Renal Papillary Necrosis—A Sixteen-Year Clinical Experience

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ABSTRACT
This study sought to characterize patients with renal papillary necrosis seen at one tertiary referral center by reviewing medical records of patients with a confirmed diagnosis between January 1, 1976 and September 1, 1992. One hundred sixty-five cases were identified. The mean age at diagnosis was 57 yr (SD 15). The female-to-male ratio was 1.1:1.0. Ninety-two percent of patients were white. Seventy-seven percent of cases were unsuspected before diagnosis, and 16% were diagnosed at autopsy. The most common associated conditions were urinary tract infection, analgesic abuse, urinary tract obstruction, diabetes mellitus, and sickle cell disease. There was considerable overlap in the presence of these conditions, with two or more identified in 36% of patients. In addition, 11% of patients had none of these well-recognized risks. Other diagnoses in this group included lupus nephritis, Wegener’s granulomatosis, and renal artery stenosis. A decline in case numbers of approximately 50% was demonstrated over the last 10 yr studied. This period was associated with a 57% reduction in the number of excretory urograms carried out, suggesting that changes in diagnostic imaging preference may have contributed. Vital status and renal outcome data after diagnosis were obtained in 93% of cases. Of those diagnosed while living, survival was lowest among diabetic patients. Ten-year survival for nondiabetics was not significantly different from the expected survival of an age- and sex-matched cohort. The overall risk for requiring renal replacement therapy after the diagnosis of renal papillary necrosis in surviving patients was low (7% of 136 patients at risk). Diabetes was the only factor associated with an increased risk of end-stage renal failure. This study emphasizes that continued recognition of papillary necrosis will necessitate an awareness of its clinical spectrum in the context of current diagnostic and therapeutic practice.

Key Words: Diabetes mellitus, analgesic abuse, urinary tract infection, urinary tract obstruction, sickle cell disease

Renal papillary necrosis (RPN) is a term used to describe a particular form of renal damage in which any or all of the papillae undergo selective necrosis in a manner that can be clearly demonstrated radiologically or histologically. The clinical syndromes that have been described as accompanying this process include acute fulminant renal failure, obstruction by a sloughed papilla, hematuria, and loin pain, passage of tissue in the urine, recurrent or severe urinary tract infection (UTI), and chronic renal failure (1–8).

From its first clear description by Friedelrich in 1877 in association with benign prostatic obstruction (9), accepted relationships have been established between RPN and diabetes mellitus, excessive use of analgesic mixtures, sickle cell disease, and urinary obstruction (6,9–12). The role of UTI as an independent risk factor remains unclear, but it is undoubtedly a frequent accompaniment (1,8,13,14). Individual reports and small collections of cases have suggested associations between RPN and a number of other conditions (15–19).

The currently available literature on the clinical spectrum of RPN draws heavily from autopsy studies (20–24), small groups of cases from single institutions (2,3,25,26), and studies confined to radiologically or surgically diagnosed cases (27–29). Only a few series have previously included large numbers of patients or a full clinical spectrum (1,8,30). Moreover, there are no recent studies of RPN to define the relevance of this lesion in modern medical practice, the prognosis over a prolonged period from the time of diagnosis, and the trends that may have occurred in the past two decades. We therefore sought to describe the characteristics of RPN at a single, large, tertiary referral center over the past 16 yr and observe trends and outcome during this period of time.

METHODS
Chart Review

By use of the Mayo Clinic’s unique medical records system, a computerized search was made of all patient visits registered between January 1976 and September 1992 for diagnoses of “renal papillary necrosis” or equivalent terms. The chart of each patient identified was reviewed. A radiologic diagnosis was accepted if excretory urography (EXU), retrograde urography, or both were reported by a consultant
radiologist at our institution as showing "changes of renal papillary necrosis" or "definite renal papillary necrosis." Reports of ultrasound and computed tomographic (CT) scans were also reviewed when available—in no case was a diagnosis of RPN made for the first time by these imaging modalities. Cases with reports stating "possible" or "probable renal papillary necrosis" were not included in the absence of other definite diagnostic evidence. Pathologic diagnosis was accepted if examination of passed tissue, a surgical specimen, or autopsy by a consultant pathologist at our institution was reported as showing RPN. Cases with pathologic or radiologic diagnosis from other institutions without subsequent review of diagnostic material at Mayo Clinic were also excluded. Of 229 charts reviewed, 165 met the above criteria. Along with basic patient characteristics, details of diagnostic procedures, relevant laboratory studies, additional medical conditions, radiologic and histologic reports, and available follow-up were recorded.

Data for analgesic abuse were accepted if a clear history of prolonged heavy use of analgesic mixtures, aspirin or phenacetin alone, or nonsteroidal anti-inflammatory drugs was documented with a compatible clinical picture. Obstruction was accepted if structural or functional urinary tract obstruction (not due to a sloughed papilla) was clearly documented. UTI was based on the presence of positive urine culture at or within 1 month of diagnosis. Details regarding prior single or recurrent pyelonephritis or simple urinary infections were also recorded when available. Sickle cell disease was accepted with hemoglobin S levels diagnostic of the heterozygous or homozygous state.

Follow-Up

An attempt was made to obtain outcome data through March 1993 on all patients. Questionnaires were sent out to those without adequate chart information on or after this date, and phone contact was attempted with nonresponders after 2 months.

Statistical Analysis

Data were analyzed with the SAS software package (SAS Institute, Cary, NC). Survival curves were constructed by use of the Kaplan-Meier method for the overall group and for selected subgroups. An expected survival curve was constructed on the basis of an age- and sex-matched cohort drawn from the 1980 Minnesota life tables. Survival free of end-stage renal failure was also estimated by the Kaplan-Meier method. Differences in survival between groups were compared by use of the log-rank test. Characteristics of those with Type I versus Type II diabetes were compared with Wilcoxon rank sum or χ² tests as appropriate. All tests were two sided with a significance level of 0.05.

RESULTS

The characteristics of the 165 patients who met our criteria for RPN are shown in Table 1. The patients were predominantly of the white race (92.1%), with a small female predominance overall. The diagnosis was suspected before radiographic or histologic diagnosis of RPN in less than one-quarter (23.0%) of patients.

### TABLE 1. Characteristics of overall group with RPN as well as subgroups with major associated conditions and a group with rare associations or no identified association

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Overall Group</th>
<th>UTI</th>
<th>Analgesic Abuse</th>
<th>Urinary Tract Obstruction</th>
<th>Diabetes Mellitus</th>
<th>Sickle Cell Disease</th>
<th>Other Cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (% Total Cases)</td>
<td>165</td>
<td>67 (40.6)</td>
<td>59 (35.7)</td>
<td>48 (29.1)</td>
<td>37 (22.4)</td>
<td>5 (3.0)</td>
<td>18 (10.9)</td>
</tr>
<tr>
<td>Age (yr) (mean ± SD)</td>
<td>57 ± 15.2</td>
<td>60 ± 15.5</td>
<td>55 ± 13.8</td>
<td>58 ± 16.0</td>
<td>56 ± 16.0</td>
<td>53 ± 13.7</td>
<td>51 ± 16.4</td>
</tr>
<tr>
<td>FM</td>
<td>1.1:1</td>
<td>1.9:1</td>
<td>1.6:1</td>
<td>1.1:3</td>
<td>1.5:1</td>
<td>1.1:5</td>
<td>1.1:3</td>
</tr>
<tr>
<td>White</td>
<td>92</td>
<td>94</td>
<td>97</td>
<td>94</td>
<td>89</td>
<td>9</td>
<td>90</td>
</tr>
<tr>
<td>Suspicion Before Diagnosis</td>
<td>23.0</td>
<td>19.4</td>
<td>37.2</td>
<td>8.3</td>
<td>27.0</td>
<td>40.0</td>
<td>11.1</td>
</tr>
<tr>
<td>Diagnostic Diagnosis</td>
<td>57.6</td>
<td>46.3</td>
<td>84.7</td>
<td>33.3</td>
<td>48.6</td>
<td>100</td>
<td>61.1</td>
</tr>
<tr>
<td>Diagnostic RU</td>
<td>15.8</td>
<td>11.9</td>
<td>16.9</td>
<td>16.7</td>
<td>27.0</td>
<td>0</td>
<td>11.1</td>
</tr>
<tr>
<td>Tissue Passed</td>
<td>4.2</td>
<td>13.4</td>
<td>3.5</td>
<td>0</td>
<td>16.2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Surgical Specimen</td>
<td>12.7</td>
<td>13.4</td>
<td>5.1</td>
<td>33.3</td>
<td>8.1</td>
<td>0</td>
<td>16.7</td>
</tr>
<tr>
<td>Autopsy Diagnosis</td>
<td>15.8</td>
<td>29.9</td>
<td>0</td>
<td>20.8</td>
<td>13.5</td>
<td>0</td>
<td>16.7</td>
</tr>
<tr>
<td>Bilateral RPN</td>
<td>63.0</td>
<td>68.7</td>
<td>79.7</td>
<td>45.8</td>
<td>51.4</td>
<td>100</td>
<td>33.3</td>
</tr>
<tr>
<td>Sepsis</td>
<td>15.8</td>
<td>26.9</td>
<td>1.7</td>
<td>18.8</td>
<td>21.6</td>
<td>0</td>
<td>16.7</td>
</tr>
<tr>
<td>Hypertension</td>
<td>43.0</td>
<td>38.8</td>
<td>49.2</td>
<td>33.3</td>
<td>51.4</td>
<td>60.0</td>
<td>38.9</td>
</tr>
<tr>
<td>History of TCC</td>
<td>6.1</td>
<td>3.0</td>
<td>1.7</td>
<td>14.6</td>
<td>5.4</td>
<td>0</td>
<td>11.1</td>
</tr>
<tr>
<td>History of Neuprothiasis</td>
<td>27.2</td>
<td>22.4</td>
<td>32.2</td>
<td>45.8</td>
<td>27.2</td>
<td>0</td>
<td>27.7</td>
</tr>
<tr>
<td>Serum Creatinine at Diagnosis (mean ± SD in μmol/L)</td>
<td>230 ± 274</td>
<td>248 ± 221</td>
<td>195 ± 230</td>
<td>230 ± 204</td>
<td>266 ± 266</td>
<td>106 ± 18</td>
<td>230 ± 504</td>
</tr>
<tr>
<td>Normal SerumCreatinine at Diagnosis</td>
<td>24.8</td>
<td>16.4</td>
<td>25.4</td>
<td>12.5</td>
<td>24.3</td>
<td>20.0</td>
<td>55.6</td>
</tr>
</tbody>
</table>

Note: Subgroups for the five major risk factors are not mutually exclusive because combinations were common. Values given are percentages except where otherwise specified. Abbreviations: RU, retrograde urogram; TCC, transitional cell carcinoma.

Conversion factor to milligrams per deciliter = 0.0113.
and was made at the time of autopsy in 26 (15.8%). A
history of hypertension or nephrolithiasis was fre-
quently present (43.0 and 27.3% overall). Bilateral
disease was demonstrated in 63.0% of patients. Of
those with unilateral disease, involvement of the right
kidney was marginally more common (35 versus 26
patients). Mean serum creatinine at diagnosis was
230 μmol/L (median, 124; range, 53 to 2,177; SD
274). Forty-one patients (24.8%) had normal serum
creatinine values at the time of diagnosis (upper limits
of normal: 106 μmol/L for men, 80 μmol/L for wom-
en). Seventy-three (44.2%) had abnormally high val-
ues that were less than twice the upper limit of normal,
and the remaining 51 (30.9%) had serum creatinine
levels higher than this. The most common
diagnostic test was EXU (57.6% of patients), with the
diagnosis being made by retrograde urography in
15.8%. Passage of tissue in the urine was recorded
predominantly in those with diabetes mellitus and
UTI. Transitional cell carcinoma of the bladder or
collecting system was diagnosed at the time of diag-
nosis of RPN or during the follow-up period in 10
patients (6.1%).

Subgroups

Patients were divided into categories of recognized
associated factors as well as a group (N = 18) in which
none were clearly demonstrated (Table 1). UTI was
treated as an independent risk factor because there
were 21 patients in whom no other major factor could
be clearly identified. There was considerable overlap
between the subgroups with 52 (31.5%) having two
major risk factors and 8 (4.8%) having three. Com-
bined risks were more prevalent among those with
diabetes, UTI, and urinary obstruction (Figure 1).
Only analgesic abuse and sickle cell disease were
present more commonly alone than in the presence of
another factor.

Patients With Rare or Uncertain Associations. This
group is labeled as "Other Cases" in Table 1. Addi-
tional diagnoses in this group included renal artery
stenosis (N = 1), Wegener's granulomatosis (N = 1),
systemic lupus erythematosus (N = 1), probable im-
munoglobulin A nephropathy (N = 1), and cirrhosis
in a patient with a single kidney (N = 1). In addition,
there was suspicion of analgesic abuse in four pa-
tients, a history of nephrolithiasis in three, and a
history of prior, but not current, UTI in three.

Patients With UTI. Of the 67 patients in whom UTI
was present by urine culture at the time of diagnosis
of RPN, 32 (47.8%) had acute pyelonephritis (clinically
and/or pathologically), 18 (29.9%) had a history of
recurrent UTI, 46 (68.7%) had one or more additional
clear predisposing factors for RPN, and 21 (47.8%)
had sepsis at the time of presentation. Twenty-one
patients could not be clearly identified as having one
of the other recognized major associated conditions
(Figure 1). Nevertheless, of these patients, 8 (31.3%)
had acute pyelonephritis, 9 (42.9%) had sepsis, 5
(23.8%) had a history of recurrent UTI, 5 (23.8%) had
a history of nephrolithiasis, and 9 (42.9%) had addi-
tional renal conditions that may have contributed to
RPN (renal artery stenosis [N = 2], acute tubular
necrosis [N = 2], congenital anomalies [N = 2], vascu-
litis [N = 1], glomerulonephritis [N = 1], interstitial
nephritis [N = 1], and surgery for acquired cyst [N =
1]). Only two patients had, clinically, a single, uncom-
plicated lower UTI. The most common organism spe-
cies cultured were Escherichia coli, Candida, and Kleb-
siella.

Patients With Diabetes Mellitus and RPN. Table 2
shows additional data on the subgroup with diabetes
mellitus. As expected, those with Type I were younger
with a longer duration of diabetes (mean, 29.6 yr
versus 13.2 yr duration) compared with Type II dia-
betes mellitus patients. In both types, current and/or
past UTI were common as were other risk factors. In
all, only six (three of each type) had no other possible
contributing factor identified. Of these, one was on
dialysis at the time of diagnosis and one was ap-
proaching ESRD. Renalopathy and neuropathy were
commonly present at diagnosis (43.2 and 48.6% over-
all, respectively), although more so in Type I (58.3 and
66.7%, respectively). This difference did not reach
statistical significance. The presence or absence of
underlying diabetic glomerulosclerosis could not be
accurately determined in this retrospective study be-
cause dipstick proteinuria was a common feature of
RPN of any cause and more formal assessment of
protein or albumin excretion rates were seldom per-
formed. The glycosylated hemoglobin was available in 14 cases and was higher in patients with Type I diabetes compared with Type II, suggesting poorer control among Type I diabetics (mean, 12.4 versus 9.7%). Because of the small numbers, this difference did not reach statistical significance ($P = 0.14$). Among the 18 patients with diabetes mellitus and UTI at the time of diagnosis, the most common organisms cultured were *E. coli* ($N = 8$) and *Candida* species ($N = 5$).

**Group With Analgesic Abuse.** Of the 59 patients with documented heavy use of analgesics, 28 (47.5%) had used aspirin/phenacetin combinations, 5 (8.5%) had used nonsteroidal anti-inflammatory drugs (NSAID) as well as aspirin/phenacetin, 6 (10.2%) had used NSAID and aspirin, and 5 (8.5%) had used NSAID alone. In eight (13.6%), the nature of analgesic abuse was not clearly documented. In only two patients was acetaminophen possibly implicated in combination with other analgesics.

**Group With Urinary Obstruction.** Urinary calculi were the most common cause of obstruction (20 [41.7%] patients). Malignancies accounted for 11 patients (22.9%) (prostate, 3; bladder or ureteral, 6; female genital, 2). Other causes included benign prostatic hypertrophy ($N = 4$), neurogenic bladder ($N = 4$), structural anomalies ($N = 6$), chronic benign bladder disease ($N = 2$), and retroperitoneal fibrosis ($N = 1$). Obstruction was unilateral in 26 patients (54.2%) and bilateral in 22 (45.8%).

**Trends Over Time**

Figures 2 and 3 show diagnostic trends from 1976 to 1992 by 4-yr time periods. The final period extends to September 1, 1992. After an initial rise from the first to second period, there was a steady decline in the number of cases diagnosed in the last 10 yr. The proportion diagnosed at autopsy has remained relatively stable. Figure 3 shows that the numbers have fallen in each of the major subgroups in a similar fashion. The mean ages at diagnosis for each time period were 55.9, 54.6, 59.8, and 63.2 yr. EXU was used in the majority of patients to establish a diagnosis of RPN. In seeking to determine whether a fall in the number of EXU being ordered was associated with the reduction in cases, we found that the number of EXU carried out each year at our institution has also dropped steadily from 10,155 in 1980 to 4,394 in 1993. In contrast, the overall number of registered patient visits per year during this same period rose from 270,064 to 316,809. In no patient was ultrasound or CT scanning the primary mode of diagnosis.

**Survival and Follow-Up**

Vital status information was available by chart review up to March 1, 1993, for 75 patients. Information

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Type I</th>
<th>Type II</th>
<th>Overall</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number (% Total)</td>
<td>12 (32.4)</td>
<td>25 (67.6)</td>
<td>37</td>
</tr>
<tr>
<td>Duration of Diabetes (yr), mean ± SD</td>
<td>29.4 ± 9.8&lt;sup&gt;a&lt;/sup&gt;</td>
<td>13.2 ± 8.0</td>
<td>18.5 ± 11.6</td>
</tr>
<tr>
<td>Age at Diagnosis of RPN (yr), mean ± SD</td>
<td>40.3 ± 13.1&lt;sup&gt;b&lt;/sup&gt;</td>
<td>63.8 ± 10.8</td>
<td>56.2 ± 16.0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>25.0&lt;sup&gt;c&lt;/sup&gt;</td>
<td>66.7</td>
<td>52.8</td>
</tr>
<tr>
<td>UTI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At diagnosis</td>
<td>33.3</td>
<td>56.0</td>
<td>48.6</td>
</tr>
<tr>
<td>Pyelonephritis</td>
<td>8.3</td>
<td>24.0</td>
<td>18.9</td>
</tr>
<tr>
<td>Past recurrent</td>
<td>41.7</td>
<td>24.0</td>
<td>29.7</td>
</tr>
<tr>
<td>Past single</td>
<td>25.0</td>
<td>32.0</td>
<td>29.7</td>
</tr>
<tr>
<td>No history of UTI</td>
<td>33.3</td>
<td>24.0</td>
<td>27.0</td>
</tr>
<tr>
<td>Other Major Risk&lt;sup&gt;d&lt;/sup&gt;</td>
<td>41.7</td>
<td>40.0</td>
<td>40.5</td>
</tr>
<tr>
<td>No Other Major Risk</td>
<td>25.0</td>
<td>12.0</td>
<td>16.2</td>
</tr>
<tr>
<td>Complications</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Retinopathy</td>
<td>58.3</td>
<td>36.0</td>
<td>43.2</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>66.7</td>
<td>40.0</td>
<td>48.6</td>
</tr>
<tr>
<td>Diabetic ulcers</td>
<td>16.7</td>
<td>15.0</td>
<td>16.2</td>
</tr>
<tr>
<td>Macrovacular</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disease</td>
<td>16.7</td>
<td>24.0</td>
<td>21.6</td>
</tr>
<tr>
<td>Serum Creatinine at Diagnosis (µmol/L), mean ± SD</td>
<td>319 ± 398</td>
<td>239 ± 177</td>
<td>266 ± 266</td>
</tr>
<tr>
<td>% Glycosylated Hemoglobin at Diagnosis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. recorded</td>
<td>6</td>
<td>8</td>
<td>14</td>
</tr>
<tr>
<td>Mean ± SD</td>
<td>12.4 ± 2.3</td>
<td>9.7 ± 3.7</td>
<td>10.9 ± 3.3</td>
</tr>
</tbody>
</table>

<sup>a</sup> Values given are percentages except where otherwise indicated.

<sup>b</sup> $P < 0.001$ for Type I versus Type II.

<sup>c</sup> $P = 0.016$ for Type I versus Type II.

<sup>d</sup> Other major risks are analgesic abuse, obstruction, and sickle cell disease.
was obtained by questionnaire in 78 of the remaining 90 patients, giving an overall follow-up of 92.7%. Of the 12 for whom information was not up to date, 9 could not be located and 3 elected not to take part. Chart data were available on these 12 patients for a mean of 1.8 (range, 0 to 9) yr from the time of diagnosis.

Mortality. Figure 4 shows overall survival from the time of diagnosis (excluding 26 diagnosed at the time of autopsy), expected survival for the whole group, and survival for diabetic and nondiabetic patients. Observed 5- and 10-yr survival rates overall were 86 and 69% compared with the expected survivals of 93 and 83.5%, respectively. The 32 diabetic patients monitored fared considerably worse, with overall 10-yr survival of 44%, compared with 77% for 107 patients without diabetes. The survival difference from expected was statistically significant for diabetics but not for nondiabetics.

Renal Outcome. Three patients were receiving hemodialysis at the time of the diagnosis of RPN. An additional 9 (6.6%) of the remaining 136 living patients went on to receive chronic hemodialysis during the follow-up period, and 1 received a renal transplant. Another patient for whom follow-up information was not available was close to requiring dialysis (serum creatinine, 850 μmol/L) at the time of diagnosis. Freedom from end-stage renal failure for patients surviving 10 yr after diagnosis was 93%. Univariate analysis for sex, age at the time of diagnosis (<60 yr or >60 yr), and the presence or absence of each of the major diagnostic subgroups showed a significant effect on renal outcome for diabetes only. Ten-year survival free of dialysis was 84% for diabetic patients compared with 95% for nondiabetics (Figure 5). Of the 11 patients who received long-term dialysis, either before or after the diagnosis of RPN, 6 had diabetes mellitus and 5 had a history of analgesic abuse. Two of these patients also had lupus nephritis.

**DISCUSSION**

This study provides a description of the clinical features, significant disease associations, and survival characteristics of a large group of patients found to have RPN at a single institution over a 16-yr period. As such, its prime aim is to provide insight into the relevance of this form of renal damage in modern practice. The historical path of RPN, from its first description in 1877, is punctuated by landmark observations that have defined our current approach to the condition (9–12). Nonetheless, there have been few new data added over the last two decades that might serve to clarify the role that RPN has occupied in more recent clinical settings. Much of the existing data is based on autopsy studies, smaller groups of cases, or surgical or radiologic reviews from the 1940s to 1970s (2,3,7,21–29). In this series, the diagnosis
I was generally made in the course of investigating cases of clinical importance.

Our population complies with the well-recognized associations of RPN with diabetes mellitus, analgesic abuse, urinary tract obstruction, and sickle cell disease (6). The distribution of the major factors in this and other larger series is variable and, no doubt, reflects differences in clinical practice, populations served, and method of case selection. Overall, there was little difference between numbers of female and male patients (ratio was 1.1:1.0). Nonetheless, among patients with diabetes, analgesic abuse, and UTI, the predominance of women was statistically significant \( (P < 0.05) \); analysis not shown. This is in accordance with previously reported series (1,8,26,30). On exclusion of those with coexisting UTI, however, these differences did not remain significant for diabetes and analgesic abuse. This suggests that increased prevalence of UTI may be the most important factor contrib-
utting to current gender differences in the prevalence of RPN.

Individual patients with conditions that have infrequently been reported to be associated with RPN (renal artery stenosis [18], retroperitoneal fibrosis [15], Wegener's granulomatosis [31], and lupus nephritis and other glomerulonephritides [16,18]) were seen among the group with none of the major factors. This underscores the potential for RPN to occur with a variety of forms of renal damage (vascular, glomerular, interstitial), while suggesting that its prevalence is low in these conditions. An association with chronic liver disease (particularly alcohol related) has been suggested previously (17,24), although there was only one patient case in this series in whom liver disease existed without another major risk factor. This does not preclude the possibility that endovascular and other changes accompanying chronic hepatic disease comprise an additional threat to papillary integrity.

The presence of a combination of risk factors in a significant number of patients has been emphasized infrequently, although we observed two or more in 36.4% of patients. The frequency of a multifactorial disposition to RPN has been highlighted by Eknoyan et al. in a series of 27 patients with the suggestion that infection, in particular, overlaps with other conditions to produce an additive risk (1). Our findings lend strength to this observation and serve to identify certain patient profiles (e.g., long-standing diabetics with severe or recurrent UTI) that should raise the suspicion of RPN. It also stresses the need to address the possibility of a second major factor in patients in whom one factor seems obvious.

Although reports of RPN associated with acute pyelonephritis alone exist (1,13), it is not clear whether UTI can be considered an independent causative factor. In this series, it was identified more often in the presence of one or more of the classic conditions predisposing to RPN than as an isolated occurrence. Even in the 21 cases without a clear additional factor, simple UTI was not the rule. Sepsis, history of renal stones, other renal conditions, and recurring UTI were frequently present. This suggests that the infection itself may be only one of a combination of factors threatening papillary integrity and that poor perfusion or intermittent obstruction may have also been present in many instances. On the basis of these observations, the role of UTI in RPN may vary from the primary initiating factor (often in patients with an existing predisposition) to an accompanying condition of little etiologic importance. It is also possible that loss of normal papillary epithelium predisposes to infection in preexisting RPN.

Such considerations raise questions about the pathogenesis of RPN (and indeed why it does not occur more often) that have remained imperfectly answered. It would seem likely that diminished papillary perfusion by various mechanisms, as well as concentration of toxins within the medulla, is likely to be involved. Nonetheless, animal models of RPN involving ureteral ligation, introduction of infection, or the use of selective toxins such as 2-bromoethyamine hydrobromide have done more to clarify the effects of papillary necrosis than the mechanisms mediating its occurrence (3,32,33). Recent insights into the papillary microenvironment may offer the best opportunity to understand how RPN develops in certain clinical circumstances. For example, the importance of osmotically active compounds whose uptake or synthesis by medullary tubular cells as well as their release can be controlled to maintain cellular integrity under extreme osmotic variability has been clearly demonstrated (34). Abnormal accumulation of at least one of these "osmolytes" (sorbitol) has been observed in diabetic animals, offering one mechanism by which diabetes might compromise normal papillary function (35-39). It is also possible that toxins produced during infection or by pharmacologic agents may directly interfere with the osmolyte system at one or more points.

Advances over the past decade in the study of regional blood flow within the kidney and the role of locally and systemically produced vasoactive substances in its control also provide new insight into the papillary microcirculation in health and disease (40). Blood supply to the inner medulla arises from juxtaposed medullary glomeruli via the vasa recta. The diffusion of oxygen directly from descending to ascending vessels results in progressive hypoxia along their course through the medulla (41). Recent reviews also emphasize that the hematocrit of this blood may be reduced by shunting of cellular components (42). The papilla may be further rendered vulnerable to ischemia through its relatively large interstitium (42). The medullary vasculature responds to an array of vasomodulatory substances that have been the subject to avid research in recent years. A number of these have been shown, experimentally, to have distinct profiles within the medulla that could serve to either preserve or compromise further the tenuous viability of this tissue under physiologic conditions. This suggests mechanisms by which certain disease states such as diabetes mellitus and sepsis (in which vasoactive profiles are altered) might directly affect regional blood flow in the kidney. Substances shown to alter renal medullary hemodynamics include angiotensin II (43), atrial natriuretic peptide (44), vasopressin (45), endothelins (46), prostaglandins (47), and the nitric oxide (48,49). It is presently unknown whether the conditions associated with RPN have increased vasoconstrictor or decreased vasodilatory substances that might predispose to papillary ischemia and necrosis. In addition, a greater recognition of the role of the papilla in long-term blood control (50-52) may explain the high prevalence of hypertension among our patients (43% of all patients).

The number of cases being diagnosed at our institution has fallen over the past decade, whereas the mean age at the time of diagnosis has risen. This raises the possibility of a true fall in the prevalence of
RPN in the population. It is possible that changes in the management of UTI and diabetes, withdrawal of certain over-the-counter analgesic mixtures, and earlier detection of obstruction have led to this decline. It is also possible that a change in diagnostic imaging studies of the genitourinary tract has resulted in fewer diagnoses of RPN. In our institution, the number of excretory urograms being performed each year has fallen from a high of 10,155 in 1980 to 4,394 in 1993 (a 56.7% reduction), despite an increase in registered patient visits. This change in practice may account for a large proportion of the fall in cases and may mean that RPN, often diagnosed fortuitously, is more likely to be missed than before. Both CT scanning and ultrasound scanning have been shown to demonstrate papillary necrosis (53,54), with characteristic features recently described (55), but no direct comparisons have been made with EXU and retrograde urography in which classic descriptions of the changes of RPN are well recognized (56,57). In addition, optimal detection rates with CT scanning and ultrasound may require a prediagnostic level of suspicion considerably greater than we have observed.

Regarding prognosis for those patients diagnosed while living, follow-up data for up to 15 yr suggested an overall increased mortality rate compared with a control population that was mainly accounted for by poor survival among patients with diabetes. This subgroup had a mean age at the time of diagnosis similar to that of the overall group but were characterized by a higher mean creatinine, a higher prevalence of additional risk factors, and an increased risk of progression to end-stage renal failure. It is not possible from our data, however, to infer a poorer prognosis for patients with diabetes and RPN compared with diabetic patients without this lesion. In those patients surviving up to 10 yr or more after diagnosis, risk of requiring renal replacement therapy was not high (7.4% of patients), particularly in the absence of diabetes (5.3%).

Future clinical interest in RPN may well center on patterns of occurrence in diabetes mellitus and those taking long term NSAID. A recent study of 76 patients with long-standing insulin-dependent diabetes mellitus revealed some evidence of RPN in 16 (23.7%) by EXU (58), whereas the generally accepted rate at autopsy has been 3 to 7% (59). The only risk factors identified were female sex and history of UTI. Our observations suggest that clinically significant RPN among diabetics without a history of UTI or other comorbidity is unusual (only 3 of 165 cases). Some evidence of poor long-term control was present in our Type 1 diabetics, although it remains to be seen whether intensive blood glucose control will affect the incidence of this diabetic complication. We observed five patients with RPN who gave a history of prolonged (usually prescribed) use of NSAID without additional use of phenacetin/aspirin mixtures. This observation, along with a recent report in which 29 of 69 newly detected patients had consumed only NSAID (60), suggests that "analgesic nephropathy" will continue to be seen, although its contribution to the population burden of chronic renal disease may not be as great as in the 1950s to 1980s.

The retrospective nature of this study and the referral population of our institute place some limitations on interpretation. Close follow-up of renal function, diabetic control and complications, development of hypertension, subsequent analgesic use, and UTI was often not available after the initial diagnosis. Prognostic analysis was, therefore, restricted to mortality and the requirement for renal replacement therapy. The predominance of white patients in this series reflects the characteristic regional and referral populations at our institution and would certainly be at variance with those of many others, particularly in the United States. As an example, the number of cases associated with sickle cell disease was small. This may mean that some of the trends we have observed will not be mirrored at other referral centers. Similar reviews from centers serving areas with different population characteristics would certainly be of interest.

In conclusion, RPN has remained, in the past two decades, a condition that is frequently unsuspected before diagnosis with a variety of clinical presentations and, often, one or more recognizable predisposing factors. UTI is a frequent accompaniment and may be etiologically important, particularly in combination with sepsis or additional renal disease. The rate of diagnosis of RPN has fallen over this period, possibly as a result of changing trends in diagnostic imaging, making a clear knowledge of the clinical circumstances under which it arises more important than ever before. Despite a long history of experimental interest in its pathophysiology, a better understanding of the mechanisms underlying papillary integrity in health and disease has only recently emerged from insights at a cellular level.

REFERENCES