Thin basement membrane nephropathy (TBMN) is a common, lifelong condition affecting the kidneys that is characterized by microscopic glomerular hematuria, minimal or no proteinuria, and normal renal function. It often is discovered incidentally, and usually has an excellent prognosis. Many cases are familial and show autosomal-dominant inheritance. The defining characteristic is a glomerular basement membrane (GBM) that is thinned to about half its normal thickness on ultrastructural examination of the renal biopsy specimen. However, occasionally patients with TBMN develop marked proteinuria or renal impairment. It is unclear whether individuals with TBMN and impaired renal function represent part of the spectrum of TBMN associated with heterozygous COL4A3 or COL4A4 mutations, or if their disease is caused by mutations of other genes, or whether it is caused by a second coexistent renal lesion or is misdiagnosed Alport syndrome.

Prevalence and Epidemiology

Indirect evidence suggests TBMN is common; large systematic population-based studies of the prevalence of TBMN are needed. Various biopsy studies of TBMN as the cause of hematuria are summarized in Table 1. Overall, TBMN is appreciably more common than immunoglobulin (Ig)A nephropathy, and is the commonest cause of isolated microscopic hematuria on renal biopsy examination. However, the selection criteria have varied in these studies and biopsy examinations have been performed more frequently in patients with microscopic hematuria and additional features that gave rise to concern. This is apparent in those series that found Alport syndrome disproportionately often. Any such bias underestimates the true frequency of TBMN. The series by Gauthier et al often is cited as evidence for the high prevalence of TBMN. However, as those researchers pointed out, none of their cases had basement membrane thinning as the sole abnormality, and some may have had Alport syndrome.

Microhematuria on a single sample (or 2 samples close in time) is an indication for renal biopsy. As TBMN is such a common cause of microhematuria, a biopsy is indicated when no other cause is found.
time) has been found in 2.5% of English men, 67 4.6% of Australian adults,68 and 13% of US men and postmenopausal women.69 The prevalence of persistent hematuria is not well known in adults, but occurs in 1% to 2% of children,70,71 furthermore, most hematuria in children is glomerular.72 If the prevalence of hematuria exceeds 1%, and TBMN is the most frequent cause, then the prevalence of TBMN causing hematuria must approximate 1% of the population. The higher frequency of thin GBMs in transplant donors (6.6%), who presumably are representative of the general population, implies that microhematuria does not occur in most individuals with thinned GBMs. If this is so, it adds another layer of complexity to the definition of TBMN and estimates of its prevalence.

Many series have shown TBMN occurs more commonly in females, both in children and adults,4,5,8,12,18,20,28,29,40,66,73 but other investigators have not confirmed this.7,20,39,54,58,62 In total, 388 of 615 (63%) of all the cases cited in these series were female. Whether this is a true biological difference or merely the result of a selection bias is not clear. Only 1 of these series routinely used genetic testing and some females reported elsewhere may have been undiagnosed carriers of X-linked Alport syndrome whereas the males with Alport syndrome were more likely to have been identified. A possible biological basis for the greater prevalence in females could be the tendency for GBM to be thinner in females than in males in both pathologic74,75 and normal76,77 kidneys. In contrast to these findings, a recent systematic study46 confirmed this finding.

Flank pain has been reported in 7% to 31% of adults with TBMN28,29,47,73 and 7 cases have been reported with loin pain–hematuria syndrome.82 A surprisingly high incidence of hypercalciuria or hyperuricosuria (39%) was found in one series of TBMN.47 Nephrolithiasis was common in these patients and a family history of nephrolithiasis was noted in 51%. However, this observation has not been confirmed. Hypertension has been reported in 11% to 31% of adults,12,39,58,63,73,79 but uncommonly in children.54 Others simply have noted that blood pressure was normal.7,40 In the absence of a uniform definition of hypertension or of contemporaneous controls, it is difficult to interpret these reports.

Proteinuria rarely is seen in children, but modest proteinuria (up to 1 g/d) has been found repeatedly in a substantial minority of patients (Table 2). The occasional patient reported to have nephrotic range proteinuria may have had focal segmental glomerulosclerosis or superimposed minimal change nephritis.83 The frequency of proteinuria summarized in Table 2 may be skewed because several series excluded patients with greater than 1 g/d of proteinuria.

In an intriguing study, Thomas et al54 examined glomerular permselectivity to polydisperse neutral dextrans. Despite

### Clinical Features

Persistent microscopic hematuria is the characteristic clinical feature of TBMN.4,5,8,18,20,25,28,29,30,40,62,79-81 Hematuria has been documented for up to 30 years,28 and from as young as age 14 to as old as age 86.20 Exceptionally, hematuria may disappear with time.73 Dysmorphic urinary erythrocytes are found readily,28,29 and red cell casts,28 including string casts, may occur. Episodes of macroscopic hematuria occur at some stage in 5% to 22% of patients.8,18,28,29,39,46,47,62,79,81 Trachtman et al81 found episodes of macroscopic hematuria to be less frequent in children with TBMN (12%) than in Alport syndrome (33%) or IgA nephropathy (88%). Piqueras et al46 confirmed this finding.

### Table 1 Prevalence of TBMN, IgA Nephropathy, and Alport Syndrome in Series of Patients Presenting With Hematuria

<table>
<thead>
<tr>
<th>Study</th>
<th>Selection Method</th>
<th>Age Range</th>
<th>Total Number</th>
<th>TBMN</th>
<th>IgA</th>
<th>Alport Syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Piel et al,80 1982</td>
<td>Unexplained hematuria</td>
<td>Children</td>
<td>57</td>
<td>65%</td>
<td>0%</td>
<td>35%</td>
</tr>
<tr>
<td>Yum and Bergstein,105</td>
<td>Asymptomatic hematuria</td>
<td>3–47 y</td>
<td>19</td>
<td>37%</td>
<td>0%</td>
<td>21%</td>
</tr>
<tr>
<td>Trachtman et al,81</td>
<td>Isolated microscopic hematuria</td>
<td>3–19 y</td>
<td>76</td>
<td>22%</td>
<td>11%</td>
<td>12%</td>
</tr>
<tr>
<td>Blumenthal et al,7</td>
<td>Isolated microscopic hematuria</td>
<td>5–65 y</td>
<td>56</td>
<td>54%</td>
<td>23%</td>
<td>23%</td>
</tr>
<tr>
<td>Perry et al,28 1989</td>
<td>Glomerular hematuria</td>
<td>16–73 y</td>
<td>92</td>
<td>28%</td>
<td>21%</td>
<td>1%</td>
</tr>
<tr>
<td>Tiebosch et al,62 1989</td>
<td>Microscopic or macroscopic hematuria</td>
<td>16–65 y</td>
<td>54</td>
<td>31%</td>
<td>?</td>
<td>0%</td>
</tr>
<tr>
<td>Schröder et al,19 1990</td>
<td>Isolated, persistent microscopic hematuria</td>
<td>Children</td>
<td>65</td>
<td>51%</td>
<td>25%</td>
<td>12%</td>
</tr>
<tr>
<td>Tanaka et al,106 1996</td>
<td>Isolated microscopic hematuria</td>
<td>Adults</td>
<td>40</td>
<td>10%</td>
<td>40%</td>
<td>0%</td>
</tr>
<tr>
<td>Piqueras et al,46 1998</td>
<td>Glomerular hematuria (biopsy examination delayed if slight or no proteinuria)</td>
<td>Children</td>
<td>322</td>
<td>16%</td>
<td>24%</td>
<td>27%</td>
</tr>
<tr>
<td>Auwardt, et al,63 1999</td>
<td>Renal biopsy examinations of patients with IgA nephropathy or TBMN</td>
<td>5–68 y</td>
<td>102</td>
<td>70%</td>
<td>30%</td>
<td>NA</td>
</tr>
<tr>
<td>van Paassen et al,58 2004</td>
<td>Hematuria</td>
<td>Adults</td>
<td>210</td>
<td>34%</td>
<td>9%</td>
<td>0%</td>
</tr>
<tr>
<td>van Paassen et al,58 2004</td>
<td>Hematuria and subnephrotic proteinuria</td>
<td>Adults</td>
<td>244</td>
<td>5%</td>
<td>31%</td>
<td>0%</td>
</tr>
</tbody>
</table>

NOTE. N = number of patients in each series. ? = not stated; NA = not applicable.
normal hemodynamics and minimal proteinuria, patients with TBMN had increased fractional clearance of neutral dextran with Stokes radius greater than 42 Å. This increased fractional clearance of neutral dextrans predicts nephrotic range proteinuria but the discrepancy between predicted heavy proteinuria and observed minimal proteinuria remains unexplained.

Renal function is described uniformly as normal in children with TBMN,19,54 whereas a small proportion of adults have some degree of renal insufficiency (see later, Table 3).

There are occasional reports of hearing loss in TBMN.29 Until more experience is obtained with defined mutations it will remain unclear whether this is a feature of some forms of TBMN, an incidental finding, or unrecognized Alport syndrome, because hearing loss is a feature of X-linked Alport syndrome and the heterozygous \( \text{COL4A3} \) or \( \text{COL4A4} \) mutations that cause autosomal-dominant Alport syndrome.85

### Complications of TBMN

Acute renal failure has been described in 1 patient with TBMN who was receiving warfarin; his biopsy examination showed widespread occlusion of tubules with erythrocytes and casts.86 Coleman et al87 described another patient with pulmonary hemorrhage and hematuria, mimicking Goodpasture’s syndrome but without anti-GBM antibodies.

### Differential Diagnosis

#### Acquired TBMN

Thin GBM has been described in minimal change nephrotic syndrome42,58,83,88-90 and Coleman and Stirling83 suggested that this thinning is acquired as a consequence of impaired production of the \( \alpha 3 \) to 4-5(IV) collagen network by podocytes. The GBM also is thinned moderately in some patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>N</th>
<th>Age Group</th>
<th>Proteinuria</th>
</tr>
</thead>
<tbody>
<tr>
<td>McConville and McAdams9</td>
<td>1966</td>
<td></td>
<td>Children</td>
<td>Proteinuria only during episodes of gross hematuria</td>
</tr>
<tr>
<td>Schröder et al19</td>
<td>1990</td>
<td></td>
<td>Children</td>
<td>No proteinuria (0%)</td>
</tr>
<tr>
<td>Piqueras et al46</td>
<td>1998</td>
<td></td>
<td>Children</td>
<td>0/50 patients (0%)</td>
</tr>
<tr>
<td>Roth et al54,55</td>
<td>2001</td>
<td></td>
<td>Children</td>
<td>≥ 1 + (33%)</td>
</tr>
<tr>
<td>Rogers et al20</td>
<td>1973</td>
<td></td>
<td>Adults</td>
<td>No proteinuria (0%)</td>
</tr>
<tr>
<td>Dische et al19,29</td>
<td>1985</td>
<td></td>
<td>Adults</td>
<td>6 had about 1 g/d proteinuria; 2 others had 2.5 and 9 g/d (8/14, 57%)</td>
</tr>
<tr>
<td>Abe et al40</td>
<td>1987</td>
<td></td>
<td>Adults</td>
<td>± to ++ proteinuria (5/8, 63%)</td>
</tr>
<tr>
<td>Aarons et al29</td>
<td>1987</td>
<td></td>
<td>Adults</td>
<td>.2–.5 g/d (45%)</td>
</tr>
<tr>
<td>Blumenthal et al7,28</td>
<td>1988</td>
<td></td>
<td>Adults</td>
<td>Mean, .39 (range, .2–3.0) g/d</td>
</tr>
<tr>
<td>Perry et al28</td>
<td>1989</td>
<td></td>
<td>Adults</td>
<td>Proteinuria, .92, 1, 1.4 g/d (3/26, 12%)</td>
</tr>
<tr>
<td>Tiebosch et al62</td>
<td>1989</td>
<td></td>
<td>Adults</td>
<td>Proteinuria, .5–3.0 g/d (6/18, 33%)</td>
</tr>
<tr>
<td>Goel et al73</td>
<td>1995</td>
<td></td>
<td>Adults</td>
<td>28% had proteinuria &gt; .2 g/d</td>
</tr>
<tr>
<td>Nieuwhof et al39,197</td>
<td>1997</td>
<td></td>
<td>Adults</td>
<td>32% &gt; .25 g/d</td>
</tr>
<tr>
<td>Auwardt et al63,1999</td>
<td>1999</td>
<td></td>
<td>Adults</td>
<td>&gt;1 g/24 h in 11% &gt; .2 g/24 h in 42%</td>
</tr>
<tr>
<td>Badenas et al12</td>
<td>2002</td>
<td></td>
<td>Adults</td>
<td>≥1 g/d in 6%</td>
</tr>
<tr>
<td>van Paassen et al58</td>
<td>2004</td>
<td></td>
<td>Adults</td>
<td>5% nephrotic range, 15% 1–5 g/d</td>
</tr>
</tbody>
</table>

SCr, serum creatinine level; ESRD, end-stage renal disease.
with rheumatoid arthritis who have hematuria or proteinuria, which has led to the suggestion that gold sodium thiomalate treatment causes GBM thinning.\

**Alport Syndrome**

Many cases of autosomal-recessive Alport syndrome are homozygotes or compound heterozygotes for the same COL4A3 and COL4A4 mutations that in the heterozygote state cause familial TBMN. One difficulty that can arise in these families with autosomal-recessive disease is that the homozygotes (who will have TBMN) do not necessarily have hematuria. Their detection is important for pointing to the mode of inheritance. The converse difficulty is recognizing occasional homozygotes or compound heterozygotes in a family with TBMN. If TBMN affects 1% of the population, there is an appreciable chance that an unrecognized carrier may marry into the family and from time to time a child with autosomal-recessive Alport syndrome will result.\n
X-linked Alport syndrome is also an important diagnostic consideration. The risk for misdiagnosing or overlooking Alport syndrome is greatest if the family is small or comprises only female carriers or the adult men develop disease late or have atypical clinical features. Families with the onset of renal failure in adulthood typically are large and family members often are unaware of their diagnosis. Skin or renal biopsy examination in at least 1 or 2 members of the kindred, with appropriate immunofluorescent and ultrastructural examination for type IV collagen chains or, alternatively, association with TBMN in individual cases or small series include aortitis,43 Crohn's disease,102 and rheumatoid arthritis.91 These associations may be coincidental.

Hill et al. clearly showed that GBM lesions mimicking Alport syndrome or TBMN occur focally in a wide variety of nephropathies. These GBM alterations are presumably a consequence of membrane damage and attempted repair and should not be equated with the widespread uniform abnormalities seen in the hereditary basement membrane nephropathies.

**Conclusions**

TBMN is the commonest inherited renal condition and the commonest cause of glomerular hematuria. Proteinuria usually is minimal and renal function remains normal, but occasionally patients develop marked proteinuria or renal impairment. It is unclear whether individuals with TBMN and impaired renal function represent part of the spectrum of TBMN associated with heterozygous COL4A3 or COL4A4 mutations, or if their disease is caused by mutations of other genes, or whether it is caused by a second coexistent renal lesion, or to misdiagnosed Alport syndrome.

**References**

9. Lemmink HH, Nillesen WN, Mochizuki T, et al: Benign familial he-
Clinical features of TBMN


