Renal Cortical Blood Flow, Cortical Fraction, and Cortical Blood Volume in Hypertensive Subjects

By Alexander G. Logan, M.D., Manuel T. Velasquez, M.D., and Jay N. Cohn, M.D.

SUMMARY
In 15 patients with essential hypertension total blood flow to a single kidney (TRBF) was measured by a constant infusion indicator-dilution technic which had previously been validated in dogs. Indocyanine green indicator-dilution curves then were used to calculate the fraction of renal flow traversing the rapid (cortical) circulation and the blood volume in this cortical compartment. TRBF ranged from 152 to 1033 ml/min/1.73m² per kidney and was closely correlated with cortical flow (r = 0.99). The cortical fraction of TRBF ranged from 46 to 93% and varied directly with total flow (r = 0.69). Noncortical flow ranged from 12 to 85 ml/min/1.73m² per kidney and showed no correlation with TRBF. Cortical blood volume varied from 12 to 85 ml/1.73m² and also was closely correlated with TRBF (r = 0.93). These data suggest that diminished TRBF in hypertensive patients is due to reduction in cortical flow with preservation of noncortical (medullary) flow and reduction in cortical blood volume. The reduced cortical fraction of TRBF could be a factor in the renal functional abnormalities which occur in hypertension.

Additional Indexing Words: Indicator-dilution method, Indocyanine green, Flowmeter, Noncortical blood flow

The RENAL VASCULAR bed consists of two anatomically and functionally separate components, the cortical and medullary circulations. The cortical blood flow provides the source of glomerular filtration to short looped cortical nephrons, which have a limited reabsorptive capacity, and is characterized by a rapid intrarenal circulation time. The medullary blood flow traverses the glomeruli of juxtamedullary nephrons, whose long loops of Henle have a greater reabsorptive capacity, and passes into the vasa recta, which have a slow intrarenal transit time and play an important role in the renal concentrating mechanism.

Patients with essential hypertension exhibit impaired renal concentrating capacity, exaggerated natriuresis in response to a sodium load, and reduced total renal blood flow. Changes in intrarenal hemodynamics could be a factor in the renal functional abnormalities; however, methods for measuring the intrarenal distribution of blood flow in man have been limited.

Hollenberg et al. applied the inert gas-washout technic to the study of renal hemodynamics in hypertensive patients and found that the first exponential of the washout curve, which they equated with outer cortical flow, was reduced in patients with more severe renal involvement. However, this technic requires uncertain analysis of multiexponential washout curves, which may give erroneous results and provides results for flow only in terms of compartmental mass, which may be altered under certain conditions.

Reubi et al. and Takeuchi and his associates have computed the area of the tail of renal indicator-dilution curves, in an attempt to quantitate flow to the slowly circulating medullary compartment. However, this terminal portion of the curve may be influenced by recirculating dye and...
the method assumes that all of the indicator that enters the medulla leaves exponentially in a single circulation, a premise which has been shown to be false.16, 17

An indicator-dilution method for separating renal blood flow into cortical and noncortical components in anesthetized dogs was recently reported from this laboratory.18 The technic eliminates the problems inherent in the previously described dye methods but retains the benefit of having flow expressed in absolute terms. The present report describes the application of a technic based on similar principles to the study of intrarenal blood flow distribution in hypertensive patients.

Methods

The modified indicator-dilution technic previously described in dogs was based on the concept that the first exponential washout of a transrenal indocyanine green dye-dilution curve represents flow through the cortical circulation. This was confirmed by radioautographs of the kidney.19 When total renal blood flow is recorded simultaneously with a flowmeter, the fraction of injected indocyanine green recovered in the rapid flow compartment and the absolute flow in the cortical and noncortical circulations can be calculated.18

In order to adapt this technic to man it was necessary to utilize an independent method which could measure total renal blood flow in a single kidney. The constant infusion indicator-dilution technic described by Shaldon and his associates19 was utilized. Indocyanine green was infused into the renal artery at a constant rate. After a 30-min equilibration period blood was sampled simultaneously from the renal vein and from a peripheral artery. Plasma was analyzed for indocyanine green concentration with a Beckman DU spectrophotometer at a wave length of 810 mμ. Renal blood flow (RBF) in ml/min was calculated from the formula:

\[
RBF = \frac{1}{C_{rv} - C_s} \times \frac{1}{1 - Hct}
\]

where \(I\) is the infusion rate in mg/min and \(C_{rv}\) and \(C_s\) represent the concentration of dye in mg/ml in the renal vein and artery, respectively.

This method for measuring renal blood flow in a single kidney was evaluated initially in dogs in whom blood flow was measured simultaneously with a cannulating electromagnetic flow probe (Statham, Q series) in the renal vein. Twenty five simultaneous measurements of renal blood flow were made with flows ranging from 41 to 166 ml/min. The close agreement between directly measured flow and flow calculated from constant infusion data is illustrated in figure 1.

Studies were then performed on 21 hypertensive patients undergoing diagnostic aortography or renal vein catheterization. Informed consent for this additional procedure was obtained prior to each study. Six studies were discarded because reproducible indicator-dilution curves could not be obtained. In most of these latter patients aberrant renal arteries were present. All antihypertensive medications were withheld for at least 48 hours prior to study except in three patients with accelerated hypertension. All studies were performed in the morning after an overnight fast and usually without sedation or premedication. In 11 of the 15 patients renal blood flow determinations were performed prior to angiography. In none of the patients was significant renal artery stenosis demonstrated. All were therefore assumed to have essential hypertension.

Precurred radiopaque polyethylene catheters inserted into a femoral artery and corresponding vein using the Seldinger technic were guided under fluoroscopy into the renal artery and ipsilateral renal vein. Two or 3 ml of radiopaque dye were injected through the catheters to check the position of the catheter tip and to confirm that contrast material did not leak retrograde from the renal artery catheter into the aorta. The renal artery catheter was prefilled with indocyanine green dye and 0.5 ml (0.625 mg) of dye was injected as a bolus while renal venous blood was withdrawn through a Gilford cuvette densitometer into a 30-ml sterile syringe at a constant rate of 24 ml/min by a Harvard withdrawal pump. Blood was immediately reinjected through the renal vein catheter after each dye curve was performed. Indicator-dilution curves were recorded on a Hewlett Packard direct-writing oscillograph. The reproducibility of serial dilution curves gave the best evidence that the catheters were positioned correctly. Nonreproducible or distorted curves required repositioning of the renal catheters. Whenever reproducible curves could not be recorded the study was abandoned and the results were discarded. Instability of renal blood flow immediately following indocyanine green injection into the renal artery has occasionally been observed in dogs in whom

![Graph](image-url)
renal blood flow was continuously monitored with a flowmeter. This phenomenon in the dog results in distorted or nonreproducible dye curves. Such a vascular effect of the injection could explain erratic dye curves noted in a few of these patients whose data were excluded from analysis. When the catheters were positioned correctly, a constant infusion of indocyanine green dye (0.5 mg/min) was delivered by a Harvard pump through the renal artery catheter. After at least 30 min of infusion, four successive blood samples were drawn slowly from the renal vein and a peripheral artery over a period of 3-5 min. The infusion was then stopped and at least three reproducible dilution curves were again recorded.

The dye curves were replotted on two-cycle semilogarithmic paper and the first exponential was extrapolated to the baseline, which always represented a point less than 5% of peak concentration. The dye recovery, in mg (R), in this rapid curve was calculated from the formula: 
\[ R = C_m \times t \times (RBF/60), \]
here \( C_m \) is mean concentration of dye during inscription of the curve in mg/ml, \( t \) is the duration of the extrapolated dye curve in sec, and RBF is the renal blood flow in ml/min calculated from the constant infusion data. Values from successive dye curves varied by less than 15%.

The fraction of flow in this rapid (cortical) circulation, the cortical fraction (CF), was calculated from the formula: 
\[ CF = R/L. \]
Cortical blood flow (CBF) therefore was represented by RBF \( \times CF, \) and noncortical blood flow (NCFB) by RBF - CBF.

Renal cortical blood volume (CBV) was calculated as the product of CBF and the mean cortical transit time of indocyanine green corrected for sampling system delay. This volume is assumed to be slightly larger than the cortical volume available to red blood cells, since plasma labels are known to have a slightly larger volume of distribution and longer intrarenal transit time than red cells.

Reported results represent the averages of at least three calculations of RBF from successive V-A differences and three successive indicator-dilution curves performed immediately after the constant infusion was discontinued. All flows were corrected to a body surface area of 1.73 m².

**Results**

The individual clinical data on the 15 patients with essential hypertension who underwent successful studies are shown in table 1. The patients ranged from 22 to 57 (average 43) years old. Twelve patients had mild or moderate hypertension and were maintained on a normal salt intake. Seven patients (T.H., A.B., T.C., J.D., G.W., J.C., and C.C.) were newly discovered hypertensives and had not been treated prior to study. Antihypertensive drugs were discontinued from 2 days to 6 weeks prior to study in five patients (table 1). Treatment had consisted of a diuretic in four and a diuretic and reserpine in patient P.H. Three patients (R.H., D.W., and L.M.) had severe hypertension with left ventricular failure, retinopathy and renal damage. Antihypertensive medications and salt-restricted diets could not safely be discontinued in these three patients prior to the study.

Renal hemodynamic data are shown in table 2. All data were obtained prior to aortography except in patients T. H., W. R., C. C., and R. H. Patient

<table>
<thead>
<tr>
<th>Pt</th>
<th>Age (yrs)</th>
<th>Race</th>
<th>MAP (mm Hg)</th>
<th>Hct (%)</th>
<th>BUN (mg %)</th>
<th>Cr (mg %)</th>
<th>Cer (ml/min)</th>
<th>Fundi* grade</th>
<th>Drug therapy</th>
</tr>
</thead>
<tbody>
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<td>T.H.</td>
<td>23</td>
<td>B</td>
<td>100</td>
<td>54</td>
<td>7</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
<td>I</td>
</tr>
<tr>
<td>A.B.</td>
<td>45</td>
<td>W</td>
<td>100</td>
<td>39</td>
<td>14</td>
<td>1.1</td>
<td>—</td>
<td>—</td>
<td>I</td>
</tr>
<tr>
<td>L.A.</td>
<td>41</td>
<td>B</td>
<td>132</td>
<td>40</td>
<td>12</td>
<td>1.0</td>
<td>—</td>
<td>—</td>
<td>II</td>
</tr>
<tr>
<td>T.C.</td>
<td>43</td>
<td>B</td>
<td>140</td>
<td>48</td>
<td>15</td>
<td>1.3</td>
<td>—</td>
<td>—</td>
<td>II</td>
</tr>
<tr>
<td>A.S.</td>
<td>53</td>
<td>W</td>
<td>96</td>
<td>43</td>
<td>13</td>
<td>1.1</td>
<td>—</td>
<td>—</td>
<td>I</td>
</tr>
<tr>
<td>D.M.</td>
<td>22</td>
<td>W</td>
<td>110</td>
<td>47</td>
<td>14</td>
<td>1.3</td>
<td>—</td>
<td>—</td>
<td>I</td>
</tr>
<tr>
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<td>B</td>
<td>110</td>
<td>42</td>
<td>20</td>
<td>1.2</td>
<td>111</td>
<td>II</td>
<td>D</td>
</tr>
<tr>
<td>J.D.</td>
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<td>B</td>
<td>128</td>
<td>37</td>
<td>10</td>
<td>1.1</td>
<td>—</td>
<td>—</td>
<td>II</td>
</tr>
<tr>
<td>G.W.</td>
<td>38</td>
<td>B</td>
<td>110</td>
<td>47</td>
<td>16</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>I</td>
</tr>
<tr>
<td>J.C.</td>
<td>52</td>
<td>B</td>
<td>116</td>
<td>37</td>
<td>13</td>
<td>1.1</td>
<td>73</td>
<td>II</td>
<td>Untreated</td>
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<tr>
<td>P.H.</td>
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<td>B</td>
<td>142</td>
<td>37</td>
<td>14</td>
<td>1.0</td>
<td>104</td>
<td>II</td>
<td>D, R stopped 1 week</td>
</tr>
<tr>
<td>C.C.</td>
<td>57</td>
<td>W</td>
<td>112</td>
<td>30</td>
<td>27</td>
<td>1.3</td>
<td>75</td>
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<td>Untreated</td>
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<td>R.H.</td>
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<td>B</td>
<td>116</td>
<td>48</td>
<td>32</td>
<td>1.9</td>
<td>60</td>
<td>III</td>
<td>A, D</td>
</tr>
<tr>
<td>D.W.</td>
<td>48</td>
<td>W</td>
<td>132</td>
<td>47</td>
<td>24</td>
<td>1.6</td>
<td>46</td>
<td>III</td>
<td>G, D</td>
</tr>
<tr>
<td>L.M.</td>
<td>56</td>
<td>W</td>
<td>124</td>
<td>42</td>
<td>40</td>
<td>4.2</td>
<td>12</td>
<td>IV</td>
<td>A, H, D</td>
</tr>
</tbody>
</table>

*Grading according to Keith-Wagner-Barker classification.

Abbreviations: MAP = mean arterial pressure; Hct = hematocrit; BUN = blood urea nitrogen; Cr = creatinine; Cer = creatinine clearance; A = methyldopa; D = diuretic; G = guanethidine; H = hydralazine; R = reserpine.
L. M. was studied 3 weeks after hospitalization with malignant hypertension. His single-kidney total renal blood flow was 87 ml/min/1.73 m². Cortical and noncortical flows could not be separated into two components because the rapid component was lost and thus nearly all the injected dye was recovered in the slowed first exponential dye-dilution curve. Data from this patient are not included in the averages shown in table 2.

RBF in the other 14 patients ranged from 152 to 1033 ml/min/1.73 m² per kidney and averaged 391 ml/min/1.73 m². The high flow observed in patient T. H. was in an hypertrophied kidney whose mate was congenitally atrophic. CBF ranged from 69 to 958 ml/min/1.73 m² and averaged 296 ml/min/1.73 m² whereas NCBF ranged from 36 to 164 and averaged 95 ml/min/1.73 m². Cortical fraction varied from 46 to 93%, cortical blood volume 12–85 ml/1.73 m², and mean cortical transit time 3.9–11.2 sec.

A significant correlation was noted between total renal blood flow and cortical blood flow, cortical fraction, and cortical blood volume (figs. 2, 3, and 4). Noncortical blood flow was not related to total renal blood flow (fig. 5).

Discussion

The anatomic localization of the flows described here as “cortical” and “noncortical” cannot be proved. However, these flows clearly represent a relatively homogeneous rapid circulation and a functionally separate slower circulation. In previous studies in the dog radioautographic localization demonstrated that the rapid circulation was confined to the cortex while the slower circulation was predominantly in the juxtamedullary cortex and the medulla. Therefore, it seems justified to assume that a similar localization would hold for the human kidney.

The differences between the intrarenal flow distribution determined by the present technic and that described by other methods needs particular emphasis. Microspheres provide data on the flow rate at different levels of the cortex. In general, it might be assumed that flow to the deeper cortex is destined for the medulla, but a clear separation of flow into cortical and noncortical flow is not possible using microspheres. Inert gas-washout technics are designed to separate flow rates of regions of the kidney whose flows differ significantly. Compartment I obtained from gas-washout curves may indeed correspond to the rapid flow in our studies, and compartment II may represent in part the slow circulation. However, accurate analysis of these multiexponential curves may depend on the “peeling off” of slower exponentials, which probably are influenced by urine flow or countercurrent diffusion. Furthermore, flow rates obtained from inert gas washout can be quantitated only in terms of compartmental mass, and cortical volume may vary considerably in response to physiologic interventions.

The method described by Reubi and Takeuchi and their associates is similar to the present

Table 2

<table>
<thead>
<tr>
<th>Pt</th>
<th>RBF (ml/min/1.73 m²)</th>
<th>CBF (ml/min/1.73 m²)</th>
<th>NCBF (ml/min/1.73 m²)</th>
<th>CF (%)</th>
<th>MTT (sec)</th>
<th>CBV (ml/min/1.73 m²)</th>
</tr>
</thead>
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<td>T.H.</td>
<td>1033</td>
<td>953</td>
<td>74</td>
<td>93</td>
<td>5.3</td>
<td>85</td>
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<tr>
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<td>538</td>
<td>104</td>
<td>84</td>
<td>3.9</td>
<td>35</td>
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<tr>
<td>L.A.</td>
<td>347</td>
<td>431</td>
<td>116</td>
<td>79</td>
<td>5.8</td>
<td>42</td>
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<tr>
<td>T.C.</td>
<td>408</td>
<td>306</td>
<td>102</td>
<td>75</td>
<td>5.9</td>
<td>30</td>
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<tr>
<td>A.S.</td>
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<td>353</td>
<td>61</td>
<td>87</td>
<td>6.8</td>
<td>40</td>
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<tr>
<td>D.M.</td>
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<td>239</td>
<td>119</td>
<td>67</td>
<td>6.0</td>
<td>29</td>
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<tr>
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<td>358</td>
<td>194</td>
<td>164</td>
<td>54</td>
<td>6.0</td>
<td>19</td>
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<td>206</td>
<td>145</td>
<td>59</td>
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<td>287</td>
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<td>89</td>
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<td>J.C.</td>
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<td>185</td>
<td>97</td>
<td>66</td>
<td>6.3</td>
<td>19</td>
</tr>
<tr>
<td>P.H.</td>
<td>239</td>
<td>145</td>
<td>93</td>
<td>61</td>
<td>5.6</td>
<td>13</td>
</tr>
<tr>
<td>C.C.</td>
<td>199</td>
<td>133</td>
<td>74</td>
<td>63</td>
<td>6.6</td>
<td>14</td>
</tr>
<tr>
<td>R.H.</td>
<td>163</td>
<td>106</td>
<td>57</td>
<td>68</td>
<td>11.2</td>
<td>24</td>
</tr>
<tr>
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<td>83</td>
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<td>10.5</td>
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<tr>
<td>L.M.</td>
<td>87</td>
<td></td>
<td>14.7</td>
<td></td>
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</tbody>
</table>

Mean ± sd 391 ± 230 296 ± 230 95 ± 35 71 ± 14 7.2 ± 2.8 29 ± 19

Abbreviations: TRBF = total renal blood flow; CBF = cortical blood flow; NCBF = noncortical blood flow; CF = cortical fraction; MTT = cortical mean transit time; CBV = cortical blood volume.
In the present studies the reduction in total renal blood flow observed in patients with more advanced hypertensive vascular disease was due to a fall in cortical blood flow. In contrast, noncortical flow was well preserved and the cortical fraction of total flow therefore was lower in subjects with more severe reduction of total flow. Based on parallel stereo microangiographic and histologic examinations of kidneys from patients with essential hypertension, Ljungqvist has reported a reduction in the vascular supply of the cortex, particularly more marked in patients with severe degrees of hypertension. The reduction in cortical blood flow in the present studies was accompanied by a reduction in cortical blood volume consistent with the contraction of the renal cortex characteristic of the nephrosclerotic kidney.

Since arterial pressure was elevated in these hypertensive patients, the reduced cortical blood flow is indicative of a considerably elevated cortical vascular resistance. How much of the narrowing of the cortical resistance vessels represents anatomic changes in the arteriolar walls and how much may be functional is not known. Thurau has suggested that the cortical vascular bed autoregulates in response to changes in arterial pressure whereas the medullary bed does not. Therefore, the preservation of medullary flow in these hypertensive patients despite a reduction in cortical flow could be attributed in part to the elevated arterial pressure.

Figure 2
Close correlation between cortical blood flow and the total renal blood flow in 14 hypertensive patients. Regression line is shown.

Figure 3
Significant correlation (P < 0.005) between the cortical fraction of renal blood flow and the total renal blood flow in 14 hypertensive patients. Regression line is shown.

Figure 4
Close correlation between cortical blood volume and total renal blood flow. Regression line is shown.
pressure. Indeed, noncortical flow showed some tendency to correlate with the arterial pressure, but the relationship was not statistically significant.

Intrarenal hemodynamic factors could play a role in the renal functional abnormalities observed in hypertension. Buckalew and associates have found inhibition of free water reabsorption and free water clearance in hypertensive subjects indicating impairment of sodium reabsorption in the loop of Henle. An increased pressure in the vasa recta because of transmission of elevated arterial pressure through a relatively nonvasoconstricted medullary vascular bed could inhibit sodium transport in the loop. The finding by Lowenstein et al. of an elevated intrarenal wedge pressure in hypertensive patients is consistent with this hypothesis. Furthermore, medullary flow out of proportion to cortical flow could reduce the normal medullary hypertonicity and might impair sodium transport by resulting in a higher velocity of tubular flow. These hemodynamic factors could be at least partly responsible for the concentrating defect and the exaggerated natriuresis observed in hypertensive subjects.

Several factors limit widespread application of the present technic in the evaluation of intrarenal blood flow distribution in man. Nonreproducibility or distortion of indicator-dilution curves prevented use of the method in 30% of the patients in the present series. The most common cause of this problem is multiplicity of renal arteries. When cortical flow falls to low levels, as in patients with severe renal disease, the slowed cortical flow apparently merges with noncortical flow and renal blood flow can no longer be separated into two components. Such a phenomenon was observed in one patient in this series with malignant hypertension. In addition, the constant infusion indicator-dilution method is not an ideal technic for measuring total renal blood flow, since it requires an equilibration period which limits its usefulness in following acute changes in blood flow. Development of a precise method for instantaneous measurement of renal blood flow would facilitate assessment of intrarenal blood flow distribution by the dye-dilution technic.

The present data also make it clear that previous use of renal indicator-dilution curves to quantitate total renal blood flow probably was in error. In normal kidneys dye curves processed by extrapolation of the first rapid downslope would be expected to overestimate total blood flow by only a small percentage, since the slow circulation probably represents less than 20% of total blood flow. However, in disease states if cortical flow is reduced out of proportion to the noncortical flow, dye curves would provide a value for blood flow considerably higher than the actual value because of the loss of a significant fraction of the dye into the slow circulation. Failure to recognize the magnitude of this discrepancy in the past may be due to the fact that in previous studies the dye-curve method was validated by comparison with PAH clearances done at a different time or not on a single kidney.

References
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