The objective of the U.K. Prospective Diabetes Study is to determine whether improved blood glucose control in type II diabetes will prevent the complications of diabetes and whether any specific therapy is advantageous or disadvantageous. The study will report in 1998, when the median duration from randomization will be 11 years. This report is on the efficacy of therapy over 6 years of follow-up and the overall incidence of diabetic complications. Subjects comprised 4,209 newly diagnosed type II diabetic patients who after 3 months' diet were asymptomatic and had fasting plasma glucose (FPG) 6.0–15.0 mmol/l. The study consists of a randomized controlled trial with two main comparisons: 1) 3,887 patients with 1,138 allocated to conventional therapy, primarily with diet and 729 allocated to intensive therapy with additional sulfonylurea or insulin, which increase insulin supply, aiming for FPG < 6 mmol/l; and 2) 753 obese patients with 411 allocated to conventional therapy and 342 allocated to intensive therapy with metformin, which enhances insulin sensitivity. In the first comparison, in 2,287 subjects studied for 6 years, intensive therapy with sulfonylurea and insulin similarly improved glucose control compared with conventional therapy, with median FPG at 1 year of 6.8 and 8.2 mmol/l, respectively (P < 0.0001), and median HbA1c of 6.1 and 6.8%, respectively (P < 0.0001). During the next 5 years, the FPG increased progressively on all therapies (P < 0.0001) with medians at 6 years in the conventional and intensive groups, FPG 9.5 and 7.8 mmol/l, and HbA1c 8.0 and 7.1%, respectively. The glycemic deterioration was associated with progressive loss of β-cell function. In the second comparison, in 548 obese subjects studied for 6 years, metformin improved glucose control similarly to intensive therapy with sulfonylurea or insulin. Metformin did not increase body weight or increase the incidence of hypoglycemia to the same extent as therapy with sulfonylurea or insulin. A high incidence of clinical complications occurred by 6-year follow-up. Of all subjects, 18.0% had suffered one or more diabetes-related clinical endpoints, with 12.1% having a macrovascular and 5.7% a microvascular endpoint. Sulfonylurea, metformin, and insulin therapies were similarly effective in improving glucose control compared with a policy of diet therapy. The study is examining whether the continued improved glucose control, obtained by intensive therapy compared with conventional therapy (median over 6 years HbA1c 6.6% compared with 7.4%), will be clinically advantageous in maintaining health. Diabetes 44:1249–1258, 1995

Type II diabetes is associated with a two- to threefold increased incidence of cardiovascular disease (1) and a substantial reduction in life expectancy (2,3). In addition, specific diabetic complications give rise to blindness, renal failure, and amputations, which seriously affect patients' quality of life and also require expensive health care resources. The current therapeutic approaches have not appreciably altered the high incidence of diabetic complications (3,4). This may be because many patients are treated primarily to avoid marked hyperglycemia that induces symptoms, and moderately raised blood glucose levels are accepted. It remains uncertain whether more intensive glycemic control will prevent the onset of complications or whether sulfonylurea, biguanide, insulin, or α-glucosidase inhibitor therapies have specific advantages or disadvantages.

The Diabetes Control and Complications Trial (DCCT) showed in 1,441 type I diabetic subjects, mean age 27 years, that intensive therapy achieved a significantly lower HbA1c than conventional therapy (7.1 vs. 9.0%) and significantly reduced the incidence and progression of diabetic microvascular disease (5). Similar data were obtained in the Stockholm Prospective Study (6). It is not known whether improved glucose control will be equally beneficial in type II diabetes, since the majority of the complications are macrovascular rather than microvascular.
The University Group Diabetes Program (UGDP), the only previous large-scale randomized controlled trial of type II diabetes, studied 1,927 type II diabetic patients. It found no clinical benefit from insulin, biguanide, or sulfonylurea therapy compared with diet alone (4). A statistically significant increase in cardiovascular mortality was found in those allocated to a sulfonylurea, tolbutamide, and to a biguanide, phenformin, but not in those with insulin therapy (7,8). This was an unexpected result in a study that had insufficient numbers of endpoints to draw definitive conclusions. Nevertheless, the resultant hypothesis, that these therapies may be tested. The binding of sulfonylureas to cardiac sulfonylurea receptors (9) provides a potential mechanism that might explain such an outcome. Treatments that raise insulin levels could, in theory, promote atherogenesis by inducing arterial wall smooth muscle proliferation and triglyceride synthesis (10). The epidemiological association in the general population between high fasting plasma insulin levels and an increased risk of myocardial infarction (11,12) is in accord with this hypothesis, although the associated dyslipidemia and hypertension may be confounding risk factors. The relevance of these studies in the general population to insulin treatment of diabetes is uncertain (13,14). UGDP found no difference in development of endpoints between those allocated to insulin or to placebo tablets (4).

The U.K. Prospective Diabetes Study (UKPDS) recruited 5,102 newly diagnosed type II diabetic subjects in 23 centers between 1977 and 1991 (15). At least 3 months’ diet, 4,209 of these asymptomatic, had raised fasting plasma glucose (FPG) between 6.0 and 15.0 mmol/l inclusive, and were included in a randomized controlled trial of different therapies. The study is designed to determine whether more intensive glycemic control of type II diabetic patients will reduce the incidence of clinical complications and whether sulfonylurea, metformin, or insulin therapies have specific advantages or disadvantages. UKPDS is due to finish in 1997 with the publication of results in 1998. The study remains blinded to the effect of the randomized therapies on the development of clinical complications but is unblinded for process variables such as glucose control. The study protocol was published in 1991 (15) and the 3-year efficacy data of the different therapies in 1995 (16).

We report on glucose control in those allocated to different therapies over 6 years, the progressive deterioration of glycemia, and the incidence of diabetic macrovascular and microvascular endpoints.

**PATIENTS AND INITIAL DIET THERAPY**

After referral by general practitioners to 23 U.K. centers, 5,102 newly diagnosed type II diabetic patients aged 25–65 years inclusive, 58% male, entered the UKPDS (15). The entry criterion was FPG >6 mmol/l on two occasions, excluding those with ketonuria >3 mmol/l. The median age at diagnosis was 53 years, median FPG 11.9 mmol/l, and mean body mass index 28.9 kg/m², with 36% of male and 67% of female patients being obese (>120% ideal body weight) (18). Hypertension (defined as systolic blood pressure >160 mmHg and diastolic blood pressure >90 mmHg or current treatment for hypertension) occurred in 37% of male and 52% of female patients (19). Approximately 50% of patients had clinical evidence of diabetic tissue damage at diagnosis (15). The ethnic groups studied were white Caucasian 82%, Asian from Indian subcontinent 10%, and Afro-Caribbean 8%. Asian Indian patients were younger and less obese with greater central adiposity than white Caucasian patients. Afro-Caribbean patients had similar obesity to white Caucasian patients but less dyslipidemia. The different ethnic groups had a similar prevalence of preexisting heart disease, retinopathy, and microalbuminuria (19).

Patients were advised by a dietitian, at monthly clinic visits for the first 3 months, to follow a low-fat high-carbohydrate high-fiber diet with energy restriction in obese subjects. On average they lost 5 kg (12 lb) weight; 86% became symptom-free, but only 17% achieved FPG <6 mmol/l. In two-thirds of these patients the FPG subsequently increased to >6 mmol/l within 3 years (15). The loss of weight required to obtain near-normal glycemia, FPG <6 mmol/l, was often more than could be realistically achieved (20).

**STUDY DESIGN, INCLUDING ALLOCATION TO DIFFERENT THERAPEUTIC POLICIES**

After the initial 3 months, 4,209 asymptomatic patients with FPG 6.0–15.0 mmol/l inclusive were randomized to either conventional or intensive therapy policies. For the conventional therapy policy, patients were allocated primarily to continue with diet therapy alone. If they subsequently became symptomatic or the FPG increased to >15 mmol/l, they were randomly allocated to the other agents, as below but with the aim of maintaining FPG <15 mmol/l with no symptoms. For the intensive therapy policy, nonobese and obese patients were allocated to sulfonylurea or insulin and obese subjects had the additional possibility of allocation to metformin. The primary aim of intensive therapy was to achieve near-normal FPG <6 mmol/l (Fig. 1).

The study is assessing two distinct pharmaceutical approaches: 1) increasing insulin supply by comparing patients allocated to intensive therapy with sulfonylurea or insulin with those allocated to conventional therapy, primarily with diet; and 2) enhancing insulin sensitivity, in obese subjects only, by comparing patients allocated to intensive therapy with metformin with those allocated to conventional therapy. The study used an unbalanced randomization to allow for the comparison of several different therapies (Fig. 1).

**Comparison 1: improving blood glucose control by increasing insulin supply with sulfonylurea or insulin therapy.** A total of 3,867 obese and nonobese patients, whose FPG remained 6.0–15.0 mmol/l after diet treatment, were randomly allocated: 1,138 to conventional therapy and 2,729 to intensive therapy with sulfonylurea or insulin, aiming if feasible to maintain FPG <6.0 mmol/l (Fig. 1).

The major analyses were made in relation to the primary allocations to conventional or intensive policies. In each allocation, additional therapies were added in a planned sequence when certain control criteria were not achieved. When patients were allocated to intensive therapy with sulfonylurea or insulin, the doses were increased until the FPG became <6 mmol/l, unless hypoglycemia occurred (16) or maximal doses were achieved (chlorpropamide 500 mg, glyburide 20 mg, or glipizide 40 mg/day, with no limit on the amount of insulin). Insulin was given primarily as a basal supplement with a once daily evening injection of ultralente insulin (21). Home blood glucose monitoring was instituted when the insulin dose became >16 U per day, with either the
Newly diagnosed diabetic subjects
Diet Therapy
n = 5102

Asymptomatic
fpg 6.0 to 15.0 mmol/L
Randomisation
n = 4206

Reached 6 years
n=2538

Conventional Therapy

Diet alone
n=676
379 / 297

Sufonylureas
n=922
529 / 393

Insulin
n=669
387 / 302

Metformin
n=251
... / 251

Intensive Therapy

FIG. 1. Flow diagram of study design and randomizations with numbers of patients who have attained 6 years of follow-up. The lowest boxes also show the numbers of nonobese/obese patients defined as < =120% ideal body weight. The dotted box outlines the patients in comparison 1, evaluating the question “Will improved glucose control by increasing insulin supply be beneficial or harmful?” The obese patients allocated to conventional therapy and metformin therapy are included in comparison 2, evaluating the question “Will improving glucose control by enhancing insulin sensitivity be beneficial or harmful?”

addition of subcutaneous regular insulin before meals or the switch to a regular and isophane insulin regimen, aiming in each case for preprandial plasma glucose concentrations 4–7 mmol/l (22). When the FPG in patients allocated to sulfonylurea therapy became >15 mmol/l or hyperglycemic symptoms occurred, metformin was added to a maximum of 2,550 mg/day with insulin therapy substituted when these criteria recurred.

The protocol deliberately continued with sulfonylurea or biguanide monotherapy as long as possible because a major aim of the study was to determine whether either therapy might increase the incidence of cardiovascular disease. In 1987, a protocol modification was introduced when increasing hyperglycemia was identified on all therapies. Patients continuing sulfonylurea therapy alone (n = 297) were randomly allocated to conventional therapy compared with 251 to metformin. In addition, 297 obese subjects in the 6-year cohort were allocated to intensive therapy, increasing insulin supply (consisting of 302 allocated to sulfonylurea and 302 allocated to insulin therapy).

The occurrence of hypoglycemia was assessed at the 3-monthly clinic visits, and the number of patients who had one or more minor hypoglycemic episodes (did not require medical assistance) or major episodes (required medical assistance or admission to a hospital) each year was noted. The average of the six annual assessments was calculated for those patients who remained on their allocated therapy throughout 6 years.

**Hypertension in diabetes study.** In 1987, in a factorial design, 1,148 patients with hypertension were allocated to policies of tight control (aiming for blood pressure <150/85 mmHg) or less tight control (aiming for <180/105 mmHg). The randomizations were independent of the UKPDS randomizations, so the blood pressure study does not effect the blood glucose control study.

**Clinical endpoints.** Twenty specific macrovascular and microvascular clinical endpoints are being assessed prospectively (15). These are aggregated into categories: 1) diabetes-related mortality: death from heart attacks, sudden death, stroke, complications from peripheral vascular disease or amputations, renal failure, or hyperglycemic or hypoglycemic coma; 2) total mortality; and 3) diabetes-related mortality and major clinical endpoints including nonfatal myocardial infarct, clinical angina with confirmatory ischemic ECG abnormality (a new ECG abnormality at rest or on exercise testing), heart failure (raised jugular venous pressure or increased left ventricular filling pressure shown by Kerley B lines on a chest X ray or by rales on auscultation), major stroke with symptoms persisting after 1 month, amputation, retinal photocoagulation, vitreous hemorrhage, blindness (visual acuity less than the logarithm of the minimal angle of resolution 1.0), and renal failure (plasma creatinine >250 µmol/L) (15). Data for clinical endpoints are assessed independently by two physicians, who are masked to allocated or actual therapy. If their assessments do not concur, a further panel of two external physicians makes the final decision.

All endpoints are reviewed regularly by the independent Data Monitoring and Ethics Committee, which assesses whether a definitive result has been obtained. The stopping criteria guidelines are whether allocation to different therapies has provided a 3 SD difference in the incidence of clinical endpoints in the three categories. Evidence from other clinical trials and epidemiological studies is taken into account.

**Subclinical endpoints.** While the clinical endpoints are the major study outcomes, macrovascular and microvascular subclinical surrogate endpoints are assessed at a major
trian trial review. The microvascular surrogate variables include color retinal photography of four horizontal 30° fields per eye with assessment of retinopathy by a modified “191” grading (15,23), albuminuria assessed on a single urine sample taken in the clinic with correction for urine dilution by regression on the urine creatinine concentration (24), and the clinicians’ assessments of whether the ankle or knee reflexes were absent even with reinforcement. The macrovascular variables include a 12-lead ECG with Minnesota coding, hypertension (defined as systolic blood pressure ≥160 mmHg, diastolic blood pressure ≥90 mmHg or on therapy for hypertension), and the clinicians’ assessment of whether either both dorsalis pedis or both posterior tibial pulses were not palpable.

**Biochemical measurements.** Plasma glucose was assayed in local laboratories with measurement monitored by the UKPDS Glucose Quality Assurance Scheme, which showed a coefficient of variation of 4% HbA1c was measured centrally in heparinized whole blood by high-performance liquid chromatography (Bio-Rad Diamat Automated Glycosylated Assay, Bio-Rad, Hemel Hempstead, Herts, U.K.). The central 95th percentile range for an age-matched non-diabetic population was 4.5–6.2% (24).

Fasting plasma insulin was measured annually with a radioimmunoassay with 100% cross-reaction with intact proinsulin (24). A structural model of glucose/insulin interactions, Homeostasis Model Assessment (HOMA), was used to estimate the β-cell function and insulin sensitivity that would induce the measured fasting insulin and glucose levels of each person (25,26). An updated model, termed HOMA 2, has been used that uses specific insulin and proinsulin concentrations and combines them to provide the equivalent of the radioimmunoassay insulin that was measured. β-cell function (%B) and insulin sensitivity (%S) were assessed in relation to a reference group of 40 normoglycemic subjects aged 18–25 years and were estimated in the subsets of the subjects who remained on their allocated therapy over 6 years. For comparison 1, these cohorts comprised 276 patients on diet therapy and 511 on sulfonylurea therapy, the latter having higher (P < 0.0001) FPG concentrations, median 7.8 and 8.3 mmol/l respectively, and higher (P < 0.05) median HbA1c, 6.6 and 6.9% respectively. For comparison 2, the cohorts comprised 110 patients on diet and 159 on metformin, the FPG concentrations at randomization being 7.5 and 8.1 mmol/l (P < 0.001) and HbA1c, 6.5 and 7.2% (P < 0.001), respectively. For both comparison 1 and comparison 2, there was no difference between the subsets studied for age or body mass index. The analysis was not feasible in patients taking insulin therapy, since the model assumed endogenous insulin secretion.

**Statistical analysis.** All analyses were according to allocated therapy, on an intention-to-treat basis, except where stated, e.g., those relating to hypoglycemia, when comparisons were according to patients who remained on their allocated therapy.

For description of the groups, means ± SD, geometric means (1 SD interval), or median (iq range) are quoted. For differences across time, data are expressed as mean (95% confidence interval).

Annual data for HbA1c, FPG, and body weight are presented as the median of three consecutive visits for each patient, i.e., the annual visit, the preceding visit, and the following 3-month visit. The median HbA1c exposure in the

<table>
<thead>
<tr>
<th>TABLE 1</th>
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<tbody>
<tr>
<td><strong>Details of patients at randomization in the 6-year cohorts assessing therapies that increased insulin supply (sulfonylurea and insulin) and enhanced insulin sensitivity (metformin)</strong></td>
</tr>
<tr>
<td>-----------------------------------------------</td>
</tr>
<tr>
<td><strong>n</strong></td>
</tr>
<tr>
<td>Age (years)</td>
</tr>
<tr>
<td>Sex (% male)</td>
</tr>
<tr>
<td>Ethnic group (% WC/AF/AS)</td>
</tr>
<tr>
<td>Body mass index (kg/m²)</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
</tr>
<tr>
<td>HbA1c (%)</td>
</tr>
<tr>
<td>Fasting plasma insulin (mU/l)</td>
</tr>
</tbody>
</table>

Data are means ± SD for age and body mass index, medians (iq range) for FPG and HbA1c, and geometric means (1 SD interval) for fasting plasma insulin. WC, white Caucasian; AF, Afro-Caribbean; AS, Asian Indian.

cohorts over the 6 years was assessed from the median 1- to 6-year values in each patient. The degree of glycemic control obtained has been categorized in regard to the proportion of patients with FPG <140 mg/dl (<7.8 mmol/l), the apparent threshold for microvascular disease (27,28), and <108 mg/dl (6.0 mmol/l), the apparent threshold for macrovascular disease (29,30).

Life table analysis of diabetic complications with the Kaplan Meier method up to censor date 30 September 1994 in all 5,102 patients was used to determine the proportion of patients who have had one or more major events within 6 years of randomization. For surrogate endpoints, the proportion of all patients who reached 6-year follow-up who had abnormal surrogate endpoints at 3 and 6 years of follow-up were assessed.

The Mann-Whitney U test or Student’s t test was used for group comparisons, and for within group changes the mean difference was tested as significantly different from zero. No significant differences were seen at randomization between the allocated groups in age, gender, ethnic group, FPG, HbA1c, body weight, fasting plasma insulin, %B, or %S.

**RESULTS**

**Efficacy of therapies**

*Increasing insulin supply with sulfonylurea or insulin therapy.* At randomization, the 2,287 nonobese and obese patients in each of the 6-year cohorts had median FPG 8.0 mmol/l and HbA1c 6.9% (Table 1). Figure 2 shows the FPG and HbA1c over 6 years. Intensive therapy with sulfonylurea or insulin over 1 year reduced the FPG concentration to median 6.8 mmol/l and HbA1c to 6.1% (Table 2). The FPG values remained >6.0 mmol/l in the majority of patients because either maximum sulfonylurea doses were insufficient or the therapies were limited by hypoglycemia. In those allocated to conventional therapy, the median FPG increased by 6 years to median 9.5 mmol/l and the HbA1c increased to 8.6% (Table 2). In those allocated to intensive therapy, a similar increase occurred from 1 to 6 years at a lower level to FPG 7.8 mmol/l and HbA1c 8.0% at 6 years. The increase from 1 to 6 years in those allocated to sulfonylurea, from median 6.7 to median 8.0 mmol/l, was greater than in those allocated to insulin therapy, from median 6.9 to median 7.6 mmol/l (P < 0.001), whereas the HbA1c rose similarly in those allocated to sulfonylurea, from median 6.0 to median 7.1%, and to insulin therapy, from 6.3 to 7.1%.
The proportions of patients allocated to conventional and intensive therapy who maintained a median FPG <7.8 mmol/l at 6 years were 24 and 49% (P < 0.0001) respectively, with those allocated to sulfonylurea or insulin therapy being 47 and 53% (P < 0.05) respectively. Similarly, the proportions maintaining FPG <6 mmol/l at 6 years were 5 and 18% (P < 0.0001) respectively, with those allocated to sulfonylurea or insulin therapy being 18 and 20% respectively.

The increase in glycaemia in the intensive group occurred despite physicians' increasing the doses of medication. At 3 and 6 years, 89 and 93% of those allocated to sulfonylurea or insulin were taking the allocated therapy. In those allocated to intensive therapy with sulfonylurea, from 3 to 6 years, the proportion taking additional metformin increased from 7 to 20% and the proportion transferred to insulin therapy increased from 5 to 10% (each P < 0.001). In those allocated to intensive therapy with insulin, at 3 and 6 years, 74 and 77% were taking insulin, with 17 and 24% (P < 0.005) being on a complex insulin regimen rather than on ultralente insulin alone. The median doses were 22 and 30 U/day (P < 0.0001) at 3 and 6 years respectively. In those allocated to conventional therapy, initially by diet alone, at 3 and 6 years, 29 and 55% (P < 0.0001) had become symptomatic or had an FPG >15 mmol/l and had been transferred to another therapy with the aim still of maintaining FPG <7.8 mmol/l.

Enhancing insulin sensitivity with metformin therapy. At randomization, the 540 obese subjects in the 6-year cohort had median FPG 8.1 mmol/l and HbA1c 6.9% (Table 1). Figure 3 shows the FPG and HbA1c in obese subjects allocated to conventional therapy, to metformin therapy, and to intensive therapy increasing the insulin supply, combining the sulfonylurea and insulin allocations. Intensive therapy with metformin over 1 year reduced the FPG concentration to median 7.2 mmol/l and HbA1c 6.4% (Table 3). In those allocated to conventional therapy, the median FPG increased by 6 years to median 9.7 mmol/l. In those allocated to metformin therapy, a similar increase occurred at a lower level to median 8.4 mmol/l and HbA1c 7.4%. This was comparable with the increase in the obese subjects allocated to intensive therapy increasing insulin supply, in whom the FPG increased from 7.1 to 8.5 mmol/l between 1 and 6 years.

At 6 years, the proportion of obese subjects who maintained a median FPG <7.8 mmol/l was 19% in the conventional group compared with 41% in those allocated to metformin and 39% to intensive therapy with sulfonylurea or insulin. Similarly, 7, 6, and 13%, respectively, maintained an FPG <6 mmol/l.

The increase in glycaemia with metformin therapy occurred despite physicians' increasing the doses. At 3 and 6 years, 86 and 84% were taking metformin. In those allocated to metformin, at 3 and 6 years, the proportion taking additional sulfonylurea increased from 7 to 14% and 2 and 6% had been transferred to insulin therapy (each P < 0.05). In obese subjects allocated to conventional therapy, initially by diet

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TABLE 2
Patient characteristics by group at randomization and 1 and 6 years of therapy: comparison 1

<table>
<thead>
<tr>
<th>Allocation</th>
<th>Randomization</th>
<th>1 year</th>
<th>6 years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Conventional</td>
<td>Intensive</td>
<td>P value</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>75.9 ± 15.1</td>
<td>75.4 ± 14.2</td>
<td>NS</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>8.0 (7.1-9.4)</td>
<td>8.0 (7.2-8.7)</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.9 (6.0-7.9)</td>
<td>6.9 (6.0-8.0)</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma insulin (mIU/l)</td>
<td>12.3 (7.3-20.5)</td>
<td>12.3 (7.2-20.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means ± SD for body weight, medians (iq range) for FPG and HbA1c and geometric means (1 SD interval) for fasting plasma insulin. †P < 0.5, ‡P < 0.01, and §P < 0.0001 for comparison with randomization within therapy allocation.

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FIG. 2. FPG (A), HbA1c (B), body weight (C), and plasma insulin (D) over 6 years in patients allocated to conventional therapy (C; n = 676), insulin therapy (R; n = 689), or sulfonylurea (A; n = 822). -- - - - - - - 6.0 and 7.8 mmol/l (A) and 6.2% (B).
alone, at 3 and 6 years, 42 and 62% (P < 0.0001) had become symptomatic or had a FPG >15 mmol/l and had been transferred to another therapy.

**Progressive β-cell dysfunction.** The increase in FPG in those allocated to conventional therapy was accompanied by decreasing fasting plasma insulin levels, indicating progressive β-cell dysfunction similar to that previously reported (31). β-cell function deteriorated over 6 years in the 37% of subjects allocated to and remaining on diet therapy at 0, 1, and 6 years, geometric means 51, 53, and 28% respectively, with a significant decrease from 1 to 6 years (P < 0.0001) (Fig. 4). In the 50% of subjects continuing on their allocated sulfonylurea therapy, geometric mean β-cell function increased in the 1st year from 46 to 78 %β (P < 0.0001), but subsequently the β-cell function decreased to 52 %β (P < 0.0001) at 6 years, the decrease being similar to that in those treated by diet over the same time period. Cross-sectional analysis at each year of all the subjects who remained on their allocated therapy gave similar results to the cohort analysis examining those who remained on their allocated therapy throughout the 6 years (data not shown). The insulin sensitivity was not affected by sulfonylurea therapy, being 62, 60, and 62% at 0, 1, and 6 years.

In the obese subjects allocated to conventional therapy and remaining on diet therapy, the β-cell function also decreased, the geometric mean values at 0, 1, and 6 years being 60, 62, and 33 %β respectively, with a significant decrease from 1 to 6 years (P < 0.0001) (Fig. 4). In the 50% of subjects who remained on their allocated metformin therapy, the β-cell function in the 1st year increased from 51 to 66 %β (P < 0.0003), with a subsequent decrease to 38 %β at 6 years (P < 0.0001) similar to that in the 36% of subjects treated by diet. In those subjects who continued on allocated metformin, insulin sensitivity increased in the 1st year from 51 to 62 %S (P < 0.003), remaining at 67 %S at 6 years.

Increasing insulin levels in those treated by insulin reflected the increasing insulin doses and have precluded assessment of β-cell function and insulin sensitivity.

**Side effects**

**Body weight.** Figure 2 shows the increase in body weight in those allocated to sulfonylurea or insulin therapy, an increase of 6 (2-10) kg and 4 (1-8) kg respectively compared with 2 (1-6) kg in those allocated to conventional therapy. Table 4 shows that the increases between 1 and 6 years were significant and that the increase in the group allocated to intensive therapy was significantly greater than that in those allocated to conventional therapy. In the obese subjects, those allocated to metformin had a similar increase in body weight 1 (3-5) kg to those allocated to conventional therapy (3-6) kg (Fig. 3). The changes between 1 year and 6 years were not significantly different between conventional and metformin therapy.

**Hypoglycemic reactions.** During the 6 years, the proportion of patients per year reporting one or more hypoglycemic

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**TABLE 3**

Patient characteristics by group at randomization and 1 and 6 years of therapy: comparison

<table>
<thead>
<tr>
<th></th>
<th>Randomization</th>
<th>1 year</th>
<th>6 years</th>
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</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td>Conventional</td>
<td>Metformin</td>
</tr>
<tr>
<td>Body weight (kg)</td>
<td>86.1 ± 14.8</td>
<td>86.7 ± 16.4</td>
<td>NS</td>
</tr>
<tr>
<td>FPG (mmol/l)</td>
<td>8.0 (7.1-9.3)</td>
<td>8.3 (7.3-9.9)</td>
<td>NS</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.8 (5.9-7.9)</td>
<td>7.6 (6.3-8.1)</td>
<td>NS</td>
</tr>
<tr>
<td>Fasting plasma insulin (mU/l)</td>
<td>15.3 (9.3-24.3)</td>
<td>15.6 (9.3-25.9)</td>
<td>NS</td>
</tr>
</tbody>
</table>

Data are means ± SD for body weight, medians (iq range) for FPG and HbA1c, and geometric means (1 SD interval) for fasting plasma insulin. *P < 0.5, †P < 0.01, and §P < 0.0001 for comparison with randomization within therapy allocation.
events was 17% in those allocated to and taking sulfonylurea and 37% in those allocated to and taking insulin compared with 0.9% in those allocated to diet therapy and remaining on it. The cumulative proportions over 6 years were 45, 76, and 3% respectively. Major hypoglycemic episodes, requiring third party assistance or admission to a hospital, occurred in 0.7% per year of those allocated to and taking sulfonylurea, 2.3% in those allocated to insulin, and 0.03% in those remaining on diet therapy. The cumulative proportions were 3.3, 11.2, and 0.15% respectively. A small number of episodes have induced serious physical injury. In the obese subjects, the proportions per year of those allocated to metformin and diet therapy who reported one or more hypoglycemic episodes were 13 and 5% and major hypoglycemic events 0.3 and 0.1% respectively.

**Fasting plasma insulin levels.** The fasting plasma insulin levels at 6 years in those allocated to sulfonylurea and insulin therapy were geometric means 12.5 and 15.4 mU/L respectively, compared with 11.6 mU/L in those allocated to conventional therapy ($P < 0.001$) (Table 2). In the obese subjects allocated to metformin, the fasting plasma insulin level at 6 years was 12.1 mU/L compared with 14.2 mU/L in those allocated to conventional therapy ($P < 0.001$). Table 3 includes changes between 1 and 6 years and shows that patients allocated to intensive therapy had a significantly greater increase in fasting plasma insulin.

**Clinical outcome**

**Clinical endpoints.** The clinical endpoints in the 5,102 patients recruited are shown in Table 4, with the proportion having each endpoint category by 6-year follow-up with a Kaplan Meier plot in Fig. 5. A total of 4.0% have died from a diabetes-related cause, 3.2% having myocardial infarction, 0.5% stroke, and 0.3% sudden death. Of the patients, 18% have had a diabetes-related fatal or nonfatal event. Macrovascular endpoints occurred in 12.1% (including 4.1% with nonfatal myocardial infarctions, 3.7% with clinical angina with an abnormal ECG, and 1.5% with a nonfatal stroke). Microvascular endpoints occurred less frequently, in 5.7% of patients (including 4.5% with retinal photocoagulation, 0.3% with renal failure, and 0.4% with amputations). In addition, 2.1% had a cataract extraction. A fatal outcome from microvascular disease, death from renal complications (0.1%), occurred fifty times less frequently than from macrovascular disease. Deaths from macrovascular disease (4.0%) accounted for 59% of all deaths. Thus, when one considers that the median age of entry was 53 years and that at that stage the majority of patients were thought to be clinically healthy, a high proportion of patients have had a clinical endpoint within 6 years of diagnosis.

**Subclinical variables of diabetic tissue damage.** Figure 6 shows in all patients in the study the increasing prevalence of surrogate indexes for macrovascular disease over the initial 6 years and the increasing prevalence of surrogate indexes of microvascular disease.

**DISCUSSION**

**Clinical efficacy of current therapies.** Allocation to intensive therapy has successfully maintained significantly reduced glycemia over 6 years compared with conventional therapy. The median difference over the 6 years between the
FIG. 6. Proportions (%) of patients who attained 6-year follow-up who had subclinical indexes of microvascular disease at their triennial reviews: retinopathy (modified Wisconsin grading) (A), albuminuria (B), ankle or knee reflexes absent (C); and those who had subclinical indexes of macrovascular disease: abnormal ECG, Minnesota Code 1 or 2 (D), hypertension (E), both foot pulses absent (F), dp, dorsalis pedis; pt, post tibial.

Progressive hyperglycemia and decreasing 6-cell function. The study has shown that progressively increasing hyperglycemia, associated with decreasing 6-cell function, was a marked feature irrespective of the therapy used. No deterioration in insulin sensitivity was observed. Neither sulfonylurea nor metformin therapy appeared to have a major effect on the underlying decrease in 6-cell function. The improvement in 6-cell function induced by sulfonylurea in the 1st year was not maintained, suggesting that the deterioration in glucose control in the sulfonylurea-treated patients was more likely to be due to the underlying progressive decrease in 6-cell function than to sulfonylurea failure. It was not possible to assess 6-cell function with the HOMA model in those patients receiving exogenous insulin.

Limitations of current therapies. Despite continuing dietary advice and increasing the doses of sulfonylurea, metformin, or insulin, by 6 years after the diagnosis of diabetes, 53, 59, and 47% respectively of patients in the intensive group had FPG above 7.8 mmol/l, the reported threshold for microvascular disease, and 82, 94, and 80% respectively of patients had FPG levels >6 mmol/l, the putative threshold for cardiovascular disease. Thus, the currently available drugs, when used primarily as monotherapies, often were unable to maintain near-normal glucose control.

The progressive hyperglycemia was such that therapy with sulfonylurea or metformin on average took 6 years before the FPG returned to the pretherapy level and 4 years before the HbA1c returned to its pretherapy level. The difference may reflect increasing postprandial hyperglycemia. While in theory it should have been possible to obtain better control with insulin therapy because there was no upper dose limit, this was often not feasible. Increasing basal insulin doses were often required to overcome both insulin resistance and impaired 6-cell function; by 6 years, 24% of patients needed additional short-acting insulin to cover meals. The mean dose of insulin at 6 years, 50 U/day, was lower than that often used in treating patients with type II diabetes, since insulin was given at an earlier stage of development of diabetes when it could have been treated by diet alone. Clinically, insulin is usually given only when patients have required sulfonylurea therapy and it is no longer successful. Nevertheless, even though the insulin requirements were not large, hypoglycemic symptoms often limited efforts to attain improved control. The middle-aged and elderly patients in the UKPDS, who were representative of diabetic patients in the general population, were often not able to give as much attention to improving glycemic control with insulin therapy as the younger volunteers in the DCCT.

Because increasing hyperglycemia requires additional therapies, in 1994, acarbose, an agent that reduces postprandial glucose excursions (34), was added in a double-blind placebo-controlled study in a factorial design across all other randomizations. A total of 1,946 eligible patients were entered to determine the degree to which acarbose improves HbA1c.

Glucose control and potential clinical outcome. The study has confirmed that macrovascular events are a major problem in patients with type II diabetes. In view of the increasing severity of 6-cell dysfunction, the improvement of glucose control that can be obtained with currently available therapies might be insufficient in type II diabetes to prevent macrovascular disease. Given that the epidemiological data suggest the glycemic threshold for macrovascular disease may be only just above the normal range (27,28). The few data available in prospective type II diabetes studies (35) are in accord with a moderately low threshold. It is not known whether it will be necessary to strive for near-normal glycemia to prevent cardiovascular disease or whether this will unnecessarily increase the risk of hypoglycemic episodes.

The UKPDS will provide comprehensive data on the relative advantages and disadvantages of sulfonylurea, bigu-
anide, or insulin therapy in terms of long-term health and potential undesirable side effects, particularly hypoglycemia. It is uncertain whether different pharmaceutical approaches will have similar clinical outcomes. Although sulfonylurea, metformin, and insulin therapies similarly improved glucose control, sulfonylurea and insulin therapy increased body weight, by 2.2 and 3.6 kg over 6 years, compared with conventional therapy. On the other hand, metformin therapy in the obese subjects had no effect on body weight compared with that of conventional therapy. Sulfonylurea and insulin therapy increased fasting plasma insulin levels by 0.9 and 3.8 nMUL respectively at 6 years compared with conventional therapy, whereas metformin decreased them by 2.1 nMUL.

It is possible that the increased body weight, increased insulin levels, and increased risk of hypoglycemia induced by sulfonylurea or insulin therapy may occur in many years be deleterious and may confound any benefit induced by improved glucose control. In addition, the possibility that sulfonylurea and biguanide therapy may have a specific effect of increasing the risk of myocardial infarctions, as suggested by UGDP, cannot be excluded. Indeed it is possible that the patients allocated to continue on diet therapy alone, with acceptance of moderate hyperglycemia, might be found to have had the optimal therapy, with less therapeutic intervention, less increase in body weight, and fewer hypoglycemic episodes.

**Clinical endpoints.** Within 6 years of the diagnosis of diabetes, 18% of patients have had a clinically presenting diabetic complication. The clinical endpoints confirmed that myocardial infarction and clinical angina were the major complications arising in the type II diabetic patients. While 12.1% of patients had a macrovascular event, only 5.7% had a microvascular event and few deaths could be attributed directly to microvascular disease. Thus, a beneficial effect of therapy in preventing macrovascular disease is a major requirement. The UKPDs includes only newly diagnosed patients, and renal failure is uncommon, whereas in other populations, possibly because of worse blood glucose or blood pressure control, renal failure is more prevalent.

**Subclinical endpoints.** The high rate of clinical endpoints that is occurring is matched by an increasing prevalence of subclinical indexes of both microvascular and macrovascular disease. Assessment of these may provide additional indexes of advantages or disadvantages arising from any therapeutic option. Although the primary analyses will include all allocated patients, additional secondary analyses will be done on the subgroups that did or did not have evidence of diabetic tissue damage at entry into the study. Thus, like the DCCT, this study is both a primary prevention and a secondary prevention study.

**Time course of the UKPDs.** The clinical study will end in 1997 when the 4,209 patients will have had a median time since randomization of 11 years (range 6–20), with 1,750 expected to have had a fatal or nonfatal diabetes-related endpoint. The Data Monitoring and Ethics Committee has so far indicated that intensive control has not been shown to be advantageous or disadvantageous and that the study should continue without change in protocol.

At diagnosis, 50% of patients had evidence of diabetic tissue damage (15). Improved glucose control may need to ameliorate preceding pathology as well as prevent future damage. Complications can take 10–20 years to develop, and a long-duration study might be needed to show clinical benefit. The number of patients with endpoints by 1997 will allow UKPDs to have an 81% power to detect a 15% advantage or disadvantage in the intensive group at the 1% level. The UKPDs will determine the extent to which currently available therapies will be able to reduce the clinical burden of the disease. Data are also being collected for health economics purposes, and quality of life is being assessed by questionnaires to patients and to a close relative, partner, or friend. It will thus be possible to assess the cost-benefit and cost-utility of the various therapeutic options that are available to type II diabetic patients.

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