contiguous endothelial-cell layer — dictates the actions of angiotensin and hence ACE inhibition.

Hopefully, this Commentary will stimulate the reader to wonder about how ACE inhibition (or AT1R blockade) can on the one hand actually repair some diseased kidneys but on the other hand interfere with normal renal development or the recovery of other diseased kidneys. Certainly studies such as those by Dr. Remuzzi and his colleagues should not be dismissed as being about 'just another rat with proteinuria that's cured by ACE inhibition'.

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Non-*Pseudomonas* Gram-negative peritonitis

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Non-*Pseudomonas* Gram-negative organisms account for over 10% of cases of peritoneal dialysis-associated peritonitis. The key findings from a paper by Szeto *et al.* are discussed and compared with those from previous publications. This type of peritonitis has a high rate of catheter removal and technique failure. Results may be better with more aggressive antibiotic treatment. Other developments in the field are reviewed.

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The superiority of the well-done randomized controlled trial over all other forms of clinical studies is widely accepted and understood. However, the relative rarity of such trials in the dialysis literature is also well recognized. There are many areas of dialysis practice where randomized trials have not been carried out or are not feasible. Therefore, the continuing importance of other forms of clinical investigations should not be forgotten. This includes the old-fashioned retrospective review of clinical experience with a large number of cases of a given condition. The article by Szeto *et al.*[1] in this issue is an excellent example.

The topic is peritoneal dialysis (PD)-related peritonitis due to Enterobacteriaceae organisms. The investigators review a decade's experience in a single large Hong Kong center with a total of 210 cases. This is the largest reported series to date of cases of what is sometimes termed non-*Pseudomonas* Gram-negative (NPGN) peritonitis.[2] The paper provides a wealth of important and helpful clinical observations, and, taken together with two earlier papers from the Unites States, it enhances our knowledge of this important condition.[2,3]

Peritonitis remains the single biggest cause of technique failure in PD. Advances over the past two decades in connectology and in *Staphylococcus aureus* prophylaxis have led to impressive decreases in the rates of

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