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RENAL FACTORS IN HYPERTENSION

SHELDON C. SOMMERS, M.D.*

High blood pressure is almost exclusively a human disease, and the most common types do not appear to have been effectively duplicated in experimental animals. The kidney, because of its filtrative, electrolyte controlling and vascular autoregulative functions, is notably involved in processes that determine the systemic blood pressure. This report is an account of the microscopic morphologic changes observed in 2500 biopsies of renal tissue obtained from patients with clinical essential hypertension, and it may help clarify the role of the kidney in the pathogenesis of arterial hypertension.

Arteriolar Nephrosclerosis. In this patient group, clinical essential hypertension with established arteriolar nephrosclerosis was present in over 75 per cent (Table I). Vasospasm is considered the most common initial mechanism of systemic hypertension. It affects many arterioles, including those of the kidney, and is reversible after bed rest. In early biopsies no renal lesions showed, but the afferent glomerular arterioles were narrowed by spasm and the proximal convoluted tubules had a reversible cloudy swelling ascribable to anoxia. Mild albuminuria was the only common renal functional change.¹²

Sufficiently persistent or recurrent spasm of arterioles apparently leads to abnormal muscle hypertrophy unevenly distributed both circumferentially and longitudinally, since the hypertrophied arterioles appeared irregularly thickened, narrowed and tortuous (Fig. 1). These morphologic changes cause eddying, vibration and increased shearing forces in the arteriolar blood flow. As a result, localized degenerative arteriolar changes developed, such as cloudy swelling and an increased permeability to plasma

Table I

RENAL ABNORMALITIES IN 2,300 SURGICAL SPECIMENS FROM HYPERTENSIVE PATIENTS

<table>
<thead>
<tr>
<th>Renal Abnormality</th>
<th>Frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arteriolar nephrosclerosis</td>
<td>81.2%</td>
</tr>
<tr>
<td>Chronic pyelonephritis</td>
<td>14.9</td>
</tr>
<tr>
<td>No lesion</td>
<td>1.6</td>
</tr>
<tr>
<td>Unilateral renovascular lesions</td>
<td>1.3</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*Department of Pathology, Delafield Hospital Division, Columbia University College of Physicians and Surgeons, New York, N. Y.
Kidney biopsy with moderately severe arteriolar sclerosis, demonstrating the irregularly thickened, tortuous small arteries. Note the tubular cloudy swelling. PAS stain, X150.

Muscle cells became hydropic, there was fraying and rupture of the basement membranes and coalescence of the ground substance. The typical intimal and elastic tissue alterations and lipid deposits of atherosclerosis were not found in arterioles. Once established, arteriolar nephrosclerosis varied in severity, but it remained characteristically unevenly distributed except in the most severe form. Usually there were intermingled or entirely separate regions of vasospasm, irregular muscular hypertrophy or degeneration and fibrosis along the courses of individual afferent arterioles in renal biopsies. A mathematical relation of diastolic blood pressure to the arteriolar wall/lumen ratio was found. This alteration occurs also in various systemic arterioles, but the relation appeared most consistent in the kidney, implicating an intrinsic renal mechanism other than arteriolar narrowing (Table II).

Table II

<table>
<thead>
<tr>
<th>Grade</th>
<th>Arteriolar Sclerosis</th>
<th>Pyelonephritis in Addition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Slight</td>
<td>100.3 mmHg</td>
<td>111.5 mmHg</td>
</tr>
<tr>
<td>Moderate</td>
<td>109.6</td>
<td>115.3</td>
</tr>
<tr>
<td>Severe</td>
<td>122.1</td>
<td>133.4</td>
</tr>
</tbody>
</table>
RENAL FACTORS IN HYPERTENSION

Figure 2
A normal-appearing juxtaglomerular apparatus, with about six nucleated juxtaglomerular cells located between the glomerular hilus and the taller specialized macula tubular cells. Bowie stain, X500.

Both the glomeruli and convoluted tubules in arteriolar nephrosclerosis suffered damage from ischemia and anoxia secondary to vasospasm. Besides albuminuria, occasional interference with water resorption and a reduced urine specific gravity were found. However, it was the juxtaglomerular apparatus that disclosed changes more intimately related to the elevated diastolic pressure.

The renal juxtaglomerular cells normally form a narrow cuff around the afferent arteriole where it enters the glomerular hilus (Fig. 2). In humans the cells are few, poorly granulated and contain only small amounts of renin. Physiologically these cells apparently function in autoregulation of the circulation to each nephron. Reduced lateral blood pressure against the lining of an afferent arteriole is thought to stimulate local renin secretion and rapid intravascular formation of angiotensin. The resulting vasopressor effect may then be exerted on the efferent arteriole of the same glomerulus and increase the filtration pressure in the glomerular capillaries. Besides contributing to circulatory autoregulation, the juxtaglomerular apparatus also responds to distal tubular sodium and, via renin secretion, stimulates adrenal aldosterone production.

In established arteriolar nephrosclerosis the renal juxtaglomerular cells are hypertrophied, hyperplastic and actively functioning, as a byproduct of the Bernouilli suction effect within the narrowed afferent arteriolar lumens (Fig. 3). While vasospasm and irregular vascular narrowing, wall thickening and fibrosis account for most of the diastolic pressure elevation attained, the arterioles retain some degree of flexibility so that medical or surgical therapy is often successful, except in the most severe and advanced cases. When an extreme diffuse arteriolar nephrosclerosis has developed, the renal parenchyma becomes atrophied, urinary function is clearly diminished and the mortality is found to be increased threefold over a 5-year period. However, both treated and untreated essential hypertensive patients ordinarily achieve considerable longevity.
Figure 3
An enlarged juxtaglomerular apparatus with JG cell hyperplasia, accompanying arteriolar nephrosclerosis. Elastic tissue stain, X300.

Figure 4
In pyelonephritis with hypertension the juxtaglomerular apparatus is usually unaltered, as shown at the hilus of the less damaged glomerulus. Interstitial inflammation and fibrosis are prominent. Bowie stain, X300.
RENAL FACTORS IN HYPERTENSION

Chronic Pyelonephritis. Next to essential hypertension the largest group of hypertensive patients studied by renal biopsies were those with chronic pyelonephritis. They constituted 15 per cent of the population with high blood pressure.1,3

Pyelonephritis generally begins pathologically near the renal corticomedullary junction. Ascending inflammatory and degenerative processes involve in sequence the distal convolutions, Henle loops and ultimately the proximal convoluted tubules. There is a natural tendency to slow progressive attrition of intact nephrons due to inflammation and fibrosis, with hypertension developing late in the natural disease course.12,13 Chronic intrarenal phlebitis and periphlebitis and compromised lymph drainage are also observed.

One important effect of interference with the venous blood and lymph drainage is the development of a concentric periglomerular and arteriolar adventitial fibrosis. Arteriolar walls become thickened and their lumens narrowed by external compression, without antecedent vasospasm.12 The juxtaglomerular apparatus is evidently not stimulated (Fig. 4).

When hypertension complicates chronic pyelonephritis, the diastolic pressure is significantly higher for the degree of arteriolar thickening than in essential hypertension, and the prognosis is poorer (Table 2).4 The renal mechanism responsible for this is unknown, but it does not seem to be the renin-angiotensin system because the juxtaglomerular apparatus appears inactive. Perhaps a progressive attrition of nephrons is implicated, particularly the proximal convoluted tubules.14

Renovascular (Goldblatt Type) Hypertension. The renal factors found in the residual approximately 5 per cent of the hypertensive population have aroused the greatest recent medical interest, discussion and controversy.

Renovascular hypertension is surgically curable in carefully selected cases. However, the diagnostic methods used do not seem satisfactorily standardized and many operations have been performed on inappropriate indications. In 1956 Homer Smith13 noted that the most common unilateral abnormality in a group of surgically treated patients was chronic pyelonephritis, and that cure of the hypertension for over one year was achieved in only about 26 per cent. Among 35 nephrectomy specimens we have studied, in which unilateral pyelonephritis was believed responsible for hypertension preoperatively, 28 (80 per cent) had ordinary diffuse pyelonephritis and their hypertension was not benefited by nephrectomy. Three cured patients had only severe diffuse atrophy, and 4 others had genuine renovascular hypertension.16,17 Unfortunately, no contralateral biopsies were taken.

In the rare condition of unilateral chronic pyelonephritis with a Goldblatt-type renovascular hypertension, wedges or bands of pyelonephritis have compromised medium-sized arteries serving the intervening uninvolved renal segments. Multiple arterial stenoses thus stimulated the juxtaglomerular cells to hypertrophy and hyperlasia.
In renovascular hypertension the juxtaglomerular cells are typically hypertrophied and hyperplastic. Compare their appearance with Figure 2. Bowie stain, X500.

A Goldblatt kidney with renal arterial stenosis is shown on the left. It is both atrophied and free from the nephrosclerotic scarring of the unprotected kidney on the right.
RENAL FACTORS IN HYPERTENSION

In renovascular hypertension, when patients have been selected with great care for surgical treatment, pyelonephritis is less common, and classical Goldblatt-type renovascular hypertension predominates. A variety of renal hilar lesions may reduce the arterial blood flow and thus activate the powerful renin-angiotension vasopressor mechanism. The juxtaglomerular cell hyperplasia present may be striking, and renal biopsies before definitive therapy are a useful guide to the probable surgical success or failure (Fig. 5). Goldblatt and associates have reminded us that the true Goldblatt kidney is protected from arterio- and arteriolar sclerosis (Fig. 6). Their presence indicates that the hypertension is of some other type. After two or more years of unrecognized Goldblatt-type renovascular hypertension, surgery has also proved less successful, but the reason is not clear.

Hypertrophy of Macula Densa. Another renal mechanism related to hypertension is electrolyte control, particularly sodium balance. Each nephron has a segment of its distal convoluted tubule that abuts on the juxtaglomerular cells. Here the tubular epithelium is crowded and histochemically specialized. It stains strongly for glucose-6-phosphate-dehydrogenase. This region is called the macula densa and is thought to function as a sodium monitor of the distal tubular fluid and as another control of the juxtaglomerular cell functions. Normally, sodium resorption in the proximal tubular segments leaves very little in the distal convoluted tubular fluid. Macula cells are hypertrophied and by inference more active when less sodium is excreted in the urine and when the ratio of urinary sodium to potassium is low.

The macula densa cells thus in theory resorb sodium and exchange it for intracellular potassium. The activity of this reaction signals the adjoining juxtaglomerular cells, presumably to secrete renin. The renin-angiotensin reaction in turn stimulates adrenal aldosterone secretion and increases distal renal tubular sodium resorption.

Both in essential hypertension and Goldblatt-type hypertension the juxtaglomerular cells are hyperplastic and the macula densa is hypertrophied (Table III). Sodium retention ensues with an increased possibility of secondary hyperaldosteronism. In cases of secondary aldosterone hypersecretion the renal macula densa may have further contributed indirectly to elevate the diastolic hypertension already present.

Table III

<table>
<thead>
<tr>
<th>Types of Hypertension</th>
<th>Cases</th>
<th>Mean JGCC and Standard Deviations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renovascular</td>
<td>34</td>
<td>259±55</td>
</tr>
<tr>
<td>Pheochromocytoma</td>
<td>7</td>
<td>240±31</td>
</tr>
<tr>
<td>Nephrosclerosis</td>
<td>51</td>
<td>235±34</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>33</td>
<td>187±60</td>
</tr>
<tr>
<td>Normotensive Controls</td>
<td>51</td>
<td>202±10</td>
</tr>
</tbody>
</table>

*The JGCC is the number of nucleated cells found in 25 juxtaglomerular apparatuses.
The renal pathologic mechanisms responsible for or contributing secondarily to diastolic hypertension are: (1) Arteriolar vasospasm and its arteriolosclerotic sequelae. A superimposed juxtaglomerular effect is present in established arteriolar nephrosclerosis with clinical essential hypertension. (2) Chronic pyelonephritis, when sufficient renal parenchymal attrition, interstitial fibrosis and arteriolar narrowing have developed. These two mechanisms are thought to account for about 95 per cent of clinical hypertension. Among less common types of hypertension are (3) arterial stenosis with unilateral renal juxtaglomerular cell hyperplasia, resulting in Goldblatt-type hypertension. Macula densa hypertrophy sometimes accompanies secondary aldosteronism, which may contribute further to increase the diastolic blood pressure.

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REFERENCES