Clinicopathologic Correlations of Renal Biopsies in Hypertension with Pyelonephritis

By Joseph C. Merriam, M.D., Sheldon C. Sommers, M.D., and Reginald H. Smithwick, M.D.

Analysis has been made of the responses to sympathectomy for hypertension and certain other aspects of 120 cases whose renal biopsies showed pyelonephritis as well as arteriolar nephrosclerosis. The sex incidence, mortality, average diastolic blood pressures, and postoperative kidney function tests differed from findings in a larger hypertensive group without pathologic evidence of pyelonephritis.

A STUDY of clinicopathologic correlations of hypertensive patients undergoing sympathectomy at the Massachusetts Memorial Hospitals has recently been reported1 that was concerned with renal biopsies and clinical follow-up data of the 1- to 9-year period after operation. The majority of the renal biopsies were diagnosed as arteriolar nephrosclerosis. The previous report dealt with this majority. In addition, clinically undiagnosed chronic pyelonephritis was found in 13.5 per cent of the total of about 1,700 renal biopsies. In this paper these cases of chronic pyelonephritis are discussed from the viewpoints of clinical findings and prognosis, comparing them with the cases of pure nephrosclerosis previously reported.

MATERIALS AND METHODS

Case records were available of 120 hypertensive patients who had undergone sympathectomy at the Massachusetts Memorial Hospitals between 1947 and 1956, and whose renal biopsy, performed at the time of operation, included the diagnosis of chronic pyelonephritis. Twelve patients had bilateral biopsies, the remaining 108 had a biopsy of only 1 kidney. The biopsies averaged about 6 by 5 by 4 mm., were composed of kidney cortex, and were removed in a manner previously described by Castleman and Smithwick.2 Pathologic alterations of the glomeruli, juxtaglomerular apparatus, tubules, stroma, and blood vessels were recorded for each specimen without knowledge of the patient's identity or status, or whether multiple biopsies had been taken.

Criteria for Diagnosis

The presence of chronic pyelonephritis in these biopsies was recognized by finding irregular scars, dilated tubules containing colloid protein casts, and plasma cells mingled with other leukocytes in the stroma (fig. 1). The most important single criterion was the presence of plasma cells. If regions of dilated tubules containing colloid casts were seen and no plasma cells could be found, a diagnosis of healed pyelonephritis was made (fig. 2). There were 17 such cases in the total group of 120 cases. If pus casts and polymorphonuclear leukocytes were seen in 1 or more tubules, in addition to evidences of chronic pyelonephritis, acute and chronic pyelonephritis was diagnosed; 3 of the 120 cases fell in this group.

These criteria agree well with histopathologic findings reported both in human autopsy and in experimental animal material.3,4 Bacteriologic cultures of the biopsies were not done.

As reported in the previous paper, the vessels in each biopsy were also studied and the degree of arteriolar sclerosis was graded as grades I, II, or III. Negative arterioles showed no alteration, grade I arteriolar sclerosis indicated minor localized thickenings of the vessel walls, grade II referred to a thickened wall equal to the diameter of the arteriolar lumen, and grade III sclerosis meant that the wall thickness exceeded the diameter of the lumen. There were 2 grade 0, 12 grade I, 96 grade II, and 10 grade III cases among the 120 cases. Thus 80 per cent of the cases of chronic or healed pyelonephritis had an associated moderate (grade II) arteriolar sclerosis.

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Aided by grants from the American Heart Association, the Massachusetts Heart Association, and the Smithwick Foundation.

Presented in part at the International Congress of Clinical Pathology, Brussels, July, 1957.
Twelve patients had bilateral renal biopsies. Five of these patients had the same diagnosis on each biopsy, the other 7 differed either by 1 grade of sclerosis, or by a diagnosis of chronic pyelonephritis on one side, and healed pyelonephritis on the other. For purposes of grouping, these patients were placed in the lower grade of arteriolosclerosis, and in the group of chronic pyelonephritis. None of the 12 cases with bilateral biopsies was considered to show only a unilateral pyelonephritis.

RESULTS

Of the total 120 patients, 73 or roughly 60 per cent were male. In the larger series of cases that showed arteriolosclerosis alone, on the other hand, there was a slight preponderance of females, 53.5 per cent.

The age and sex distributions of the 120 cases were as follows: In the age-range of 19 to 29 years, 5 patients, 3 male and 2 female; 29 to 39, 28 patients, 15 male and 13 female. In the age-range 39 to 49, 58 patients, 37 male and 21 female. In the age-range 49 to 60 (the oldest patient was 60 at operation), 29 patients, 18 male and 11 female.

Survival for 5 years after operation for each grade of arteriolosclerosis accompanying pyelonephritis is charted in figure 3. Overall survival at 5 years, for the 75 patients followed that time or longer, was 64 per cent. There were only 3 patients with severe (grade III) arteriolosclerosis, of whom 1 was alive after 5 years. Twenty patients followed for 10 years or more had a survival rate of 65 per cent at the end of 10 years (fig. 4). The mortality for the hypertensive patients who had the added factor of chronic or healed pyelonephritis was somewhat higher than those in the previous study, in which there was approximately a 90 per cent 5-year survival for all arteriolosclerotic groups except grade III.

As in the previous study, a preoperative diastolic blood pressure level was defined as the lowest value obtained in the recumbent patient, and the average pressure was computed for each of the vascular grades I, II, and III. In table 1 are seen the average diastolic pressures, and number of patients used to compute the averages. For comparison, figures from the previous paper are included. By the statistical "t-test," the difference between grade I and II average pressures in the group with pyelonephritis is not significant. The differences in cases...

Fig. 1. Left. Example of a kidney biopsy with severe chronic pyelonephritis and grade-II arteriolar sclerosis of the vessels in center of the illustration. Parenchymal atrophy, interstitial scarring, and abundant leukocytes are evident. H & E, X 125.

Fig. 2. Right. Focus of healed pyelonephritis with scarring, renal parenchymal atrophy, and a large colloid cast in a dilated tubule. Grade-II arteriolar sclerosis is shown. This biopsy elsewhere showed acute and chronic pyelonephritis. PAS, X 125.
with pyelonephritis between grade I or II and III average diastolic pressures, however, are significant. Also for each vascular grade there was a significantly higher average diastolic pressure in the presence of pyelonephritis.

The so-called "Smithwick groups" offer another method of comparing the biopsy interpretations with the preoperative clinical evaluations. These are 6 groups into which patients are classed, during the preoperative workup, according to factors of age, diastolic blood pressure level and its response to sedation, eyebound observations, renal function, and cardiac and cerebrovascular status. The over-all clinical evaluation then falls into 1 of 6 groups, with the comparatively early and mild cases being assigned to groups 1 and 2, and the most severe and advanced hypertensive disease to group 6. In table 2 are presented data of 117 of the cases of pyelonephritis, comparing the preoperative Smithwick group with the grade of arteriolar sclerosis.

As compared to the results of analysis of the noninfected nephrosclerotic cases in the previous paper, the following distinction may be pointed out. More than half of the 117 cases of chronic pyelonephritis fell into the more "severe" groups of 4, 5, and 6, whereas only one quarter of the purely nephrosclerotic cases were in groups 4, 5, 6.

Postsympathectomy Follow-up

Eighty-three patients have been followed for 5 years or more after sympathectomy. Of these, 50 have had rather thorough follow-up studies from 1 to 10 years after operation. We wish to report some of the follow-up studies, and to compare them with studies reported in the previous paper.

The postoperative response of diastolic blood pressure has been analyzed according to Smithwick's criteria. The 50 pyelonephritic patients in this respect did about as well as the pure nephrosclerotic group, since approximately one third of the pyelonephritic and the nephrosclerotic groups each fell into grades I to III of postsympathectomy response.

Grading of retinal vascular changes (Keith-Wagener) was compared before and after

**TABLE 1.**—Average Diastolic Blood Pressures in mm. Hg

<table>
<thead>
<tr>
<th>Grade</th>
<th>Arteriolar sclerosis only</th>
<th>Pyelonephritis and arteriolar sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>100.3 (100 cases)</td>
<td>111.5 (12 cases)</td>
</tr>
<tr>
<td>II</td>
<td>109.6 (100 cases)</td>
<td>115.3 (96 cases)</td>
</tr>
<tr>
<td>III</td>
<td>122.1 (29 cases)</td>
<td>133.4 (10 cases)</td>
</tr>
</tbody>
</table>

**TABLE 2.**—Clinical Hypertensive Groups Compared with Kidney Biopsy

<table>
<thead>
<tr>
<th>Pyelonephritis and arteriolosclerosis</th>
<th>Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group</td>
<td>1 2 3 4 5 6</td>
</tr>
<tr>
<td>Grade I (12 cases)</td>
<td>0</td>
</tr>
<tr>
<td>Grade II (95 cases)</td>
<td>5</td>
</tr>
<tr>
<td>Grade III (10 cases)</td>
<td>1</td>
</tr>
<tr>
<td>Total 117 cases</td>
<td>6</td>
</tr>
</tbody>
</table>
operation for both the pyelonephritic and the pure nephrosclerotic groups of patients. The incidence of hypertensive retinopathy of grades III and IV was 45 per cent in the pyelonephritis series as opposed to 24 per cent in the nephrosclerotic group. After sympathectomy the pyelonephritic series showed an incidence of 46 per cent of improvement in the eye grounds, which compares almost exactly with the figure of 48 per cent improvement reported previously for the nephrosclerotic series.

Thus both series did roughly equally well postoperatively with respect to lowering of blood pressure and improvement in eye grounds.

An attempt was also made in the previous paper to assess kidney function in terms of the phenolsulfonphthalein test before and after operation. Because of the relatively few (50) cases of pyelonephritis that were observed for 5 years, all of the cases were pooled, and the data obtained compared to the total data of the nephrosclerotic series.

As compared with the nephrosclerotic series, the pyelonephritic series showed a trend toward greater severity of renal impairment in more patients, and a less frequent improvement of the renal function after sympathectomy.

Also in contrast to the series of nephrosclerotic patients, in which only 3 patients had nonprotein nitrogen serum values of over 45 mg. per cent preoperatively and all improved after sympathectomy, in the pyelonephritic series 10 out of 120 patients had serum nonprotein nitrogen levels of over 45 mg. per cent. Only 1 of these patients improved postoperatively, and 7 died of uremia within 2 years.

Thirty-three patients with hypertension and pyelonephritis have died altogether, 12 of uremia, 10 of cerebrovascular accidents, 6 of myocardial infarct, and 1 each of ruptured aorta, cancer of the bladder, acute enteritis, and congestive heart failure. Autopsies were performed in 7 cases at the Massachusetts Memorial Hospitals. Studies of their kidneys post mortem showed good general agreement between the biopsy and the autopsy kidney findings, except in 1 case, in which no obvious stigmata of chronic or healed pyelonephritis, or of arteriolar sclerosis, were found at autopsy in a woman previously diagnosed by biopsy as having chronic pyelonephritis and grade I arteriolar sclerosis (figs. 5 and 6).

### Discussion

This investigation was undertaken to see whether there were any differences in the clinical evaluation, course, and prognosis of 2 series of sympathectomized hypertensive patients, one group in which renal biopsies showed only arteriolar nephrosclerosis, and the other group with arteriolar sclerosis and the additional factor of chronic pyelonephritis. It must be emphasized again that these cases of pyelonephritis were diagnosed pathologically by biopsy, and that practically none of these patients had been previously recognized clinically as having chronic pyelonephritis. Exhaustive investigation into their past histories was not done, but the impression was gained from the available records that few of these patients were aware of any previous episode of kidney infection.

In comparing the 2 series of noninfected and infected cases, an obvious associated factor in the study is the much larger proportion in the nephrosclerotic group of cases diagnosed as grade-I nephrosclerosis. The total group of pure nephrosclerotic cases represented nearly an equal mixture of grade-I

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### Table 3

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Postoperative</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Normal</td>
<td>Impaired</td>
</tr>
<tr>
<td></td>
<td>Sl. Mod. Mkd.</td>
<td>Improved</td>
</tr>
<tr>
<td>Nephrosclerosis (265 cases)</td>
<td>25 7 4</td>
<td>10 69 18</td>
</tr>
<tr>
<td>Chronic pyelonephritis (50 cases)</td>
<td>52 8 14</td>
<td>54 18 28</td>
</tr>
</tbody>
</table>

THAT A SLIGHT MAJORITY OF MALES OVER FEMALES WAS FOUND IN THE CHRONIC PYELONEPHRITIS GROUP IS SURPRISING, IN VIEW OF THE FACT THAT CHRONIC PYELONEPHRITIS IS SUPPOSED TO BE MUCH COMMONER AMONG FEMALES THAN MALES.

THE PATHOGENETIC RELATIONSHIP OF THE PYELONEPHRITIS TO THE HYPERTENSION IS OBSCURE, AND THIS PAPER DOES NOT PRETEND TO ILLUMINATE THE MYSTERY. LATELY THERE HAS BEEN RENEWED INTEREST IN THE POSSIBILITY THAT UNILATERAL KIDNEY INFECTION OR ISCHEMIA MAY CAUSE HYPERTENSION THAT IS CURABLE BY NEPHRECTOMY. SMITH\textsuperscript{9} ESTIMATED THAT LESS THAN 2 PER CENT OF ALL PATIENTS WITH DIASTOLIC HYPERTENSION CAN BE HELPED BY RENAL SURGERY. ONE PATIENT OF THE 120 UNDERGOING SYMPATHETOMY ALSO HAD A REMOVAL OF AN ATROPHIC, CHRONICALLY INFECTED KIDNEY, AND 4 YEARS LATER SHOWED A GRADE-I OPERATIVE RESPONSE WITH REDUCTION IN THE DIASTOLIC BLOOD PRESSURE OF 20 MM. Hg OR MORE, AND BELOW 90 MM. This patient’s biopsy from the opposite kidney showed chronic pyelonephritis and arteriolar sclerosis, grade II. Four other atrophic kidneys were removed in the series, but these patients had incomplete follow-up studies.

SUMMARY

RENAL BIOPSIES FROM 120 CASES OF HYPERTENSION TAKEN DURING SYMPATHETOMY WERE DIAGNOSED PATHOLOGICALLY PARTLY AS CHRONIC PYELONEPHRITIS. CLINICAL COMPARISONS WERE MADE WITH A LARGER SERIES OF HYPERTENSIVE PATIENTS.
whose biopsies did not demonstrate pyelonephritic infection. The pyelonephritic series had a somewhat increased mortality, significantly higher average diastolic blood pressures for the same grades of arteriolar sclerosis, and did not show as frequent improvement of impaired kidney function postoperatively as the purely nephrosclerotic group. Approximately one third of each series responded with a lowering to normal levels of the diastolic blood pressure after sympathectomy, and nearly one half showed a postoperative improvement in the hypertensive retinopathy.

**SUMMARIO IN INTERLINGUA**

Biopsias renal ab 120 casos de hypertension, obtinente durante sympathectomia, supportava in parte le diagnose pathologic de pyelonephritis chronic. Comparationes clinic esseva facite con un plus grande serie de patientes hypertensive in qui le biopsias non demonstrava le presentia de infection pyelonephritie. Le serie pyelonephritic monistrava un leve augmento del mortalitate e significativamente plus alte valores medie del pression de sanguine diastolic pro le mesme grado de sclerosis arteriolar sed attingeva minus frequentemente un melioration del dysfunciation renal post le operation que le serie purmente nephrosclerotic. Circa un terto del patientes in ambe gruppos respondeva al sympathectomia per le redescendita a nivellos normal del pression de sanguine diastolic, e quasi un mediate demonstrava un melioration post-operatori in le retinopathia hypertensive.

**REFERENCES**


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Circulation. 1958;17:243-248
doi: 10.1161/01.CIR.17.2.243
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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