SUMMARY A retrospective 5-year study examined the relationship between blood pressure and the severity and progression of mild background retinopathy in 48 patients with non-insulin-dependent diabetes and 38 with insulin-dependent diabetes who did not receive treatment in either eye for at least 3 years from their initial visit. All patients had annual medical and ophthalmic examinations including fundus photography. Retinopathy was assessed from fundus photographs using the Hammersmith grading system. Initial mean systolic and diastolic blood pressures (mm Hg) were significantly higher in those with non-insulin-dependent diabetes (149/88) than in patients with insulin-dependent diabetes (129/81). The former had significantly worse retinopathy than the latter initially and at 5 years. When non-insulin-dependent patients were grouped according to systolic blood pressure, those with readings above 160 mm Hg had significantly more severe retinopathy than those with readings below 140 mm Hg. Blood pressures initially and at 3 years were not significantly different between patients who received photocoagulation (five with insulin-dependent and six with non-insulin-dependent diabetes and those who did not in either group. There was significant correlation between systolic blood pressure and severity of retinopathy in patients with non-insulin-dependent disease, but the change in severity of retinopathy at 5 years did not correlate with blood pressure in either group.

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KEY WORDS photography non-insulin-dependent diabetes insulin-dependent diabetes fundus

DIABETIC retinopathy is the commonest cause of registered blindness in the age range 35 to 65 years in the United Kingdom and the United States. Mild background retinopathy is often detected as the first visible sign of diabetic eye disease, and it is therefore most important to identify treatable factors that influence its progression to more severe forms of retinopathy. Good evidence exists that hypertension accelerates renal failure due to diabetic nephropathy, but evidence for a similar effect on retinopathy is inconclusive.

This report is of a 5-year study on the relationship between blood pressure and the severity and progression of diabetic retinopathy in patients with non-insulin- (NIDD) and insulin-dependent (IDD) diabetes who had mild background retinopathy at their initial visit to a diabetic retinopathy unit.

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Patients and Methods

Patient Selection

As part of a long-term study, all diabetic patients attending the retinopathy unit at Hammersmith Hospital had annual medical and ophthalmic examinations. In those with NIDD, diabetes was diagnosed after the age of 30 years and they did not initially require insulin; in patients with IDD, diabetes had occurred at or before the age of 30 years and they required insulin at onset. The two criteria for eligibility were as follows:

1. Untreated mild background retinopathy present in one or both eyes at the initial visit. Mild background retinopathy was defined as the presence of microaneurysms, hemorrhages, hard exudates, no more than five cotton-wool spots (retinal infarcts), and no preproliferative or proliferative retinopathy or macular edema.

2. Medical and ophthalmic follow-up for at least 3 years during which neither eye received photocoagulation or specific treatment (e.g., aspirin).

The first criterion was satisfied by 55 patients with NIDD and 39 with IDD, of whom 7 and 1 patients, respectively had been treated within 3 years and thus were excluded by the second criterion. At the initial
visit the remaining 48 with NIDD were of mean age 57 years (range 35–74 years) with duration of disease 9 years (range less than 1–74 years); 38 patients with IDD were of mean age 37 years (range 20–71 years) with duration of diabetes 18 years (range 7–45 years). Photocoagulation of either eye was an end point in this study.

Medical Assessment

The ponderal index (body weight expressed as percentage of ideal weight), urea, and creatinine were noted at the initial and subsequent visits. Estimations of glycosylated hemoglobin were not available until 1979, and therefore diabetic control could not be assessed in the majority of patients. For each patient the annual blood pressures were averaged over 3 and 5 years. Patients were grouped according to initial and subsequent mean systolic (<110, 110–119, 120–139, 140–160, and >160 mm Hg) and diastolic (<80, 80–89, 90–109, 110–120, and >120 mm Hg) pressures and the severity of retinopathy was evaluated within these groups. Patients receiving antihypertensive therapy were noted.

Eye Assessment

The ophthalmic examination included fundus photography (Zeiss, Oberkochen, West Germany) of five standard 30-degree fields in each eye: superior and inferior temporal, nasal, macular, and disk. Fundus photography allowed a more detailed inspection of the lesions and their progression. The Hammersmith system was used to grade the severity of component lesions of retinopathy in each of the five photographic fields. This system grades the component lesions from 0 (no lesion) to 5 (severest lesion) in comparison with standard photographs. Microaneurysms and small intraretinal hemorrhages were graded together according to their number. Hard exudates were graded according to the area of retinal involvement. Cotton-wool spots were counted for each eye. Drusen were excluded from the analysis.

The mean gradings of hemorrhages and hard exudates per field were calculated for each eye separately and for both eyes. This method overcame the difficulties that occasionally arose when, for various reasons, parts of the eye or a whole eye could not be assessed. Paired t tests were used to examine the significance of a change in severity of retinopathy from an initial value in the same eye. Univariate regression analysis was used to measure the correlation coefficient (r) between blood pressure and retinopathy grading (a single mean value for all fields per patient). A value of p < 0.05 was regarded as significant.

Results

Medical Data

There were no significant differences in initial mean ± SD ponderal index (percentage), which was 110 ± 18 (range 82–183) in NIDD and 116 ± 15 (range 82–152) in IDD. Two patients with NIDD had diabetic nephropathy. All others had normal renal function as assessed by measurements of plasma urea and creatinine. The rise in systolic blood pressure at 5 years within the two groups was not significant, although those with NIDD had significantly higher systolic and diastolic pressures than those with IDD (p < 0.001; Table 1) throughout.

The mean 5-year blood pressure was higher (169/95 ± 20/8) in 9 patients with NIDD who were receiving hypertensive therapy than in the 27 (151/85 ± 18/6) with untreated NIDD (systolic p < 0.05, diastolic p < 0.01). In three patients with IDD who were receiving antihypertensive therapy, the mean 5-year blood pressure was 142/90 ± 11/5 compared with 131/78 ± 19/6 in the 29 with untreated IDD. The number of patients was too small for statistical comparison.

Retinopathy

No differences were noted in initial gradings of microaneurysms and hemorrhages between NIDD and IDD, although patients with NIDD had significantly (p < 0.03; Table 2) more grading of severe hard exudates. At 5 years, those with NIDD who did not receive photocoagulation (untreated) had more severe grading of hard exudates (p < 0.001; Table 2), and microaneurysms and hemorrhages (p < 0.002; Table 2) than patients with untreated IDD. Few patients dem-

Table 1. Blood Pressure in Insulin- and Non-Insulin-Dependent Diabetic Patients Before and After Separation into Those Who Subsequently Received Photocoagulation (treated) and Those Who Did Not (untreated)

<table>
<thead>
<tr>
<th>Patients</th>
<th>Initial Mean 3 years</th>
<th>Mean 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>IDD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>129/81 ± 20/10 (38)</td>
<td>131/81 ± 16/7 (38)</td>
</tr>
<tr>
<td>Untreated</td>
<td>130/81 ± 19/10 (33)</td>
<td>131/81 ± 14/7 (33)</td>
</tr>
<tr>
<td>Treated</td>
<td>124/79 ± 29/7 (5)</td>
<td>136/80 ± 27/5 (5)</td>
</tr>
<tr>
<td>NIDD</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>149/88 ± 25/12 (48)</td>
<td>153/87 ± 20/8 (48)</td>
</tr>
<tr>
<td>Untreated</td>
<td>148/88 ± 25/13 (42)</td>
<td>151/87 ± 19/9 (42)</td>
</tr>
<tr>
<td>Treated</td>
<td>153/88 ± 20/5 (6)</td>
<td>167/87 ± 22/5 (6)</td>
</tr>
</tbody>
</table>

Mean systolic/diastolic ± SD.
Number of patients in parentheses.
IDD = patients with insulin-dependent diabetes; NIDD = patients with non-insulin-dependent diabetes.
TABLE 2. Retinopathy Grading in Patients with IDD and NIDD Before and After Separation into Those Who Subse-
quently Received Photocoagulation (treated) and Those Who Did Not (untreated)

<table>
<thead>
<tr>
<th>Retinopathy</th>
<th>Initial</th>
<th>3 years</th>
<th>5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Microaneurysms and hemorrhages</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.96 ± 0.62 (75)</td>
<td>0.98 ± 0.62 (75)</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>0.98 ± 0.64 (65)</td>
<td>0.90 ± 0.53 (63)</td>
<td>0.82 ± 0.52 (63)</td>
</tr>
<tr>
<td>Treated</td>
<td>0.86 ± 0.48 (10)</td>
<td>1.58 ± 0.80 (10)</td>
<td></td>
</tr>
<tr>
<td>NIDD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>1.16 ± 0.78 (94)</td>
<td>1.22 ± 0.64 (97)</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>1.04 ± 0.66 (82)</td>
<td>1.06 ± 0.60 (79)</td>
<td>1.16 ± 0.68 (69)</td>
</tr>
<tr>
<td>Treated</td>
<td>2.00 ± 0.96 (12)</td>
<td>2.23 ± 0.76 (12)</td>
<td></td>
</tr>
<tr>
<td><strong>Hard exudates</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IDD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.44 ± 0.42 (75)</td>
<td>0.34 ± 0.40 (73)</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>0.42 ± 0.44 (65)</td>
<td>0.28 ± 0.36 (63)</td>
<td>0.36 ± 0.40 (63)</td>
</tr>
<tr>
<td>Treated</td>
<td>0.52 ± 0.34 (10)</td>
<td>0.64 ± 0.56 (10)</td>
<td></td>
</tr>
<tr>
<td>NIDD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>0.60 ± 0.60 (94)</td>
<td>0.70 ± 0.62 (91)</td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>0.56 ± 0.60 (82)</td>
<td>0.60 ± 0.56 (79)</td>
<td>0.72 ± 0.68 (69)</td>
</tr>
<tr>
<td>Treated</td>
<td>0.96 ± 0.40 (12)</td>
<td>1.32 ± 0.64 (12)</td>
<td></td>
</tr>
</tbody>
</table>

Mean grading ± SD.
Number of eyes in parentheses.

Non-Insulin-Dependent Patients

Patients with NIDD whose initial systolic pressure was over 160 had worse grading of hard exudates \((p < 0.02; \text{Figure 1})\) and hemorrhages and microaneurysms \((p < 0.002; \text{Figure 2})\) than those with pressure below 140 mm Hg. Correlation was significant between initial systolic blood pressure and grading of hard exudates \((r = 0.33, p < 0.05)\) and microaneurysms and hemorrhages \((r = 0.39, p < 0.05)\). No such associations existed between the severity of retinopathy and initial diastolic blood pressure (Figures 1 and 2).

At 5 years, patients with NIDD with systolic blood pressure above 160 still had worse gradings for hard exudates \((p < 0.001; \text{Figure 3})\) and microaneurysms and hemorrhages \((p < 0.002; \text{Figure 4})\) than those with systolic pressures below 140 mm Hg. Two patients with preproliferative and one with proliferative retinopathy and three with maculopathy received photocoagulation, and six were lost to follow-up. Patients who received photocoagulation had more severe retinopathy at their initial and 3-year visits than those who did not \((p < 0.003; \text{see Table 2})\).

In 69 untreated eyes of 36 patients with NIDD there was a nonsignificant increase in severity of retinopathy grading from initial to 5 years for hard exudates \(0.14 \pm 0.70\) and microaneurysms and hemorrhages \(0.08 \pm 0.60\). No correlation was noted between these

\[\text{Mean grading} \pm \text{SD.}\]
\[\text{Number of eyes in parentheses.}\]
changes in severity of retinopathy and the mean 5-year blood pressures. There was still a correlation between the mean 5-year systolic blood pressure and grading of hard exudates ($r = 0.41, p < 0.001$) and microaneurysms and hemorrhages ($r = 0.50, p < 0.01$), and also between the 5-year diastolic pressure and hard exudate grading ($r = 0.40, p < 0.02$).

**Insulin-Dependent Patients**

No association was found between the severity of retinopathy and initial systolic or diastolic blood pressures in patients with IDD as fewer had initial systolic blood pressure above 140 mm Hg (see Figure 2). At 5 years, these patients still had no association between severity of retinopathy and blood pressure. Four patients with proliferative retinopathy and one with maculopathy received photocoagulation in one or both eyes and one was lost to follow-up; all were excluded from the 5-year follow-up data. There was no significant difference in the severity of retinopathy between patients with untreated and subsequently treated IDD. However at 3 years a significant deterioration (Table 2) was seen in those who subsequently received photocoagulation (paired $t$ test, $p < 0.05$).

In 63 untreated eyes of 32 patients with IDD, nonsignificant improvement in retinopathy grading occurred between initial and 5-year examinations of 0.08 ± 0.46 for hard exudates and 0.11 ± 0.57 for microaneurysms and hemorrhages. Those who subsequently received photocoagulation did not have significantly higher initial or 3-year blood pressures in comparison with untreated patients (see Table 2).

**Patients Receiving Antihypertensive Therapy**

At 5 years, the mean microaneurysm and hemorrhage grading in 6 eyes of 3 patients with IDD who were receiving antihypertensive therapy was 1.00 ± 0.52 (vs 0.80 ± 0.56 in 57 eyes of 29 patients receiving no therapy; $p > 0.10$); in 18 eyes of 9 patients with NIDD who were receiving therapy grading was 1.24 ± 0.60 (vs 1.04 ± 0.70 in 51 eyes of 27 patients receiving no therapy; $p > 0.10$). The corresponding exudate grading was 0.44 ± 0.52 (vs 0.34 ± 0.40; $p > 0.10$) in IDD and 0.74 ± 0.66 (vs 0.72 ± 0.70; $p > 0.10$) in NIDD patients. The differences in retinopathy grading at the initial visit between patients receiving and those not receiving antihypertensive therapy were also not significant.

**Patients Excluded by Entrance Criteria**

The initial blood pressure was 173/94 ± 21/8 mm Hg in the seven excluded patients with NIDD, with the systolic pressure being significantly higher ($p < 0.03$) than in the 48 patients with NIDD (see Table 1). All

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**Figure 2.** Initial mean grading of microaneurysms and hemorrhages per field in all eyes of patients grouped according to initial systolic and diastolic blood pressures ($n =$ number of patients; vertical bars = SD).

**Figure 3.** Five-year mean grading of hard exudates per field in all eyes of patients grouped according to mean 5-year systolic and diastolic blood pressures ($n =$ number of patients; vertical bars = SD).
excluded patients had normal renal function.

Compared with the 94 eyes of patients with NIDD (see Table 2), the 14 eyes of the excluded patients had initially more severe retinopathy gradings of microaneurysms and hemorrhages of $1.68 \pm 0.80 (p < 0.04)$ and hard exudates of $0.86 \pm 0.64$, although the latter was not significantly higher. Of the excluded patients with NIDD, two received photocoagulation treatment within 1 year (one because of proliferative retinopathy and the other for maculopathy) and five were treated between 2 and 3 years of their initial visit (two because of proliferative retinopathy and three for maculopathy).

The one excluded patient with IDD who had received photocoagulation for proliferative retinopathy within 6 months of the initial visit had a blood pressure of 140/90 mm Hg.

Discussion

This study showed that the severity of mild background retinopathy was increased in patients with NIDD whose systolic pressures were greater than 160 mm Hg at initial and 5-year assessments. The absence of a similar relationship in patients with IDD could be due to fewer patients with elevated blood pressures in this younger group. The lack of association between severity of retinopathy and diastolic pressure could again be due to few patients in this study having diastolic pressure over 100 mm Hg. We did not demonstrate a correlation between a change in severity of retinopathy and blood pressure over 5 years in either group.

The excluded patients with NIDD who had had photocoagulation within 3 years had higher initial systolic blood pressure and worse retinopathy than others with NIDD. Those who had photocoagulation after 3 years also had worse retinopathy initially than those who did not need such treatment, but blood pressure was similar in both groups. In the excluded group, it was difficult to conclude whether the coexistence of severe retinopathy and higher systolic blood pressure was merely a correlated feature of widespread vascular disease or whether the rapid deterioration in retinopathy was due to the higher blood pressure. Patients with IDD who subsequently received photocoagulation (mostly for proliferative retinopathy) could not be differentiated by the severity of retinopathy at the initial visit, but showed rapid deterioration at 3 years. Insufficient numbers of patients received antihypertensive therapy to evaluate whether such treatment influenced the severity and progression of retinopathy.

Harold\textsuperscript{5} used the Hammersmith grading system in 63 patients (mostly with NIDD), many with more advanced retinopathy than those in our study, and found an increased frequency of streak hemorrhages in those with diastolic pressures above 90 mm Hg. Otherwise the retinopathy was similar to those with diastolic pressures below 90 mm Hg. Streak hemorrhages are a feature of hypertensive rather than diabetic retinopathy. In our study, hemorrhages were graded together and therefore this finding was not confirmed.

The breakdown of the blood-retinal barrier may be important in the pathogenesis of diabetic retinopathy. Recently, vitreous fluorophotometry in mildly hypertensive nondiabetic subjects showed an increased leakage of fluorescein through the barrier into the vitreous, which is reversed with effective treatment of hypertension.\textsuperscript{6} It is thus possible that blood pressure can influence the early evolution of retinopathy, but progression to more severe retinopathy is determined by other factors such as differences in susceptibility or quality of diabetic control.

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