Susceptibility of Rats with Renal Hypertension to Pyelonephritis, and Predisposition of Rats with Chronic Pyelonephritis to Hormonal Hypertension

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With the technical assistance of Helen Conry

Although pyelonephritis and hypertension seem related clinically, a number of inconsistencies attend the view that the renal inflammation is the direct cause of the vascular disease. Furthermore, when experimental chronic pyelonephritis is produced in rats by hematogenous infection with any one of several different bacterial species, significant hypertensive vascular disease fails to develop, even when renal function is impaired severely. With the addition to the experimental model of a mixed infection and a reduction of renal mass by unilateral nephrectomy, hypertension still does not supervene.

These observations have suggested two alternative explanations to account for the clinical coincidence of pyelonephritis and hypertension. They are: (1) hypertension increases susceptibility to experimental acute pyelonephritis; and (2) chronic pyelonephritis renders the organism more vulnerable to stimuli affecting the vascular system and thus predisposes to the development of hypertension.

The demonstrations of increased susceptibility to experimental acute pyelonephritis and of aggravation of hypertension by infection, in rats with hormonal hypertension, have provided data pertinent to the first hypothesis. An evaluation of susceptibility to acute pyelonephritis in rats with moderately severe renal hypertension, and a test of the second hypothesis by the administration of desoxycorticosterone (DCA) and saline to rats with experimental chronic pyelonephritis, constitute the purposes of the present investigation. A preliminary study provided the background for the current experiment.

Methods

Susceptibility to Acute Pyelonephritis in Renal Hypertension

Male albino rats of the Carworth strain, initially weighing 100 to 150 Gm., were fed rat chow and allowed tap water ad libitum. In order to produce moderately severe hypertension, rats first were subjected to a right nephrectomy; two weeks later the left renal artery of 60 per cent of these rats, selected by means of a table of random numbers, was constricted with a silver clip. Before application, the clip was bent around a strip of copper-foil, 0.3 mm. thick, so that the degree of constriction of each artery was kept reasonably constant.

Systolic blood pressures were determined every two weeks after surgery with a tail plethysmograph. Approximately 10 per cent of the rats died, but most of the survivors became hypertensive (systolic blood pressure 140 mm. Hg and over) within 4 to 12 weeks. Surgery was done under aseptic conditions, and both operated and control rats were given 10 mg. of tetracycline intramuscularly immediately postoperatively. Eight to 12 weeks after surgery, susceptibility to pyelonephritis was compared in the hypertensive "nephrectomy-clipped" (NpK), and the normotensive "nephrectomy only" (NpO) groups, and in a group of intact normotensive controls, employing the same plan as in the previous study in rats with DCA hypertension.

This technique relies on the observation that hematogenous inoculation of *Escherichia coli* in normotensive rats results in a high incidence of acute pyelonephritis only if the kidneys are subjected to gentle massage through the intact abdominal wall immediately after introduction of bacteria, whereas without massage pyelonephritis rarely develops. Accordingly, to compare susceptibility in normotensive and hypertensive rats, 0.5 ml.
of an 18-hour tryptose broth culture of the strain of E. coli used in previous studies was injected by the intracardiac route without renal massage. The rats were sacrificed two weeks later for bacteriological and pathological studies. To maintain a check on the continued virulence of the E. coli in the present experiment, a group of normal rats were injected, with renal massage, and the incidence of gross lesions noted at two weeks. Bacteriological, pathological, and biochemical methods have been described in our previous publications.

The intensity of infection in animals sacrificed at two weeks was expressed on a 1+ to 4+ scale, based on the growth on culture plates of inocula prepared from the ground kidney.11 Because of some question about the significance of difference in incidence of positive cultures at two weeks (see Results) and in order to determine the number of bacteria in the kidneys in a more quantitative fashion, an additional group of hypertensive NpK, normotensive NpO, and intact normotensive rats were sacrificed twice with a three-week interval. Osmolality was measured six weeks after the first massage.

### Table 1

<table>
<thead>
<tr>
<th>Period of deprivation</th>
<th>Massaged*</th>
<th>Not massaged</th>
</tr>
</thead>
<tbody>
<tr>
<td>24 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Number of rats</td>
<td>Osmolality (mOsm./Kg.)</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2275 ± 146</td>
</tr>
<tr>
<td>48 hours</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2926 ± 258</td>
</tr>
<tr>
<td>24 hours plus</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2531 ± 277</td>
</tr>
<tr>
<td>Pitressin†</td>
<td>5</td>
<td>2008 ± 291</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2749 ± 551</td>
</tr>
<tr>
<td></td>
<td>5</td>
<td>2452 ± 528</td>
</tr>
</tbody>
</table>

*Rats were massaged twice with a three-week interval. Osmolality was measured six weeks after the first massage.

†One hundred milliequivalents of Pitressin Tannate in oil administered six hours after onset of fluid deprivation.

The consistency of results despite lack of maximum concentration, urine osmolality was compared in normal rats after 24- and 48-hour periods of dehydration, and after 24-hour dehydration accompanied by the administration of Pitressin Tannate in oil (table 1). In addition, since other authors have referred to renal massage as "trauma,"12-14 whereas we have demonstrated repeatedly that renal massage produces only temporary renal engorgement, no elevation of BUN, and no pathological change in the kidneys,3,10 both massaged and unmassaged rats were included in this comparison.
Table 2

Susceptibility to Pyelonephritis in Rats with Hypertension

<table>
<thead>
<tr>
<th>Group</th>
<th>Number of rats sacrificed</th>
<th>Gross lesions</th>
<th>Histological lesions</th>
<th>Positive cultures</th>
<th>Preinoculation systolic BP (mm. Hg)</th>
<th>BUN (mg./100 ml.)</th>
<th>Final body weight (Gm.)</th>
<th>Heart weight (mg./100 Gm.)</th>
<th>Kidney weight (mg./100 Gm.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unilateral nephrectomy-artery clip (NpK)</td>
<td>30</td>
<td>43.3</td>
<td>51.8</td>
<td>54.0</td>
<td>158</td>
<td>34.4</td>
<td>406 ± 9.1</td>
<td>304 ± 11.4</td>
<td>512 ± 10.4</td>
</tr>
<tr>
<td>Unilateral nephrectomy only (NpO)</td>
<td>31</td>
<td>12.9</td>
<td>17.2</td>
<td>34.5</td>
<td>120</td>
<td>27.2</td>
<td>381 ± 10.4</td>
<td>253 ± 5.0</td>
<td>538 ± 9.5</td>
</tr>
<tr>
<td>Intact controls</td>
<td>25</td>
<td>11.9</td>
<td>9.8</td>
<td>4.4</td>
<td>113</td>
<td>21.0</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

\[ P^2 \text{ or } F \]

\[ P < 0.01^* < 0.01^* \]

\[ 0.10^* < 0.01^* < 0.01^* \]

\[ P^2 \text{ for individual group comparisons} \]

| NpK vs. NpO | 0.01* | 0.01* | 0.15 | 0.001* | 0.01* | > 0.05 | 0.001* | > 0.05 |
| NpK vs. controls | 0.01* | 0.02* | 0.04* | 0.001* | 0.001* | |
| NpO vs. controls | > 0.05 | > 0.05 | > 0.05 | > 0.05 | 0.02* |

Statistical analyses as follows: Analysis of variance or chi-square test for three categories (values italicized) were employed when data were available for three groups. F values greater than 4.9 are significant at 1 per cent level for degrees of freedom represented here; chi-square values greater than 6.0 are significant at 5 per cent level for two degrees of freedom and greater than 9.2 at 1 per cent level. Chi-square or t-test for two categories was performed for individual group comparisons or when data for only two groups were available, and in these instances the \( P \) value only is given in the table. The standard errors to the groups' means are indicated in instances where a t-test only was performed.

*Significant values.

Since intact controls had two kidneys, the results can be recalculated on the basis of numbers of kidneys rather than numbers of rats; this difference then becomes highly significant \( (P < 0.01) \).

Results

Susceptibility to Acute Pyelonephritis in Rats with Renal Hypertension

Incidence of Acute Pyelonephritis

Comparison of susceptibility in the hypertensive NpK group with that in the NpO and intact control groups is presented in table 2. The incidence of gross and histological lesions of acute pyelonephritis at two weeks, as determined by criteria described previously, was significantly greater in the hypertensive rats than in either of the normotensive groups. Positive cultures for \( E. \ coli \) also were more frequent in the hypertensive animals; the difference was significant in comparison with the intact controls \( (P = 0.04) \), although not as compared with the NpO group \( (P = 0.15) \). However, the "intensity of infection index"* in the NpK group was 0.405 as compared with 0.211 in the NpO animals, indicating that the infected kidneys in the latter group generally had only a few organisms, and coinciding with the observation that positive cultures in the NpO group often were unaccompanied by significant histological lesions of pyelonephritis. Blood cultures were sterile in all animals.

In keeping with their hypertension, the relative heart weights of the NpK rats were greater than those in the NpO group. Relative heart weights were significantly greater in the hypertensive rats than in either of the normotensive groups. Positive cultures for \( E. \ coli \) also were more frequent in the hypertensive animals; the difference was significant in comparison with the intact controls \( (P = 0.04) \), although not as compared with the NpO group \( (P = 0.15) \). However, the "intensity of infection index"* in the NpK group was 0.405 as compared with 0.211 in the NpO animals, indicating that the infected kidneys in the latter group generally had only a few organisms, and coinciding with the observation that positive cultures in the NpO group often were unaccompanied by significant histological lesions of pyelonephritis. Blood cultures were sterile in all animals.

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\[ \text{Intensity index} = \frac{\text{sum of grades (1+ to 4+) in infected kidneys}}{\text{total number of kidneys in group} \times 4} \]
Unilateral nephrectomy. contralateral clip (hypertensive)

- Unilateral nephrectomy only (normotensive)
- Intact normotensive controls

**Figure 1**

Concentration of bacteria per gram of kidney tissue following inoculation of *E. coli* without renal massage. Numbers in parentheses represent the number of kidneys examined at each period in each group.

Tissue kidney weights were the same in these two groups, indicating that the renal hypertrophy which developed following the unilateral nephrectomy did not account for the vulnerability to pyelonephritis.

Blood urea nitrogen was significantly higher in both unilaterally nephrectomized groups than in the intact controls and was higher in the NpK rats than in the NpO animals. Whereas an elevated BUN may have played a role in the increased vulnerability of the NpK group, the difference in BUN between NpO and intact control groups was not associated with an increase. Indeed, the elevations of BUN occurred usually in infected rats and may have been secondary to their pyelonephritis.

Thirty-two normotensive intact rats were injected with *E. coli* followed by renal massage during the course of this experiment. Ninety per cent developed typical gross lesions of pyelonephritis, indicating the virulence of the strain of *E. coli* and reconfirming the ability of renal massage to localize infection in the kidney.\(^{10, 11}\)

Uninoculated NpK rats which died spontaneously after surgery, either before or after becoming hypertensive, showed no gross pyelonephritic lesions, and those which were examined bacteriologically had sterile kidneys.

**Number of Bacteria in Kidneys of Hypertensive and Normotensive Rats**

The bacterial counts of the inocula given to the rats which were sacrificed at intervals of 1, 3, and 24 hours after inoculation were in the $10^9$/ml range. As indicated in table 3, at 24 hours the number of bacteria in the kidneys of six of the eight hypertensive NpK rats was from 10 to 1,000 times greater than the number in the normotensive NpO group, a difference significant at the 1 per cent level (Mann-Whitney test\(^{15}\)). The difference was even more pronounced between the kidneys in the NpK group and those in the intact normotensive group ($P = 0.002$). The counts in the NpO group were not significantly greater than those in the intact group ($P = 0.10$). Blood cultures at 24 hours were sterile in many of the rats and never over $10^9$/ml. The differences in numbers of bacteria in the kidneys at one and three hours were in the same direction (fig. 1), but were small and not significant, particularly since blood cultures done at one hour in all three groups were in the range of $10^4$ to $10^5$ bacteria/ml.

**Pathological Changes Due to Hypertension**

Lesions attributable to hypertension appeared to be minimal. Slight to moderate medial hypertrophy of arterioles was noted in hypertensive NpK rats. Other parenchymal changes noticed at two weeks could be attributed to the pyelonephritis. Noninflammatory changes were best studied in the animals serially sacrificed at 1, 3, and 24 hours, since even the earliest histological lesions of pyelonephritis, consisting of cellular infiltration only, do not develop during the first 24 hours following bacterial inoculation.\(^{11}\) In the 16 NpK animals in this group, gross lesions were absent. On histological examination, not more than a third showed parenchymal changes resembling those described by Wilson and Byrom\(^3\) and consisting of a scattering of dilated tubules which occasionally contained eosinophilic material. Less commonly, glomer-
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Influence of DCA given in doses of 12.5 mg. intramuscularly on the eighth, thirteenth, and twenty-third weeks of the experiment to rats with chronic pyelonephritis. The figures for urine osmolality represent the mean and standard error determined on the sixth week of the experiment. Each blood pressure point represents the mean and standard error for all surviving rats at the week of the experiment indicated. The blood pressures of rats which died are included in the average up to and including the period immediately prior to their deaths. The figures in parentheses represent the number of animals at the start and at the end of the experiment.

Figure 2

Effect of DCA administered rapidly after a period of 17 weeks of no treatment in rats with chronic pyelonephritis. 6.25 mg. were given intramuscularly weekly from the eighteenth through the twenty-first weeks, and on the twenty-fifth and twenty-sixth weeks of the experiment. Notations are as in figure 2.

Figure 3

Further evidence is derived from a study which has been reported previously only in part,7 and in which the left kidney was clipped but the right kidney was left in situ. Accordingly, blood pressure elevation was mild and in 37 rats the average maximum level attained was only 137 mm. Hg, and the average final pressure prior to inoculation only 121 mm. Hg. Gross pyelonephritis after challenge with E. coli was noted in 29.7 per cent and positive cultures in 40.4 per cent of the rats in this group; of particular pertinence to the present discussion, however, was the comparison of incidence in the intact right kidneys and in the clipped left kidneys. Gross pyelonephritis was present in 9 of 37 unclipped right kidneys and in 6 of 37 clipped left kidneys; positive cultures were noted in 14 of 37 unclipped and in only 6 of 37 clipped. These data indicate clearly that the clipped kidney certainly is not more vulnerable than the intact kidney in terms of vulnerability to pyelonephritis.

Thus, in table 4, the incidence of pyelonephritis in the NpK group is expressed in relationship to the degree of hypertension; and the levels of blood pressure and heart weights in the infected versus the noninfected rats are compared. Although with these small subgroups the differences are not statistically significant, they indicate a similar trend in all the parameters, suggesting that higher pressures are associated with more infection.

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its unclipped mate. Moreover, it will be noted that more than 80 per cent of the left kidneys (32 of 37) did not become infected or develop lesions when only a slight elevation of blood pressure was present, despite the presence of the renal artery clip.

**Effect of DCA and Saline on Rats with Experimental Chronic Pyelonephritis**

**Blood Pressure**

Figures 2 to 5 indicate the blood pressure curves during the course of each of the four experiments. The findings at autopsy are outlined in table 5.

All four pyelonephritic groups demonstrated similar decreases in urine osmolality. In group I (fig. 2), saline was started three weeks after the second inoculation of bacteria, and DCA was given in three doses of 12.5 mg. at widely spaced intervals. The pyelonephritic rats achieved a significantly higher pressure than the controls after the third injection and maintained this difference until sacrifice at 34 weeks. Average levels of blood urea nitrogen and final body weights were the same, but relative heart weights were greater in the pyelonephritic rats. In group II (fig. 3), rats were followed for almost five months after bacterial inoculations before DCA and saline were administered. Hypertension did not de-
velop. DCA was then given more rapidly than in the previous experiment but to the same total dosage (37.5 mg.). Hypertension promptly appeared in the pyelonephritic rats, and although the noninfected rats also eventually became hypertensive, they remained significantly lower. Likewise, the hearts of the pyelonephritic animals were heavier, while final body weights again were identical. Infection was less intense than in the rats in group I which were sacrificed nine weeks earlier, but was still present in the majority.

Rats in which a "figure-of-8" tie of one kidney was performed (group III, fig. 4) and rats with pyelonephritis alone (group IV, fig. 5) did not become hypertensive nor were their pressures ever significantly higher than those of their respective control groups. The intensity of infection and the severity* of pyelonephritis, however, were of the same order in groups III and IV as in the two groups receiving DCA.

Pathology

Grossly, the kidneys in all four pyelonephritic groups showed the scarring and distortion which we have described previously. Renal stones, secondary to the infection with Proteus, were present in approximately 25 per cent of the rats (9 of 37 survivors, 10 of 31 which died during the study). In the "figure-of-8" group, the ligated kidney was shrunken rather than hypertrophied as is the case with this procedure when the contralateral kidney is removed and the animal becomes hypertensive.17

Microscopically, the typical changes of chronic and active pyelonephritis were present including "pus casts" in animals with positive kidney cultures. The arterioles in the pyelonephritic rats in groups III and IV were normal and similar to those in control animals. In pyelonephritic and control rats in the two groups receiving DCA, however, medial hypertrophy was noted, while glomeruli were swollen and occasionally showed hyalinization. In addition, in several of the pyelonephritic rats which received DCA and developed severe hypertension, a few arterioles displayed hyperplastic changes and intimal thickening suggesting accelerated nephrosclerosis (fig. 6).

Saline Intake in Pyelonephritic Rats Receiving DCA

The ad libitum saline consumption of pyelonephritic and normal rats receiving DCA in group II was compared on two occasions. Daily intakes were measured for one week, and the average consumption (ml. of saline per 100 Gm. of body weight per day) was calculated. In the pyelonephritic rats, the mean values and standard errors were 44 ± 4 ml. and 48 ± 4 ml. during the twenty-fourth and thirty-fourth weeks of the experiment, respectively. The control rats averaged 28 ± 2 and 30 ± 5 at these same times. Differences between the pyelonephritic and control rats

\*Severity index = \frac{\text{sum of grades (1+ to 4+ of severity)}}{\text{total number of kidneys} \times 4}
### Table 5

**Autopsy Data in Rats with Chronic Pyelonephritis**

<table>
<thead>
<tr>
<th></th>
<th>Group I (DCA-1)</th>
<th>Group II (DCA-2)</th>
<th>Group III (&quot;figure-of-8&quot;)</th>
<th>Group IV (pyelonephritis only)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Experimental</td>
<td>Control</td>
<td>Experimental</td>
<td>Control</td>
</tr>
<tr>
<td>Number of rats</td>
<td>15</td>
<td>15</td>
<td>7</td>
<td>8</td>
</tr>
<tr>
<td>Week of sacrifice</td>
<td>34</td>
<td>34</td>
<td>43</td>
<td>43</td>
</tr>
<tr>
<td>(after initial</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>infection)</td>
<td></td>
<td></td>
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<tr>
<td>Final weight (Gm.)</td>
<td>292</td>
<td>303</td>
<td>305</td>
<td>334</td>
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<tr>
<td>Standard error</td>
<td>8.1</td>
<td>7.8</td>
<td>9.7</td>
<td>9.9</td>
</tr>
<tr>
<td>(±) <em>P</em></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
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<tr>
<td>Final blood pressure</td>
<td>152</td>
<td>126</td>
<td>176</td>
<td>147</td>
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<tr>
<td>(mm. Hg)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard error</td>
<td>4.9</td>
<td>4.9</td>
<td>6.2</td>
<td>9.5</td>
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<tr>
<td>(±) <em>P</em></td>
<td>0.001*</td>
<td>0.02*</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
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<tr>
<td>Heart weight</td>
<td>346</td>
<td>302</td>
<td>344</td>
<td>297</td>
</tr>
<tr>
<td>(mg./100 Gm.)</td>
<td>14.3</td>
<td>7.3</td>
<td>11.9</td>
<td>9.0</td>
</tr>
<tr>
<td>Standard error</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(±) <em>P</em></td>
<td>0.015*</td>
<td>0.01*</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>BUN (mg./100 ml.)</td>
<td>19.5</td>
<td>17.1</td>
<td>21.3</td>
<td>24.1</td>
</tr>
<tr>
<td>Standard error</td>
<td>1.1</td>
<td>0.5</td>
<td>1.1</td>
<td>1.9</td>
</tr>
<tr>
<td>(±) <em>P</em></td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
<td>&gt;0.05</td>
</tr>
<tr>
<td>Rats infected with</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td><em>P. morganii</em></td>
<td>15</td>
<td>1</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td></td>
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<tr>
<td>Rats infected with</td>
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<tr>
<td><em>S. zymogenes</em></td>
<td>13</td>
<td>1</td>
<td>4</td>
<td>0</td>
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<tr>
<td><em>Intensity index'</em></td>
<td>0.905</td>
<td>0.008</td>
<td>0.445</td>
<td>0</td>
</tr>
<tr>
<td>+Severity index'*</td>
<td>0.600</td>
<td>0</td>
<td>0.570</td>
<td>0</td>
</tr>
<tr>
<td>Rats with stones</td>
<td>4</td>
<td>0</td>
<td>0</td>
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</table>

*Significant values.
†See text for definition.
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Discussion

Susceptibility to Infection in Hypertension

The data indicate that rats with renal hypertension, like rats with DCA hypertension, show an increased susceptibility to pyelonephritis. Brackett and Smythe have reported similar findings in rats with mild hypertension following renal encapsulation. This vulnerability may be the result of renal injury secondary to hypertension or ischemia. De Navasquez has demonstrated that scarring of the kidney favors localization of bacteria, and Roeha et al., using microcautery to produce small focal scars, have confirmed that the localization occurs in areas of intrarenal or medullary hydronephrosis. The possibility that lesions of this type were present in our experimental preparation is quite real; small infarcts or areas of hydronephrosis could escape detection or be obscured by changes secondary to infection. However, gross scarring other than that resulting from pyelonephritis was not noted, and while histological examination of the kidneys from some of the rats did reveal damage which could have provided a focus for bacterial trapping, these lesions were absent in the majority of animals. Wilson and Byrom also have noted that renal pathology is not present consistently despite marked and sustained hypertension and have been impressed particularly by absence of lesions in the clipped kidney. These considerations suggest that anatomical injury may not be the sole cause of the vulnerability to pyelonephritis.

The elevation of BUN in the NpK group may have favored development of infection, although we are not aware of a mechanism by which azotemia would enhance growth of

*The water intake of normal rats, determined in this fashion, was approximately 5 to 10 ml./100 Gm. body weight per day, and of pyelonephritic rats, approximately 10 to 15 ml./100 Gm.

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E. coli. Moreover, the retention of urea could have been secondary to the pyelonephritis. On the other hand, Braude and Siemienski have demonstrated that elevated levels of urea in the kidney favor infection with bacteria of the Proteus group which contain a urease capable of urea breakdown. The relative inadequacy of renal oxygenation in the hypertensive kidney, which Huckabee has observed, also has been suggested as a metabolic cause for the increased susceptibility.

A hemodynamic mechanism for increased susceptibility is suggested by the old observation that the kidney swells following administration of epinephrine, and by the more recent studies of Mehrizi and Hamilton in dogs given norepinephrine. These investigators noted a fall in renal blood flow and a marked delay in renal transit time of plasma when blood pressure was maintained at levels of 140 to 200 mm. Hg by norepinephrine infusion, and attributed the delay to an increase in the vascular volume of the kidney. Although these acute hemodynamic effects of pressor drugs cannot be considered analogous to the situation in the chronic state nor, to our knowledge, has transit time in chronic hypertension been studied, it is interesting to speculate whether a slowed passage of blood through a hypertensive kidney might "trap" bacteria long enough to permit interstitial accumulation and establishment of infection.

In summary, renal damage secondary to hypertension seems to be the most likely reason for the vulnerability to pyelonephritis noted in these rats. Ischemia and its consequences per se may play a role, but without significant elevation of blood pressure cannot entirely explain the findings. Metabolic and hemodynamic factors, which might account for increased susceptibility in mild hypertension without renal damage, require further study.

Predisposition to Hypertension in Chronic Pyelonephritis

Enhancement of the pressor effects of DCA and saline in rats with chronic pyelonephritis is not surprising in view of previous observations of the sensitizing and additive effects of adrenal steroids and of sodium chloride following other types of renal injury. Thus, although parenchymal renal damage from chronic pyelonephritis per se has not produced hypertensive vascular disease in the rat in our studies, the animal seems "sensitized" to the mineralocorticoid factors which ordinarily can cause hypertension. However, the pyelonephritic rats consumed significantly greater amounts of saline than normals. This may be obligatory because the pyelonephritic rat, in its poorly concentrated urine, loses more fluid than the normal rat and to increase water intake when saline is the only drinking fluid offered, the animal must take additional sodium chloride. Accordingly, since the amount of sodium apparently is the determining factor in the development of DCA hypertension, the aforementioned "sensitization" may be merely a quantitative phenomenon caused by greater retention of sodium in the pyelonephritic animals. The equal terminal body weights in both groups suggest that this was not the case, but the point could only be established clearly by sodium-balance data which were not obtained in this study. In any event, whether directly by "sensitization" to the stimulus, or indirectly by an obligatory exaggeration of the stimulus as the result of the tubular injury, pyelonephritis was the primary factor in the enhancement of hypertension.

With the exception of renoprival hypertension, renal hypertension as produced experimentally is associated usually with interference with blood supply to the kidney. In pyelonephritis, however, the disease is parenchymal, and although Kincaid-Smith has suggested that the inflammatory lesion may injure arterioles and cause ischemia, Hepinstall et al. have demonstrated that a diminution of the vascular bed does not result. By taking radiographs of kidneys following injection of contrast material, they have shown that renal vasculature in chronic pyelonephritis remains patent despite parenchymal scarring and contraction. Maintenance of an adequate blood supply and absence of ischemia may explain the failure of hyper-
tension to develop with any consistency in chronic pyelonephritis, while the parenchymal lesion, as suggested from our data, may enhance the effects of other stimuli to hypertensive disease.

It is worth noting that pyelonephritic rats in which one kidney was damaged by "figure-of-8" ligature did not develop hypertension although the contralateral kidney was diseased, whereas with this type of ligature and contralateral nephrectomy, hypertension invariably develops. The observation that the ligated kidneys were shrunken suggests an explanation which would emphasize the difference between renal parenchymal disease and renal ischemia in the pathogenesis of hypertension. When hypertension develops following "figure-of-8" ligature and contralateral nephrectomy, the ligated kidney is hypertrophied and, indeed, greater mass tends to correlate with more severe hypertensive disease. It is suggested that this hypertrophy, in the presence of the constricting ligature, results in ischemia and subsequent hypertension. Contrariwise, when the contralateral kidney is left in situ as in the present study, although it is affected by parenchymal disease (i.e., pyelonephritis), it does not stimulate hypertrophy. Accordingly, the ligated kidney atrophies and, presumably because ischemia fails to develop, hypertension does not supervene.

Summary
Renal hypertension was produced in rats by unilateral nephrectomy and constriction of the artery to the remaining kidney. Both an increased concentration of bacteria in the kidney 24 hours after inoculation of Escherichia coli, and an increased incidence of lesions of pyelonephritis two weeks after inoculation were noted in these hypertensive rats. Administration of desoxycorticosterone (DCA) and saline to rats with chronic experimental pyelonephritis resulted in development of hypertension of greater severity than in normal rats. Chronic pyelonephritis alone did not result in hypertension, nor did unilateral "figure-of-8" ligature in the pyelonephritic rat. Increased susceptibility to pyelonephritis in hypertension and predisposition to hypertension in chronic pyelonephritis thus can account for a relationship between hypertension and pyelonephritis in the rat. If these results can be applied to the problem in man, they suggest an explanation for the clinical coincidence of the two diseases which seems more consonant with existing facts than a relationship of direct etiology.

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