Clinicopathologic Correlations of Renal Biopsies from Essential Hypertensive Patients

By Myron Saltz, M.D., Sheldon C. Sommers, M.D., and Reginald H. Smithwick, M.D.

The pathologic findings of kidney biopsies in an extensive series of patients undergoing sympathectomy are reported. The findings are correlated with the clinical status, level of hypertension, postoperative course, and length of survival.

RENAL tissue was obtained by biopsy from 1,251 hypertensive patients who underwent sympathectomy at Massachusetts Memorial Hospitals in the 10 years 1946 through 1955. A clinicopathologic correlation has been attempted on the basis of a pathologic analysis of approximately 1,700 specimens and of 305 case histories.

The purpose of the present study is to determine how accurate an estimation may be made of the clinical status, level of hypertension, renal function, response to sympathectomy, and probable course of essential hypertension by histologic examination of a small portion of kidney tissue; some comparison of the relative value of different individual tests in hypertension is also possible.

Materials and Methods

The renal biopsies were about 6 by 5 by 4 mm., were almost exclusively composed of kidney cortex, and were removed as described by Castleman and Smithwick. In 348 patients, bilateral biopsies were removed; 6 patients had 3 biopsies.

Pathologic alterations of the glomeruli, juxtagramellar apparatus, tubules, stroma, and blood vessels were recorded for each specimen, without knowledge of the patient's identity or status. The morphologic observations are presented elsewhere, but for the present purpose all recognized diseases other than arteriolar nephrosclerosis have been excluded, except as specifically mentioned. Grading of abnormalities of the small arterioles was based upon the degree of thickening of their walls, at the expense of the lumen. Negative arterioles showed no evident alteration, grade I arteriolar sclerosis indicated minor localized thickenings of the walls, grade II change referred to a thickened wall equal to the diameter of the lumen, and grade III sclerosis meant that the wall thickness exceeded the diameter of the lumen. The grade recorded was the estimated average arteriolar thickening throughout the specimen.

Vascular necrosis was separately recorded as generalized or focal. Most of the latter lesions accompanied grade II arteriolar sclerosis. Clinicopathologic analysis of 40 such cases showed no significant distinctions from similar kidneys lacking focal vascular necrosis. For the clinical analyses, all available cases of the less common grades were reviewed, as well as 100 consecutive cases of the more common grades operated on in 1946 and subsequent years. Two cases of pyelonephritis were included in the group with grade III arteriolar sclerosis and vascular necrosis.

Results

Pathologic Observations. In table 1 are summarized the diagnoses for the entire series. It is evident, as found also by others, that severe renal vascular disease was uncommon, (5.0 per cent of the total cases) while moderate or slight arteriolar sclerosis predominated (93.7 per cent) in these persons with essential hypertension. On the bases of these cases and the occasional ones without any pathologic change (1.1 per cent) structural alterations of renal arterioles evidently do not constitute the etiologic basis of essential hypertension.

Vascular necrosis of the diffuse fibrinoid type occurred in 25 cases; 18 with grade III and 7 with grade II arteriolar sclerosis. Necrosis was thus not a complication only of the most advanced arteriolar disease, nor was it purely a terminal finding. In previous series the incidences reported varied from 0 of 600 biopsies to 13 of 50 cases. Schottstaedt and Sokolow found 4 cases with necrosis among 35 autopsied instances of clinically malignant hypertension with papilledema.

Pyelonephritis, as Heptinstall indicated, is
not accurately diagnosed by renal cortical biopsies; the low over-all incidence of 13.4 per cent may be due to the technic employed. The acute, chronic, and healed stages were pooled in the present study. While separate consideration of the relation of pyelonephritis to hypertension is planned, it was concluded that in this series the severity of arteriolar sclerosis was not significantly altered by the presence of pyelonephritic inflammation.

Comparison of diagnoses of the 346 graded bilateral biopsies, examined as unknowns, revealed the same grade in 60.7 per cent and a difference of one grade in 38.7 per cent. Castleman and Smithwick's reported the same grade bilaterally in 75 per cent of their cases. The intervals between multiple biopsies were from 8 days to 3 weeks. No consistent differences were found between the first and second biopsies.

**Clinical Information.** As shown in table 2, age tended to be greater in the groups with more severe arteriolar nephrosclerosis. Striking examples of this have been reported.\(^2\) A majority of male patients were within the groups with advanced vascular disease.

Survival at a 5-year postoperative interval for each grade of arteriolar nephrosclerosis is recorded in figure 1. Except for grade III arteriolar sclerosis, which was more common in older persons and pathologically more diffuse as well as of extreme degree, there were no significant group differences in the survivals after operation. All other groups had high survival rates, including those with vascular necrosis. In patients treated by sympathectomy no graver prognosis was associated with diffuse vascular necrosis, contrary to previous impressions from study of autopsy material.

Diastolic blood pressure levels, defined as the lowest values obtained in the recumbent patients, were found to be elevated corresponding to the independently assayed histologic grade of arteriolar sclerosis. With negative kidney biopsies the mean preoperative diastolic level was 100 mm. Hg; with grade I arteriolar sclerosis it was 103; grade II, 109; grade III, 122; grade III with vascular necrosis, 117. By Student's \(t\) test the mean diastolic values differed significantly between grade I, II, and III \((p \leq 0.05)\).
It was of interest that the mean diastolic blood pressure level with grade III arteriolar sclerosis and vascular necrosis was below the 130 mm. Hg thought requisite by Heptinstall\(^6\) and Pickering\(^8\) for development of this lesion. Focal necrosis was observed at considerably lower pressure levels. No case with diffuse vascular necrosis showed azotemia.

Post sympathectomy responses of blood pressure have been graded as follows according to criteria previously devised.\(^{10,11}\)

Postoperative reductions of diastolic blood pressure were: grade 1, 20 or more mm., and below 90 mm.; grade 2, 20 or more mm., and below 110 mm.; grade 3, 10 to 19 mm., and below 110 mm.; grade 4, 10 to 19 mm., not below 110 mm.; grade 5, no change, plus or minus 9 mm.; grade 6, none, increase of 10 mm. or more. Among the 77.4 per cent of the total 305 cases successfully followed medically for 5 years, the best over-all responses of blood pressure were among those with grade III arteriolar sclerosis with or without vascular necrosis, since, of these, 46 per cent and 59 per cent respectively fell into grades 1 to 3. Approximately one third of those with negative kidneys or grades I or II arteriolar sclerosis showed blood pressure reductions of grades 1 to 3. Heptinstall\(^\)\(^6\) likewise has reported substantially reduced blood pressure levels after sympathectomy in hypertension with advanced nephrosclerosis.

Retinal grading of vascular changes (Keith-Wagener) was compared with the renal histology, and the postoperative improvement in eyegrounds was analyzed. Hypertensive retinitis was not frequently severe in the entire series, since 76.7 per cent of the cases analyzed had retinal grades 0, I, and II. No definite correlation was found between the degrees of vascular change in the retina and kidney. More severe retinal changes were concentrated in older age groups, as expected. Grade IV retinitis occurred with grades I, II, and III arteriolar nephrosclerosis, but was not observed with renal vascular necrosis. More specific criteria for hypertensive retinopathy are desirable, as Minsky\(^12\) suggested.

After sympathectomy 48.6 per cent of the cases analyzed showed improvement in the appearance of the eyegrounds, without apparent relation to the different grades of arteriolar nephrosclerosis. Few abnormal eyegrounds returned to normal after sympathectomy (13.0 per cent).

Renal function, as measured by the phenolsulfonphthalein excretion, was compared before and after sympathectomy on the basis of the last available follow-up test, 1 to 9 years after operation (table 3). Impaired phenolsulfonphthalein excretion was judged as slight when less than 25 per cent dye was excreted in 15 minutes, or below 60 per cent in 2 hours; as moderate, when less than 20 per cent was excreted in 15 minutes; or marked, when less than 15 per cent was excreted in 15 minutes.

A tendency was found to decreased phenolsulfonphthalein excretion with more severe and

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<th>Table 3.—Phenolsulfonphthalein Excretion Tests before and after Operation, Compared with Renal Vascular Alterations</th>
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<tr>
<td>Kidney biopsy</td>
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<tr>
<td>18 negative</td>
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<tr>
<td>Arteriolar sclerosis</td>
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<td>100 grade I</td>
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<td>100 grade II</td>
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<td>20 grade III</td>
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<td>18 grade III and vascular necrosis</td>
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<td>Totals</td>
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extensive arteriolar nephrosclerosis. At the extremes, 83 per cent of the hypertensive persons with histologically negative kidney biopsies had normal phenolsulfonphthalein tests, in contrast to 56 per cent of those with severe arteriolar sclerosis and diffuse vascular necrosis. After sympathectomy this latter group had the least improvement of phenolsulfonphthalein excretion (33 per cent) and most commonly showed progressive impairment postoperatively (50 per cent). Among the intermediate grades of arteriolar sclerosis no significant differences in phenolsulfonphthalein excretion were evident.

Values of serum nonprotein nitrogen exceeding 40 mg. per 100 ml. were found in only 3 of the 305 cases preoperatively. One showed a negative kidney biopsy and the others were of grades I and III nephrosclerosis. All had normal phenolsulfonphthalein tests. Postoperatively all of the nonprotein nitrogen determinations were normal, and only the last case mentioned had subsequently impaired phenolsulfonphthalein excretion.

Clinical grouping of hypertensive patients, in terms of age, cerebral, cardiac and renal disease, eye-ground changes, and response to sedation have been employed for previous analyses. Among the 6 so-called Smithwick groups, an increased severity is accorded a higher group number, with groups 4 through 6 representing the most advanced. Comparison of the biopsy interpretations with the clinical groupings showed a good agreement between the clinical and pathologic data (table 4).

SELECTIVE factors naturally were involved in the choice of patients for sympathectomy, but it is notable that of 41 cases in the clinical group 1, 25 had negative arterioles or arteriolar sclerosis grade I in kidney biopsies (61 per cent), while of 16 cases in groups 5 and 6, 13 (81 per cent) showed renal arteriolar sclerosis grades II and III.

**Discussion**

From the clinical viewpoint, the value of kidney biopsy at the time of sympathectomy was not great, except that when arteriolar sclerosis grade III was present, a significantly lower percentage of survival was found 3 and 5 years postoperatively. In this subgroup, with the most severe and generalized renal vascular alterations, the pathologic grading pointed more accurately to a less favorable outcome than the clinical hypertensive grouping. Because patients with arteriolar nephrosclerosis grade III were older, the most essential factor responsible for the increased mortality appeared to be the irreversible generalized damage to their vascular systems.

All other groups with varying degrees of renal arteriolar sclerosis had practically the same rather favorable postoperative survival rates after sympathectomy. This is interpreted to mean that, short of the most generalized and extreme arteriolar sclerosis, some relaxation of renal vessels and an interruption of the natural tendency to progression of hypertensive cardiovascular disease was achieved. This benefit from sympathectomy in essential hypertension has been independently reported by White. 

Kidney function, judged by phenolsulfonphthalein excretion, decreased postoperatively in only 13 per cent of the entire group, except for those with diffuse vascular necrosis. Sympathectomy perhaps benefited renal vessels relatively more than coronary or cerebral arteries. Diffuse fibrinoid necrosis of arterioles is often regarded as the morphologic indication of a clinically malignant hypertension, but this view is based usually upon retrospective investigations of autopsied cases. The present biopsy study emphasizes that diffuse fibrinoid arteriolar necrosis is found in the absence of

**Table 4.— clinical Hypertensive Groups Compared with Kidney Biopsy Findings**

<table>
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<tr>
<th>Cases in preoperative hypertensive group</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
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<tbody>
<tr>
<td>Kidney biopsy</td>
<td>18 negative 4</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Arteriolar sclerosis</td>
<td>100 grade I 21</td>
<td>19</td>
<td>45</td>
<td>12</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>100 grade II 16</td>
<td>12</td>
<td>42</td>
<td>23</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>29 grade III 0</td>
<td>3</td>
<td>15</td>
<td>5</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>18 grade III and vascular necrosis 0</td>
<td>4</td>
<td>8</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>265 Total</td>
<td>41</td>
<td>30</td>
<td>122</td>
<td>47</td>
<td>9</td>
<td>7</td>
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</table>
retinal papilledema,7, 8, 15 at diastolic blood pressure levels below 150 mm. Hg8, 9 and without the renal insufficiency16 thought to be a requisite of malignant hypertension.

Arteriolar sclerosis as an effect of hypertension upon the renal vasculature was again supported by the pathologic findings; consequently abnormal arteriolar spasm was considered to precede any recognizable structural alterations.2, 4

Pathologic analysis suggests that fibrinoid necrosis reflects acceleration of the arteriosclerotic process, and that when interrupted by sympathectomy the process need not continue to a lethal conclusion. It is notable, however, that with fibrinoid arteriolar necrosis, a progressive postoperative decline in renal function occurred in 50 per cent of the cases analyzed, so that local destructive renal lesions often are to be expected accompanying vascular necrosis.

Arteriolar sclerosis with essential hypertension as judged by this and other studies was focal and irregular in its involvement of the renal arterioles, except in the most advanced stage. A similar irregular alteration of the arterial blood vessels elsewhere in the body may explain the lack of correlation between appearances of the renal and retinal arterioles. The status of the eye grounds and renal vessels reflected in part the general alterations of the vascular system due to hypertension, and these single diagnostic facets were of most value when combined with all other available clinical and laboratory data to provide a composite evaluation of the patient. In this selected group treated by sympathectomy, the kidney biopsy did not usually prove of greater value than other methods of evaluating the severity and probable course of essential hypertension.

Summary

Renal biopsies from 1,251 cases of essential hypertension, obtained at sympathectomy, have been analyzed pathologically. Severe arteriolar sclerosis was found in 5.0 per cent, arteriolar necrosis in 2.0 per cent, and pyelonephritis in 13.4 per cent of cases. Moderate local variations in the arteriolar alterations were found in single biopsies and in about 40 per cent of bilateral specimens.

Clinicopathologic correlations in 305 patients showed a general correspondence between the degree of renal arteriolar sclerosis and the clinical evaluation, postoperative blood pressure response, and renal function judged by phenolsulphonphthalein excretion tests. Severe arteriolar sclerosis was associated with more advanced age and a higher mortality.

Diffuse fibrinoid arteriolar necrosis was not correlated uniformly either with papilledema or other clinical criteria of malignant hypertension, and was not indicative of a uniformly grave prognosis. The kidney biopsy is considered as ancillary to the other methods used in the clinicopathologic evaluation of the hypertensive state.

SUMMARIO IN INTERLINGUA

Biopsias renal obtenite al sympathectonia ab 1,251 casos de hypertension essevate analysate pathologicamente. Sever sclerosis arteriolar esseva trovate in 5,0 pro cento, necrosis arteriolar in 2,0 pro cento, e pyelonephritis in 13,4 pro cento. Moderate variationes local in le alterationes arteriolar esseva trovate in biopsias unica e in circa 40 pro cento del specimens bilateral.

Correlaciones clinico-pathologic in 305 paientes monstrava un correspondentia general inter le grado de sclerosis reno-arteriolar e le evaluation clinic, le responsa de pression sanguine postoperatori, e le function renal secundo tests del excretion de phenolsulphonphthaleina. Sever grados de sclerosis arteriolar esseva associate con etates major e un augmento del mortalitate.

Diffuse necrosis arteriolar fibrinoide non esseva uniformemente correlate con papilledema o con altre criterios clinic de hypertension maligne. Illo non esseva un indication uniforme de prognosis disfavorabile. Le biopsia renal es considerate como ancillari a altre methodos usate in le evaluation clinico-pathologic del stato de hypertension.

REFERENCES

1 Smithwick, R. H.: A technic for splanchnic resection for hypertension. Surgery 7: 1, 1940.
2 Castleman, B., and Smithwick, R. H.: The relation of vascular disease to the hypertensive state,
based on a study of renal biopsies from 100 hypertensive patients. J. A. M. A. 121: 1256, 1943.


Southey’s Tubes

By Robert W. Buck, M.D.

Southey’s tubes. These are described by Reginald S. Southey (1835–1899) in the report of a case of "Chronic Parenchymatous Nephritis of Right Kidney. Left Kidney Small and Atrophied. Old Scrofulous Pyelitis" which was read before the Clinical Society of London, April 27, 1877 and which appears in the Transactions of the Clinical Society 10: 152–157, London, 1877.

"I determined to endeavour to relieve her dropsy by mechanical means, and to this end employed an apparatus which is, I believe, novel in England. I had a small trocar made, with tiny well-fitting canulas, but little larger than the ordinary subcutaneous injection needles; these canulas, instead of terminating with a protecting rim, end with a little bulbous extremity.

"They are inserted into the subcutaneous cellular tissue with great facility, and with no more pain than the ordinary needle-prick produces; the canula, inserted parallel to the surface, is left stuck in the skin; and a long, fine capillary india-rubber tubing is now drawn over the protruding bulb and tied in situ. This tying in of the canula is not essential or even often necessary.

"The long ends of the capillary tubes are now carried outside the bed and into a pan beneath it, into which the serous dropsical fluid drips or drains away.

"One drainage canula was inserted into each leg, and through the two tubes about 2!2 ounces, or, in fact, 71 ounces, of dropsical effusion drained away each 24 hours, with considerable relief, of course, to the tension."
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Circulation. 1957;16:207-212
doi: 10.1161/01.CIR.16.2.207
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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