Salt-Sensitive Hypertension Develops After Short-Term Exposure to Angiotensin II

Donna Lombardi, Katherine L. Gordon, Patti Polinsky, Shinichi Suga, Stephen M. Schwartz, Richard J. Johnson

Abstract—We hypothesized that short-term exposure to angiotensin II (Ang II) could result in structural and functional changes in the kidney that would favor sodium retention and the development of sustained hypertension. To test this hypothesis, rats were exposed to pressor doses (435 ng · kg⁻¹ · min⁻¹) of Ang II for 2 weeks. The infusion of Ang II was associated with acute hypertension, renal dysfunction, proteinuria, and focal tubulointerstitial and vascular damage. At sites of the tubulointerstitial damage, there was a reduction in peritubular capillary endothelial cell staining. By use of immunostaining, we found focal loss of endothelial nitric oxide synthase (eNOS) in the peritubular capillaries at sites of injury and a generalized reduction in eNOS in collecting ducts, thin loops of Henle, and vascular bundles in the medulla. When the Ang II infusion ended, the rats became normotensive and renal function returned toward normal. However, exposure of the rats to high salt diet (4% NaCl) resulted in the redevelopment of hypertension after 3 to 4 weeks. Rats maintained on a high salt diet with no prior exposure to Ang II and rats placed on low salt diet (0.1% NaCl) after exposure to Ang II remained normotensive. Thus, we report a new model of salt-sensitive hypertension induced by transient exposure to pressor doses of Ang II. The mechanism may relate to microvascular injury with peritubular capillary loss coupled with functional changes, such as a loss in intrarenal nitric oxide formation, that could alter the ability of the kidney to excrete a salt load. (Hypertension. 1999;33:1013-1019.)

Key Words: angiotensin II ■ nitric oxide ■ capillaries, peritubular ■ hypertension, sodium-dependent

Studies performed nearly 50 years ago by Byrom and Wilson⁴ suggested that a transient period of angiotensin II (Ang II)–mediated hypertension could result in the permanent development of hypertension in rats. Using the 2-kidney, 1 clip Goldblatt model, in which acute hypertension is mediated by renin release from the ischemic (clipped) kidney, these authors found that early removal of the clip or surgical removal of the clipped kidney often results in rapid resolution of the hypertension. However, once sufficient vascular and tubulointerstitial (TI) injury occurred in the unclipped kidney, hypertension would persist despite removal of the ischemic kidney.¹ The authors suggested that this may cause a “vicious circle” in hypertension, in which renal injury induced by hypertension could lead to persistent hypertension, despite removal of the initiating source.

The possibility that transient exposure to Ang II can lead to persistent hypertension was also suggested by the studies of Koletsky et al.² These authors examined the short- and long-term effects of direct injection of Ang II into rats. Like others, they found that the infusion of Ang II results in transient hypertension followed by the rapid return of blood pressure (BP) to normal on cessation of the infusion. However, the authors reported that if injections of Ang II were administered over 6 to 10 days, the period of normotension that follows would be transient and permanent hypertension would develop after an average of 4 months. Recently, Zou et al³ also reported that elevated BP can persist for a number of days after rats are exposed to pressor doses of Ang II.

The mechanisms by which transient Ang II–mediated BP elevation can lead to persistent hypertension have not been completely elucidated in these studies. In the experiments using the Goldblatt model, hypertension was thought to result as a consequence of severe structural changes in the unclipped kidney.¹ However, severe structural changes in the unclipped kidney may not always be observed and often are only focal and mild, consisting of tubular atrophy and dilation, interstitial macrophage infiltration and collagen deposition, and a change in the phenotype of interstitial fibroblasts, in which they express contractile (α-smooth muscle actin) proteins.⁴,⁵ Evidence of vascular injury, such as afferent arteriolar sclerosis and hyalinosis, and glomerular changes are also present focally.¹,⁴ These histological findings are similar to what is found in kidneys of rats that have been administered exogenous Ang II.⁶

Recently, Johnson and Schreiner⁷ proposed a hypothesis for the development of some forms of salt-dependent hyper-

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tension in man. The hypothesis proposes that subtle injury to the peritubular capillaries (PTC) and tubulointerstitium of the kidney may result in both structural (PTC loss leading to a shift in the pressure natriuresis curve) and functional (ischemia induced alterations of vasoactive mediators leading to enhanced sodium reabsorption) changes that result in a sodium-retentive state and the development of hypertension. According to this hypothesis, PTC and TI injury could result secondary to the hemodynamic consequences of a hyperactive sympathetic nervous system or an activated renin-angiotensin system or by other mechanisms that could cause PTC and TI injury, such as toxins (lead) or drugs (cyclosporine).

We therefore decided to investigate whether short-term Ang II infusion could induce a persistent, salt-sensitive hypertension and to characterize some of the functional and structural changes that occur in this model (Table 1).

### Methods

#### Experimental Protocol

Male Sprague-Dawley rats (Zivic Miller, Allison Park, Pa) (300 to 400 g, n = 7 per group, groups I through IV) received Ang II (435 ng · kg⁻¹ · min⁻¹) for 2 weeks via subcutaneous osmotic minipumps (Alzet model 2002, Alza Corp) containing Ang II (Sigma Chemical Co) dissolved in Ringer’s lactate. During the initial 2 weeks, rats received 2 to 4 measurements per week. The BP value was recorded as the mean value of 3 separate measurements obtained at each session.

### BP Measurements

Systolic arterial BP measurements were performed in conscious, restrained rats by tail-cuff plethysmography (Narco Biosystems). Rats were conditioned twice before the experiment was initiated and received 2 to 4 measurements per week. The BP value was recorded as the mean value of 3 separate measurements obtained at each session.

### Renal Histological Studies

Methyl Carnoy’s fixed tissue was processed and paraffin-embedded, and 4-μm sections were stained with the periodic acid/Schiff reagent (PAS). An indirect immunoperoxidase method was used to identify the following antigens: osteopontin (OPN), with goat anti-OPN (OPN199) antibody (gift of C. Giachelli, University of Washington, Seattle, Wa); macrophages, with ED-1 (Harlan Bioproducts, Indianapolis, Ind); α-smooth muscle actin (a marker of smooth muscle cells and interstitial myofibroblasts), with 1A4 (Sigma Chemical Co); endothelial cells, with RECA-1 (Harlan Bioproducts); endothelial nitric oxide synthase (eNOS; NOS III), with mouse anti-eNOS (Transduction Labs, Lexington, Ky); and brain nitric oxide synthase (nNOS; NOS I), with rabbit anti-nNOS (Transduction Labs). TI injury was graded (grade 0 to 5) in a blinded manner based on the presence of tubular cellularity, basement membrane thickening, dilation, atrophy, sloughing, or interstitial widening, as follows: 0, no changes present and grade 1, <10%; grade 2, 10% to 25%; grade 3, 25% to 50%; grade 4, 50% to 75%; and grade 5, 75% to 100% TI involvement. For each biopsy, the entire cortical and juxtamedullary regions were evaluated (16 to 30 fields of 1 mm²) and a mean score per biopsy was calculated. A second TI injury score was based on observations that OPN expression by injured tubules is a sensitive marker of TI injury. Using computer-assisted image analysis software (Optimas, version 6.2, Media Cybernetics) and digitized images, the percentage area occupied by OPN-positive tubules (including the entire cortical and juxtamedullary regions, exclusive of glomeruli) was measured per field (4 mm² at ×50 and the mean % area was calculated for each biopsy. The number of macrophages (ED-1–positive cells) per ×200 field in the cortical and juxtamedullary regions and the number of nNOS-positive cells (counted at ×400) in the macula densa adjacent to glomeruli (n = 100 per biopsy) were also quantified.

Glomerular injury was graded for cellularity (grade 0 to 4), sclerosis (grade 0 to 4), and capillary tuft collapse (percentage), the last as a marker for glomerular ischemia. Glomerular collapse was defined as shrinkage of the glomerular tuft to one half the diameter of Bowman’s capsule. For each biopsy, all glomeruli (n > 140) were examined.

#### Digitized Images

Digitized images ranging from ×50 magnification to ×630 magnification were acquired using a Leica DMRB microscope fitted with a Microimage i308 low-light video camera with a 1/2-in HyperHAD high-density image sensor (World Video Sales), a computer with a Flashpoint video framegrabber board (Integral Technologies), and Optimas version 6.2 software. The very-low-power images (×7) were obtained by scanning the immunostained tissue directly from microscope slides using a Sprinscan 35 scanner enhanced with a PathScan enabler (Polaroid Corp) and Adobe PhotoShop software.

#### Additional Measurements

Serum creatinine was measured by picric acid (Jaffe) assay. Urinary protein was measured by sulfosalicylic acid assay with Labtrol (bovine serum albumin) as the protein standard.

#### Statistical Methods

Values are expressed as mean ± SE. A comparison between groups was made by ANOVA with the Fisher’s protected least significant difference test for multiple comparisons.

### Results

#### Exposure to Ang II Results in Salt-Dependent Hypertension

Blood pressures rose markedly with acute Ang II infusion and were most elevated at days 10 to 14 (Figure 1). BP rose in Ang II–infused rats on both high (groups I and II) and low (groups III and IV) salt diets, although the rats receiving the high salt diet achieved higher BP than those on a low salt diet at days 10 (P < 0.0001) and 14 (P = 0.0011).

After 2 weeks, the minipumps containing the Ang II were removed and BP returned to normal in all groups (Figure 1). Subsequently, rats were placed on a low or high salt diet for an additional 6 weeks. Three weeks after the

### Table 1. Group Protocols

<table>
<thead>
<tr>
<th>Group</th>
<th>Initial 2 Weeks</th>
<th>Subsequent 6 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Ang II + high salt diet</td>
<td>High salt diet</td>
</tr>
<tr>
<td>II</td>
<td>Ang II + high salt diet</td>
<td>Low salt diet</td>
</tr>
<tr>
<td>III</td>
<td>Ang II + low salt diet</td>
<td>High salt diet</td>
</tr>
<tr>
<td>IV</td>
<td>Ang II + low salt diet</td>
<td>Low salt diet</td>
</tr>
<tr>
<td>V</td>
<td>High salt diet</td>
<td>High salt diet</td>
</tr>
</tbody>
</table>

*Note: Ang II = Angiotensin II; salt diet = sodium-retentive state; TI = tubulointerstitial injury.*
A new diet was begun, elevated BP redeveloped in rats placed on a high salt diet; rats placed on a low salt diet remained normotensive (Figure 1). High salt diet elicited increased BP elevation in rats that had received a high salt diet during Ang II infusion (Figure 1A, group I) versus rats that had received a low salt diet during Ang II infusion (Figure 1B, group III). Control rats (group V), which received a high salt diet during the entire 8 week period but were not given the Ang II infusion, remained normotensive throughout the study.

Renal Histology at the End of the Ang II Infusion (2 Weeks)

As previously reported, Ang II infusion was associated with focal vascular and TI injury involving both the juxtamedullary region and the superficial cortex. Injury was greater in the rats on a high salt diet that received the Ang II infusion (groups III and IV) (Table 2). Glomeruli largely appeared normal in Ang II–infused rats and displayed minimal glomerular cellularity or sclerosis, although 5% to 6% of glomeruli showed capillary-tuft collapse consistent with glomerular ischemia (Table 2). Only control rats on a high salt diet displayed minimal or no glomerular, TI, or vascular injury (Table 2, group V).

The principal histological findings present at the end of the Ang II infusion are shown in Figure 2. Light microscopy (with PAS) showed focal areas of tubular dilation and atrophy, an infiltration of mononuclear cells into the interstitium, and some widening of the interstitial space (Figure 2). Rare preglomerular arterioles showed fibrinoid necrosis, especially in the rats that had received high salt diet during the Ang II infusion. The TI damage was associated with expression of OPN by the injured tubules and with a local infiltration of macrophages (Figure 2 and Table 2). The degree of OPN staining correlated both quantitatively ($r^2=0.75$, $P<0.0001$) and spatially with the
macrophage infiltration at 2 weeks and correlated with the degree of tubular injury by PAS at 2 weeks ($r^2=0.72$, $P<0.001$). As previously observed, the infusion of Ang II was also associated with the expression of $\alpha$-smooth muscle actin by interstitial fibroblasts, and these "myofibroblast-like" cells frequently surrounded dilated and damaged tubules.

An important new finding was the apparent loss of PTC at sites of TI injury. Using the RECA-1 antibody, which stains vascular endothelium, the PTC could be easily identified in control rats on a high salt diet (Figure 3). This lacy capillary network around tubules was also present in the normal-appearing cortex in rats that were administered Ang II. However, there was focal loss of RECA-1 staining in the areas of TI injury, which was most marked in the rats given both high salt and Ang II (groups I and II) (Figure 3).

The distribution of NOSs was examined by immunohistochemistry. The neuronal isoform (bNOS) was identified in the macula densa in all groups. Control rats only on a high salt diet (group V) had $97\pm14$ bNOS-positive macula densa cells per 100 glomeruli, which was lower but did not reach significance compared with normal rat tissue ($124\pm12$ cells per 100 glomeruli; $n=4$; $P=NS$, data not shown). Exogenous Ang II administered with a high salt diet was associated with a further decrease in bNOS-positive cells ($P<0.05$ versus group V, Table 2). In contrast, Ang II administered with a low salt diet had more (though not significant) bNOS-positive cells compared with rats only on a high salt diet (group V) (Table 2), a finding consistent with the known ability of a low salt diet to stimulate bNOS expression at this site.

The endothelial isoform of NOS (eNOS) was localized in normal rat tissue to the endothelium of the arteries and arterioles, to the glomerular endothelium, and to the PTC (light staining) (Figure 4). Staining of eNOS also occurred in collecting ducts, thin loops of Henle, the thick ascending limb, and vascular bundles in the outer medulla. In rats that received Ang II (on either a high or low salt diet), there was a loss of eNOS staining in the PTC at areas of TI damage (Figure 4). At these sites, occasional mononuclear cells with reactivity to the anti-eNOS antibody could be identified (Figure 4), consistent with reports that monocytes/macrophages also express eNOS. There also appeared to be a marked decrease in tubular eNOS staining in the medulla of the Ang II–infused rats (groups I to IV) involving the thin and thick loops of Henle, collecting ducts, and vascular bundles (Figure 4). In these rats, most of the eNOS reactivity was absent in the medullary tubules, although some residual staining was noted in occasional collecting ducts and in the vascular bundles.

<table>
<thead>
<tr>
<th>Group</th>
<th>Diet During Ang II Infusion</th>
<th>TI PAS, Grade 0–5</th>
<th>OPN, % Cortex</th>
<th>ED-1, cells/HP</th>
<th>Macula Densa bNOS, cells/100 glomeruli</th>
<th>Sclerosis, Grade 0–4</th>
<th>Cellularity, Grade 0–4</th>
<th>Collapse, % Glomeruli</th>
</tr>
</thead>
<tbody>
<tr>
<td>I and II*</td>
<td>High salt</td>
<td>3.7±0.1†</td>
<td>3.8±0.4†</td>
<td>36.0±5.6</td>
<td>66.5±6.7†</td>
<td>0.03±0.02</td>
<td>0.006±0.004</td>
<td>6.0±1.2†</td>
</tr>
<tr>
<td>III and IV‡</td>
<td>Low salt</td>
<td>2.8±0.2†</td>
<td>1.0±0.2</td>
<td>21.7±3.0†</td>
<td>109.0±1.5</td>
<td>0.01±0.00</td>
<td>0.003±0.003</td>
<td>4.7±1.2†</td>
</tr>
<tr>
<td>V (at 8 weeks)*</td>
<td>High salt§</td>
<td>0.9±0.1</td>
<td>0.2±0.1</td>
<td>7.2±1.2</td>
<td>97.0±13.6</td>
<td>0.02±0.00</td>
<td>0.010±0.007</td>
<td>0.2±0.2</td>
</tr>
</tbody>
</table>

*P<0.05 vs group V.

§Group V (control) rats did not receive Ang II.
Renal Function Changes at the End of the Ang II Infusion (2-Week Time Point)

Ang II infusion was associated with marked proteinuria, which was greatest in rats concurrently on a high salt diet (Table 3). Serum creatinine levels were also elevated at 2 weeks in all rats given Ang II and were greater in the rats on a high salt diet versus those on a low salt diet (Table 3).

Histological Changes and Renal Function at 8 Weeks (6 Weeks After Cessation of the Ang II Infusion)

Biopsies taken at 8 weeks showed evidence of partial resolution of the TI injury by PAS staining, but evidence of injury and fibrosis was still present (Table 4). However, the percentage area of OPN staining was substantially less and approached that observed in control rats (Table 4). ED-1–positive macrophage numbers were not significantly reduced at 8 weeks (Table 3). Most of the macrophages remaining at 8 weeks continued to be associated with the remaining areas of OPN expression. There also remained focal areas of decreased PTC (indicated by RECA-1 staining) in association with decreased eNOS staining in the cortex. Some decrease in eNOS staining in the medulla also remained, but in general the changes were milder than those observed at 2 weeks.

Along with the mild improvement in histology, resolution of the proteinuria and improvement in the serum creatinines was observed in all groups (Table 5). However, serum creatinine levels in groups I and II remained significantly higher than in group V (control) rats at the end of the study.

Discussion

Our hypothesis was that Ang II infusion should produce structural and functional changes in the kidney that could alter the ability of the kidney to excrete salt and lead to a salt-sensitive hypertension. To test this hypothesis, rats were infused with pressor doses of Ang II for 2 weeks. After this period, the infusion of Ang II was stopped and the rats became normotensive. Biopsies of the kidneys at this time demonstrated focal TI damage, PTC loss, and a decrease in eNOS immunostaining at the sites of TI injury. In addition, a
generalized reduction of eNOS immunoreactivity occurred in the medulla. Subsequent exposure of the rats to a high salt diet resulted in the redevelopment of hypertension within several weeks, whereas rats placed on a low salt diet remained normotensive, as did control rats, which were on a high salt diet but were never exposed to Ang II. Thus, a new model of salt-dependent hypertension could be induced in rats after only a short-term exposure to Ang II.

The development of hypertension after Ang II exposure was greater in rats that were administered a high salt diet than in those administered a low salt diet during the initial Ang II infusion. This may be due to the fact that Ang II–infused rats on a high salt diet had higher BP during the Ang II infusion, resulting in greater TI injury, proteinuria, and decreased renal function at the end of the infusion period. The mechanism by which the high salt diet augmented the Ang II effects could relate to the effects of volume expansion or the ability of high salt diet to upregulate angiotensin type I receptors in the kidney and to increase the renal vasoconstrictive effect of Ang II.12

The kidneys examined at the end of the Ang II infusion demonstrated focal injury primarily to the blood vessels and tubulointerstitium, with tubular atrophy, macrophage infiltration, and collagen deposition.6 Tubular expression of OPN, a macrophage chemotactic protein associated with TI injury, was also increased.8 The preglomerular arterial vessels (that is, the afferent arteriole and interlobular artery) demonstrated focal injury primarily to the blood vessels and tubulointerstitium, with tubular atrophy, macrophage infiltration, and collagen deposition.6 Tubular expression of OPN, a macrophage chemotactic protein associated with TI injury, was also increased.8 These histological findings are similar to what is observed in the unprotected (unclipped) kidney in the 2-kidney, 1 clip Goldblatt model14,15 and are also similar to what is observed in several other experimental and human conditions associated with salt-sensitive hypertension, such as occurs with cyclosporine, in aging, and in hypertensive African Americans.7

The mechanism for the development of hypertension after exposure to Ang II is of great interest. Ang II has multiple sites of action and can cause vascular smooth muscle hypertrophy and contraction, cardiac remodeling, stimulation of the sympathetic nervous system, and stimulation of aldosterone synthesis. While it is conceivable that one of these mechanisms could be operative, most studies have suggested that persistent BP elevation is mediated by the kidney.13,14 Indeed, the general hypothesis initially put forth by Borst and Borst-deGeus14 and later by Guyton15 that the defect in primary hypertension relates to a relative inability of the kidney to excrete salt has been confirmed in a variety of experimental and human settings.

It is possible that the renal mechanism for the development of hypertension may relate to the acute changes in the glomerular filtration rate induced by the Ang II infusion. Although serum creatinine levels improved in the period after Ang II infusion, values were still higher at the end of the study in groups I and II (rats initially administered high salt diet and Ang II) than group V (controls on high salt diet). Another possibility is that the development of hypertension after cessation of the Ang II infusion may relate to microvascular injury with focal PTC rarefaction that could be documented at the sites of TI injury. Damage to the PTC

### TABLE 3. Renal Function in Rats at End of Ang II Infusion

<table>
<thead>
<tr>
<th>Groups</th>
<th>Diet During Ang II Infusion</th>
<th>Creatinine (2 Weeks), mg/dL</th>
<th>Proteinuria (2 Weeks), mg/dL</th>
</tr>
</thead>
<tbody>
<tr>
<td>I and II*</td>
<td>High salt</td>
<td>0.88±0.05†</td>
<td>75±29</td>
</tr>
<tr>
<td>III and IV†</td>
<td>Low salt</td>
<td>0.73±0.09†</td>
<td>17±2</td>
</tr>
<tr>
<td>V‡§</td>
<td>High salt</td>
<td>0.50±0.07</td>
<td></td>
</tr>
</tbody>
</table>

* n=4 per group; † n=3 per group.
§Group V (control) rats did not receive Ang II.
||At 4 weeks.

### TABLE 4. Renal Histologic Findings at 8 Weeks (6 Weeks After Cessation of Ang II Infusion)

<table>
<thead>
<tr>
<th>Group</th>
<th>Diet During Ang II Infusion</th>
<th>OPN, % Cortex</th>
<th>ED-1, Cells/LPF</th>
<th>bNOS, Cells/100 Glomeruli</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>High salt</td>
<td>2.6±0.2*</td>
<td>0.3±0.1</td>
<td>27.4±3.1*</td>
</tr>
<tr>
<td>II</td>
<td>High salt</td>
<td>2.4±0.2*</td>
<td>0.7±0.3</td>
<td>23.5±2.7*</td>
</tr>
<tr>
<td>III</td>
<td>Low salt</td>
<td>2.9±0.2*</td>
<td>0.4±0.2</td>
<td>27.4±3.9*</td>
</tr>
<tr>
<td>IV</td>
<td>Low salt</td>
<td>1.7±0.2*</td>
<td>0.2±0.04</td>
<td>31.4±3.7*</td>
</tr>
<tr>
<td>V</td>
<td>High salt</td>
<td>0.9±0.1</td>
<td>0.2±0.1</td>
<td>7.3±1.3</td>
</tr>
</tbody>
</table>

LPF indicates low-power field. n=4 to 5 per group. Group V was not given Ang II. * P<0.05 vs group V.
could theoretically shift the pressure-natriuresis curve to the right. Also, we have recently documented focal PTC loss in aging rats\(^1\) in which salt-dependent hypertension also develops, and Bohle et al\(^\text{16}\) have reported that focal PTC loss is present in renal biopsies of patients with essential hypertension.

Our studies suggest that alterations in intrarenal nitric oxide (NO) production may be involved in the post Ang II hypertension. NO is a vasodilator that promotes natriuresis directly by affecting the renal tubule and indirectly by decreasing tubuloglomerular feedback sensitivity.\(^17\) Although we did not measure renal NO production, we did examine the expression for the constitutive enzymes (NOS) responsible for its synthesis. Interestingly, we noted a relative reduction in immunostaining for eNOS at sites of PTC loss as well as a marked loss of immunoreactivity in the medulla. Also, a significant reduction in bNOS expression was noted in the macula densa of rats that were initially administered Ang II while on a high salt diet, which was the group that became most hypertensive in the post–Ang II period in the presence of high salt diet. Although we noted occasional mononuclear cells expressing eNOS, the overall findings are consistent with observations in other experimental models of salt-sensitive hypertension in which it has been reported that intrarenal NO or NOS are reduced and that the elevated BP can be corrected by stimulation of NO synthesis with L-arginine.\(^8,18–20\)

Ang II infusion can also lead to intrarenal Ang II generation and accumulation\(^3,21\) as well as endothelin\(^22\) production, which could also be involved in the later development of hypertension.

In summary, we report a new model of salt-dependent hypertension induced by short-term (2-week) exposure of the rat to Ang II at pressor doses. Both structural (loss of PTC) and functional (loss of eNOS) changes occurred with the acute Ang II infusion that could contribute for the change in sodium avidity. One must conclude that a “vicious circle” as proposed originally by Byrom and Wilson\(^1\) may occur even when structural renal damage is not severe. This conclusion raises the interesting possibility that this type of mechanism may be important in other conditions associated with salt-dependent hypertension, such as the hypertension that occurs in African Americans or diabetics, with cyclosporine use, or with aging.

Acknowledgments

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References


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