Original Articles

Diabetes Control and Complications Trial (DCCT): Results of Feasibility Study

THE DCCT RESEARCH GROUP

The Diabetes Control and Complications Trial (DCCT) is a multicenter, randomized, clinical study designed to determine whether an intensive treatment regimen directed at maintaining blood glucose concentrations as close to normal as possible will affect the appearance or progression of early vascular complications in patients with insulin-dependent diabetes mellitus (IDDM). We present the baseline characteristics and 1-yr results of the initial cohort of 278 subjects randomized in phase II of the trial, a phase designed to answer several feasibility questions before initiating a full-scale trial.

During phase II, recruitment was completed on schedule. The 191 adults and 87 adolescents were randomized either to standard treatment (90 adults and 42 adolescents), designed to approximate conventional diabetes treatment, or to experimental treatment (101 adults and 45 adolescents), designed to achieve near-normal blood glucose and HbA_{1c} concentrations. With few exceptions, baseline demographic, ophthalmologic, renal, and other medical characteristics were evenly distributed by randomization between the two treatment groups in both age strata. Glycemic control at baseline, as assessed by HbA_{1c} concentrations and by blood glucose profiles, was comparable between the treatment groups in both age strata.

The treatment strategies employed produced statistically significant and clinically meaningful differences in HbA_{1c} concentrations and blood glucose profiles between the experimental- and standard-group subjects for both adults and adolescents. These differences were maintained throughout the feasibility phase. Except for an increased incidence of hypoglycemia in the experimental group, the two treatment regimens maintained or improved the clinical well-being of subjects in both groups. Adherence and completeness of follow-up were excellent (>95%), and the methods employed to measure biochemical and pathologic characteristics of IDDM proved to be reliable, reproducible, and precise.

The feasibility phase of the DCCT demonstrated that a complex multicenter, randomized study of the relationship between diabetes control and complications can be performed. The full-scale, long-term trial therefore has been initiated. *Diabetes Care* 10:1–19, 1987

The relationship between the metabolic control and the vascular complications of diabetes mellitus remains to be completely defined. Some (1–4) but not all (5,6) retrospective human studies and one prospective trial (7), as well as a number of animal studies (8–11), have suggested that elevated blood glucose levels cause or contribute to the development of microvascular complications in insulin-dependent diabetes mellitus (IDDM). Several short-term, randomized clinical trials recently completed in North America and Europe have failed to show any beneficial effect of intensive insulin treatment on the progression of diabetic retinopathy (12–14).

The Diabetes Control and Complications Trial (DCCT) was initiated to test the hypothesis that two treatment regimens resulting in statistically significant and clinically meaningful differences in chronic blood glucose control would result in clinically significant differences in the rate of appearance or progression of the early vascular complications

of IDDM (15). Retinopathy was specified a priori as a principal outcome with nephropathy, neuropathy, and cardiovascular disease to be studied conjointly. The operational plan of the trial included four phases: phase I, planning; phase II, a feasibility study; phase III, the full-scale trial; and phase IV, final data analysis.

The specific objectives of phase II were *1*) to determine whether in a reasonable period a well-informed cohort of volunteers fulfilling stringent eligibility criteria could be recruited for a long-term, randomized study; *2*) to determine whether both a clinically meaningful and statistically significant difference in the level of blood glucose control (assessed by blood glucose and HbA_{1c} measurements) could be achieved between patients randomly assigned either to standard treatment (1 or 2 daily injections of intermediate- and/or short-acting insulin) or to experimental treatment (intensive regimens directed at normalizing of blood glucose); *3*) to monitor the clinical well-being and safety associated with the two treatment regimens; *4*) to determine whether each of the randomly assigned therapies would be acceptable to patients as assessed by measurements of adherence to the two regimens over time and by completeness of follow-up; and *5*) to determine whether the biochemical and pathological characteristics of IDDM could be measured and documented with acceptable precision and accuracy in the context of a multicenter study.

In response to concern that this trial might not be feasible in adolescents, the first four objectives of the feasibility phase were to be evaluated separately for adolescents and adults. Therefore, randomization was stratified by clinic and by age (adolescents aged 13–17 yr and adults aged 18–39 yr).

Randomization for phase II occurred between August 1983 and March 1984, when 278 patients were enrolled in the trial. Our purpose is to describe the baseline demographic and clinical characteristics of the randomized subjects and provide the results with regard to the phase II objectives of the first full year of study.

METHODS

The organization and design of the feasibility phase of the study have been presented in detail (15). We restrict the description of methods here to a brief review of the pertinent features of selection criteria, data collection, randomization strategy, and treatment regimens employed. Phase II of the DCCT was conducted in 21 clinical centers, a coordinating center, and 7 supporting central laboratories or reading units. The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) appointed the Policy Advisory Group (PAG) and the Data Safety and Quality Review Group (DSQ) to provide external peer review and to monitor the progress of the trial.

Selection Criteria

The characteristics of the study subjects were mostly dictated by the eligibility and exclusion criteria for entry into the DCCT (15). All subjects were to be at least 13 and <40 yr of age and with a duration of IDDM of 1–15 yr at randomization. They were to be free of advanced microvascular complications of diabetes, suffer from no other significant medical or psychiatric disorders that might complicate their care or limit their participation in the study, and be willing to carry out the responsibilities demanded by the DCCT protocol, including fastidious record keeping, daily self-monitoring, and regular clinic attendance. Patients who had IDDM for 1–5 yr, no retinopathy by stereoscopic fundus photography, and <40 mg albuminuria/24 h were considered to be primary prevention subjects. Patients who had IDDM for 1–15 yr, retinopathy less than Diabetes Retinopathy Study level P2 (16), and ≤200 mg albuminuria/24 h were considered to be secondary intervention subjects.

The target sample size was 252 subjects with a minimum of 126 adults (6 subjects/clinic) and 84 adolescents (4 subjects/clinic). This sample size was necessary to provide power >0.90 to detect differences in mean absolute values of HbA_{1c} of at least 1.5% and in blood glucose of at least 40 mg/dl between the treatment groups in the total study and to provide power >0.75 within each age stratum.

Selection Procedures

Each clinical center used a series of interviews and medical procedures to identify eligible participants (15). A two-part informed consent was used; part 1 was administered before eligibility screening and part 2 before baseline studies. The interviews and tests were arranged in a sequence determined by each clinic. All eligibility and baseline assessments were completed before randomization. No more than 4 mo could elapse between the date of the patient's first examination or procedure and the date of the randomization visit. Baseline biochemical assessments (HbA_{1c}, blood glucose profiles, and blood lipids) were performed within the 2-wk period before randomization. All baseline assessments were reviewed by the appropriate central unit, and notification of their suitability was relayed to the coordinating center before a patient could be randomized.

Randomization

Each clinic was masked to the randomization sequences. After all eligibility/exclusion criteria were satisfied and verified, patients entering the trial were randomized to the standard- or experimental-treatment groups by a telephone call from the clinic to the coordinating center. The randomization sequences were stratified by clinic and by age within each clinic (adolescents vs. adults). This ensured approximately equal numbers of patients assigned to standard and experimental groups within each of the 42 clinic-age strata (21 clinics by 2 age strata). A restricted randomization procedure was implemented to prevent an imbalance in the number of subjects assigned to standard and experimental groups. Because of the small number of patients to be recruited within each clinic-age stratum, the initial four random allocations within each stratum were generated by a random permutation of two experimental and two standard allocations, thus providing balance after four allocations. Thereafter, the Urn

procedure (17) was employed to generate the remainder of the random allocations within strata.

Summary of Therapeutic Regimens

Subjects in the standard-treatment group received a conventional regimen of one or two insulin injections per day with appropriate education regarding diet and exercise. Primary goals for the standard group included absence of symptoms attributable to glycosuria or hyperglycemia, absence of ketonuria, maintenance of normal growth and development and ideal body weight, and freedom from frequent or serious hypoglycemia. Home monitoring was primarily by urine testing with self-monitoring of blood glucose when required to achieve and maintain clinical well-being. No predefined targets for glycemic control were set. However, investigators were notified if a subject's HbA_{1c} value exceeded an upper action limit of 2 SD above the mean of a sample of current IDDM patients (13.11%). If this occurred, therapy was adjusted, and HbA_{1c} was measured monthly until the situation was corrected.

Subjects in the experimental-treatment group received insulin either by continuous subcutaneous insulin infusion (CSII) or by multiple ($\geq$3) daily injections (MDI). In addition to the primary goals shared with the standard-treatment group, experimental-group subjects were expected to self-monitor blood glucose at least 4 times daily, and specific target values were defined. These included premeal blood glucose levels between 70 and 120 mg/dl, postmeal levels <180 mg/dl and >65 mg/dl at 0300 h, and HbA_{1c} values within the normal range (<6.05%).

HbA_{1c} values were measured quarterly in the standard group. Because the standard group's treatment regimen was not directed toward achieving specific glycemic targets, investigators were masked to these values except when the upper action limit was exceeded. HbA_{1c} was determined monthly in the experimental group, and values were unmasked for medical management purposes because the experimental group's treatment regimen was directed toward achieving specific targets.

Centrally Determined Phase II Outcome Measurements

Clinical and biochemical outcome evaluations were conducted at baseline and during follow-up according to a predefined schedule: quarterly for measurements of capillary blood glucose profile and HbA_{1c}, 3, 6, and 12 mo for fundus photographs, and annually for assessment of complications other than retinopathy. Fluorescein angiography was performed only at baseline.

Except for HbA_{1c} in experimental-group subjects, all centrally determined outcome measurements were masked from the DCCT clinic staffs and from the subjects. If an interim outcome measurement dictated a change in subject management, the results were promptly communicated to the DCCT clinic, which informed the subject and instituted appropriate therapy.

Capillary blood glucose. Capillary blood glucose levels were measured by the central biochemistry laboratory (CBL) from specimens obtained quarterly with a Profilset (Boehringer-Mannheim, Indianapolis, IN). Seven samples were collected: before and 90 min after each of the three major meals and before bedtime. These were frozen at completion, brought to the clinical centers, and shipped on dry ice to the CBL for analysis by the hexokinase method.

HbA_{1c}. HbA_{1c} levels for all subjects were measured by the central HbA_{1c} laboratory (CHL). Whole venous blood samples were collected and shipped on wet ice (~4°C) to the CHL where hemolysates were prepared, "pre-HbA_{1c}" was removed by incubation, and samples were then assayed with a high-performance liquid-chromatography method (18).

To establish limits for eligibility screening and clinical management, HbA_{1c} was measured in the CHL in blood obtained from 124 nondiabetic subjects age 13–39 yr and from a sample of 205 IDDM patients in the same age range. The IDDM sample was drawn from other patients treated in each of the 21 DCCT clinical centers. Based on the mean and standard deviation of the normal subjects (5.05 ± 0.50%) and the IDDM patients (8.95 ± 2.08%), the following limits were adopted: for eligibility, >6.55% (mean + 3 SD of nondiabetic subjects); for the upper action limit, >13.11% (mean + 2 SD of IDDM patients); and for the experimental-group treatment target, <6.05% (mean + 2 SD of nondiabetic subjects).

Fundus Photographs

Stereoscopic fundus photographs were obtained by certified DCCT photographers with procedures adapted from the Early Treatment Diabetic Retinopathy Study (ETDRS) (19). Mounted and labeled slides were mailed to the central ophthalmic reading unit (CORU) where they were first graded for quality (i.e., rated as excellent, good, fair, acceptable, or inadequate). Photographic sets of at least acceptable quality were first graded for lesions of diabetic retinopathy with the Modified Airlie House Classification of Diabetic Retinopathy, as adapted for previous studies (19). Overall retinopathy status was then established with an approach developed for previous studies (20). Because the DCCT enrolled subjects with a range of retinopathy from none detectable to no more than moderate nonproliferative, these grading scales were modified to provide better discrimination at the level of minimal changes. The retinopathy status of each eye was individually graded with the following scale. A normal fundus is graded at level 10. Level 20 indicates retinal microaneurysms only. At level 30, the fundus has microaneurysms with one or more of the following: hemorrhages, hard exudates, venous loops, questionable soft exudates (cotton-wool spots), questionable intraretinal microvascular abnormalities (IRMA), or questionable venous beading. A fundus at level 40 has microaneurysms with mild but definite soft exudates and/or mild but definite IRMA. Level 45 has microaneurysms with one of the following: moderate soft exudates, moderate IRMA, retinal hemorrhages/microaneurysms equaling or exceeding those in standard photograph 2A or any venous beading. Levels 50 and 55 denote severe nonproliferative retinopathy

(correspond approximately to group P2 in the ETDRS). Levels 60 and above denote proliferative retinopathy.

After grading each eye separately, the retinal status of each patient was expressed by a system devised by the CORU. With this system each patient was first classified according to the more severely involved eye and then allocated to one of two subgroups on the basis of the other eye, i.e., an equal level of retinopathy in the second eye (e.g., 40/40) or a lower level in the second eye (e.g., 40/<40). The resulting nine levels that were considered eligible for the DCCT were as follows: 10/10 (for primary prevention subjects) and 20/<20, 20/20, 30/<30, 30/30, 40/<40, 40/40, 45/<45, and 45/45. For efficiency and to reduce the turnaround time for establishing eligibility, photographic sets from all subjects screened for the study received a preliminary grading for eligibility (i.e., evaluated only with regard to eligibility criteria) by two senior graders. Photographic sets from each patient actually entered in the study were subsequently and independently graded by two graders (with differences resolved through regrading and, if necessary, through adjudication by a senior grader) to determine baseline retinopathy status according to the nine-step scale.

Clinical Well-Being

The well-being of the subjects was objectively measured by the occurrence of adverse events and by tests of subjects' psychologic well-being. The latter was assessed at baseline and 12 mo with the SCL-90 questionnaire (21) and by a quality-of-life (QOL) questionnaire developed specifically by the DCCT. Validation of this instrument showed a high level of internal consistency, a high level of test-retest reliability, and a good correlation with the SCL-90 global severity index ($r = .60$, $P < .0001$) (22).

Quality-Control Procedures

To ensure accurate measurement of the principal study outcomes, the CORU, CBL, and CHL established internal quality-control procedures that were used in conjunction with day-to-day operations. In addition, a program of external quality control was established with duplicate masked samples. For the CBL and CHL, 10% of all samples were randomly selected and duplicate aliquots prepared and submitted to the central laboratories with all other subject specimens. For the CHL, a backup laboratory that used identical methods was established. It ran the same long-term quality control performed at the CHL to demonstrate within-assay and between-assay coefficients of variation across time. Additionally, 10 split duplicates from study subjects were analyzed at the backup laboratory every 6 mo. The CORU reevaluated 60 masked sets of randomly selected photographs from the 278 randomized subjects. These duplicate results allowed assessment of the overall precision and reliability of the study data.

Definition and Ascertainment of Adverse Events

Criteria were established at the outset to ensure uniform and complete reporting of major adverse effects of diabetes or of the treatment protocols. Subjects were instructed to report each adverse event to the clinic. These were promptly recorded on an intercurrent-event form that was then sent to the coordinating center. In addition, subjects were routinely questioned at each quarterly visit about the interval occurrence of these adverse events to be certain that all had been reported. The following definitions were employed.

Ketoacidosis. Symptoms such as polydipsia and polyuria, nausea, or vomiting; and presence of serum ketones or large or moderate urinary ketones; and either arterial blood pH <7.25 or serum bicarbonate <15 meq/L; and treatment provided within a health-care facility.

Hypoglycemia. An event resulting in seizure, coma, confusion, irrational or uncontrollable behavior, or other symptoms consistent with hypoglycemia (e.g., sweating, palpitations, hunger, or blurred vision) in conjunction with *1*) a

TABLE 1
Exclusion rates for major exclusion criteria

IDDM duration	C-peptide*		HbA_{1c}†		Retinopathy‡		Albuminuria§	
	Screened (*N*) (total 610)	Excluded (%) (total 12%)	Screened (*N*) (total 561)	Excluded (%) (total 6%)	Screened (*N*) (total 483)	Excluded (%) (total 12%)	Screened (*N*) (total 448)	Excluded (%) (total 5%)
Adolescents (13–17 yr)								
≤5 yr	79	15	81	5	71	0	69	9
>5 yr	75	0	73	3	67	22	64	5
Adults (18–39 yr)								
≤5 yr	160	18	143	11	111	1	106	8
>5 yr	296	11	264	4	234	21	209	3

*Basal C-peptide >0.2 pmol/ml. Sustacal-stimulated C-peptide >0.5 pmol/ml for patients with ≤5 yr duration of IDDM; stimulated C-peptide >0.2 pmol/ml for patients with >5 yr duration of IDDM.
†HbA_{1c} ≤6.55 (mean ± 3 SD from the DCCT sampling of non-IDDM individuals).
‡Based on the eligibility grading, not on the detailed color grading.
§>200 mg albumin/24 h on 4-h urine collection for secondary intervention patients; >40 mg for primary prevention patients.

laboratory-determined or fingerstick blood glucose <50 mg/dl, or 2) amelioration by treatment that raises blood glucose, or 3) prodromal symptoms of hypoglycemia (e.g., sweating, palpitations, hunger, or blurred vision) remembered by the subject as occurring shortly before the event. A severe hypoglycemic reaction was defined as coma or seizure or a reaction requiring hospitalization or intravenous glucose or glucagon.

Infusion catheter infection. Any infection at the site of the infusion catheter that required antibiotic treatment or surgical incision and drainage.

Statistical Methods

All statistical analyses were conducted with the Statistical Analysis System (SAS) with the total cohort. Regardless of subjects' compliance, they were counted in the treatment group to which they were originally assigned. Assessment of efficacy was based on a least-squares analysis of variance to compare the means between the randomized groups. Covariant analysis was used to adjust values at follow-up for differences between groups in values at baseline. Linear regression was employed to compare mean HbA_{1c} and respective mean capillary blood glucose results. The incidence of hypoglycemia, ketoacidosis, and catheter infection was calculated as events/100 patient-yr. The κ-statistic was used to test the departure from chance agreement in the analysis of the reproducibility of the gradings of the fundus photographs (23). Coefficients of reliability were used to estimate the proportion of total variability between subject values that was not due to measurement error (24). The method of Woolf (25) was used to estimate the common-odds ratio for stratified two-by-two tables. Analyses comparing subjects in the primary prevention with secondary intervention subjects were based on postrandomization stratification.

RESULTS

Recruitment

A total of 1037 candidates completed an initial visit to 1 of the 21 clinics. Of these, 656 (63%) signed the first informed consent agreeing to proceed with prerandomization eligibility testing. This group of volunteers yielded the 278 subjects finally admitted to the trial. The median number of patients recruited per individual center was 13 (range 11–17). The 278 subjects exceeded the target number of 252. The additional 26 patients had successfully completed almost all eligibility tests when the target was reached. Thus they were permitted to volunteer if they fulfilled the remaining eligibility criteria. Six months were required to recruit the target number of subjects.

Table 1 summarizes the number of volunteers screened and the percent excluded by each of the major eligibility criteria. A higher proportion of candidates was excluded by their own or the investigator's decision that they were unsuited for the study than by any other single criterion (104 of 656 subjects = 16%). The randomization process assigned 146

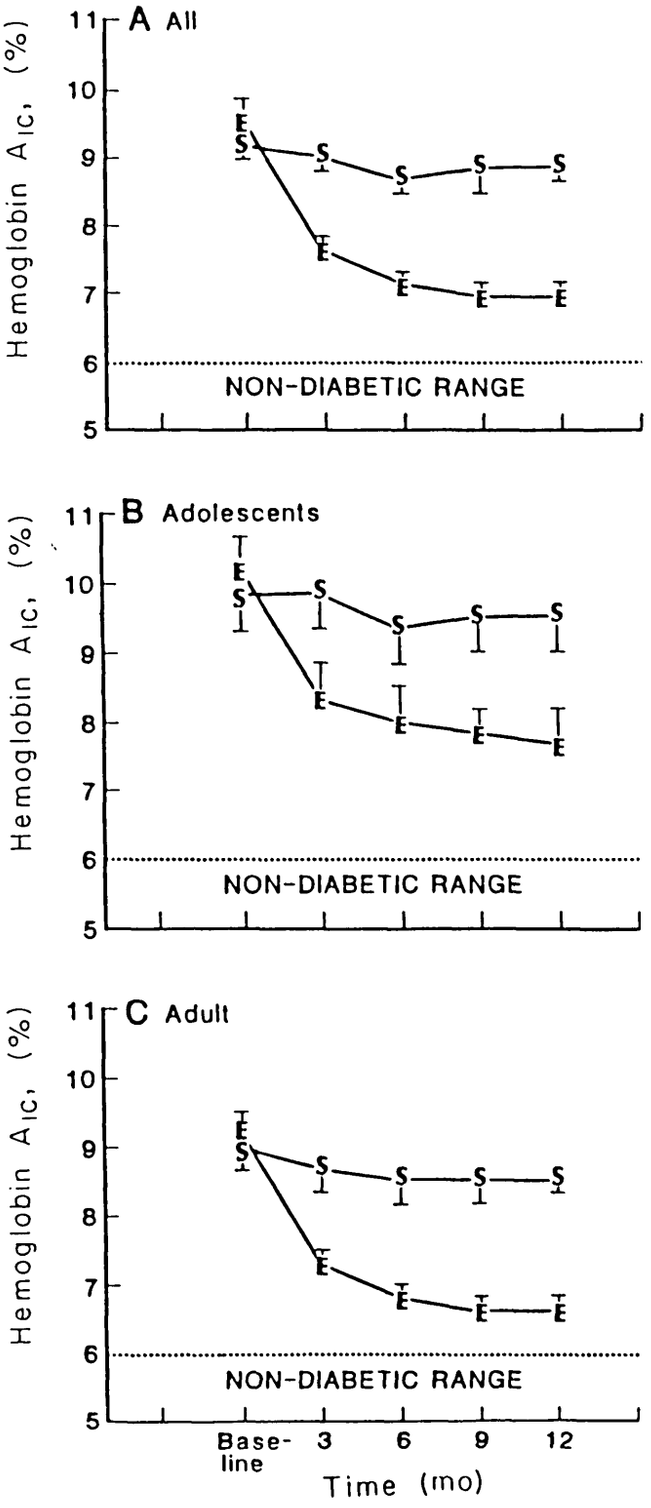

FIG. 1. Mean HbA_{1c} (± 2 SE) for feasibility study. Standard-group subjects (S) compared with experimental-group subjects (E) for all subjects (A), adolescents (B), and adults (C). Differences between treatment groups significant ($P < .0001$) for all time points after baseline.

TABLE 2
Selected baseline characteristics of randomized patients

	Adolescents		Adults	
	Experimental (*N* = 45)	Standard (*N* = 42)	Experimental (*N* = 101)	Standard (*N* = 90)
Demographic characteristics				
Men (%)	47	41	50	51
Age (yr)				
Mean	15	15	28	28
SD	1.3	1.3	5.8	5.8
IDDM characteristics				
Duration of IDDM (mo)				
Mean	66	64	87	89
SD	41	41	51	55
Stimulated C-peptide (pmol/ml)				
Mean	0.08	0.08	0.08	0.08
SD	0.11	0.12	0.11	0.09
Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)				
Mean	0.95	0.94	0.62	0.65
SD	0.31	0.32	0.19	0.20
Subjects performing self-monitoring of glucose (%)				
Urine	56	52	48	54
Blood	67	83	67	59
Patients hospitalized in past year for DKA (*N*)	5	2	5	4
Medical characteristics				
Systolic sitting blood pressure (mmHg)				
Mean	112	109	114	119*
SD	11	10	11	11
Diastolic sitting blood pressure (mmHg)				
Mean	71	71	73	73
SD	10	11	10	12
Ideal body wt (%)				
Mean	100.4	96.0	106.2	108.1
SD	12.7	13.4	12.2	12.7
Current smokers (%)	2	0	26	26
Glycemic control				
HbA_{1c}				
Mean	10.14	9.83	9.24	8.98
SD	1.88	1.79	1.43	1.36
Plasma glucose (mg/dl)§				
Mean	279	263	237	228
SD	113	115	80	81
Ocular characteristics				
Best corrected visual acuity (20/20 Snellen Equivalent = 85)				
Mean	88.3	88.6	89.3	89.4
SD	5.1	4.3	4.0	4.0
No retinopathy (%)	47	57	29	32
Microaneurysms only (%)	47	26	44	37
Mild nonproliferative retinopathy (%)	4	12	13	12
Moderate nonproliferative retinopathy (%)	2	5	15	19
Lipids				
Cholesterol (mg/dl)				
Mean	170	165	175	180
SD	31	29	37	32
Triglyceride (mg/dl)				
Mean	114	82†	81	86
SD	88	31	40	41
HDL cholesterol (mg/dl)				
Mean	43	49‡	50	47
SD	9	11	11	12

TABLE 2 (*Continued*)

	Adolescents		Adults	
	Experimental (N = 45)	Standard (N = 42)	Experimental (N = 101)	Standard (N = 90)
Lipids (*Continued*)				
LDL cholesterol (mg/dl)				
Mean	105	100	109	116
SD	30	25	31	28
Renal function				
Albumin excretion (mg/24 h)‖				
Primary patients				
Mean	21.5	16.6	11.0	15.4
SD	27.9	9.5	7.9	8.6
Secondary patients				
Mean	25.4	28.7	26.5	26.1
SD	22.6	37.0	33.0	37.3
Standard creatinine clearance (ml · min^{-1} · 1.73 m^{-2})				
Mean	144	136	126	129
SD	49	28	24	39
Serum creatinine (mg/dl)				
Mean	0.70	0.67	0.80	0.81
SD	0.16	0.11	0.15	0.15

DKA, diabetic ketoacidosis.
*Two-sample t test (two-tailed) P = .003.
†Two-sample t test (two-tailed) P = .03.
‡Two-sample t test (two-tailed) P = .006.
§Mean of 7 capillary home blood glucose profiles.
‖ Calculated from 4-h collection.

subjects (101 adults and 45 adolescents) to the experimental-treatment group and 132 subjects (90 adults and 42 adolescents) to the standard-treatment group. After randomization, 14 subjects (6 experimental and 8 standard) were found to have reasons for exclusion that had gone undetected before treatment assignment. The major cause of improper randomization was a discrepancy between the initial evaluation of fundus photographs for eligibility purposes and the consensus grading of the same photographs later to assign baseline status. Thus, 11 subjects with duration of diabetes >5 yr (mean duration 8.3 ± 2.74 yr) but no detectable retinopathy were inappropriately included. These subjects continued in their assigned treatment groups and were reclassified as primary prevention subjects.

Table 2 compares selected baseline data in the two treatment groups. A total of 54 baseline characteristics were used to compare standard and experimental groups for both adults and adolescents (108 separate tests). There were no significant differences in demographic characteristics, in IDDM characteristics including endogenous β-cell function, or in indices of retinal or renal microvascular disease. Only 3 factors were significantly different at $P < .05$. In adolescents, mean triglyceride was higher (P = .03) and HDL cholesterol lower (P = .006) in the experimental group. In adults, systolic blood pressure was higher in the standard group (119 vs. 114 mmHg, P = .003).

Efficacy of Treatment

HbA_{1c} concentrations. The HbA_{1c} concentrations at baseline are shown in Fig. 1 and Table 2. There were no significant differences in HbA_{1c} between the experimental- and standard-treatment groups as a whole, between experimental- and standard-group adults, or between experimental- and standard-group adolescents. However, within each treatment group, baseline HbA_{1c} was significantly higher in the adolescent subjects than in the adults (Table 2, experimental P = .0001, standard P = .0004).

The HbA_{1c} levels in the 1st yr of treatment are shown in Fig. 1. In the experimental group, as well as in its adult and adolescent subgroups, HbA_{1c} decreased significantly from baseline by 3 mo and either reached a nadir or was still falling slightly by 12 mo. Although only 17% of all experimental-group subjects achieved a HbA_{1c} in the nondiabetic range, >95% of them achieved a HbA_{1c} at 1 yr that was less than the mean HbA_{1c} at baseline. In the standard group, a small but significant early decrease in HbA_{1c} also occurred, which then plateaued at 6 mo. At all time points, HbA_{1c} was significantly lower in the experimental than in the standard groups in all subjects and in both age strata. At 12 mo, the absolute difference in mean HbA_{1c} between experimental and standard subjects was 1.87 for all subjects, 1.86 for the adults, and 1.87 for the adolescents (Table 3).

The randomization process yielded similar HbA_{1c} values

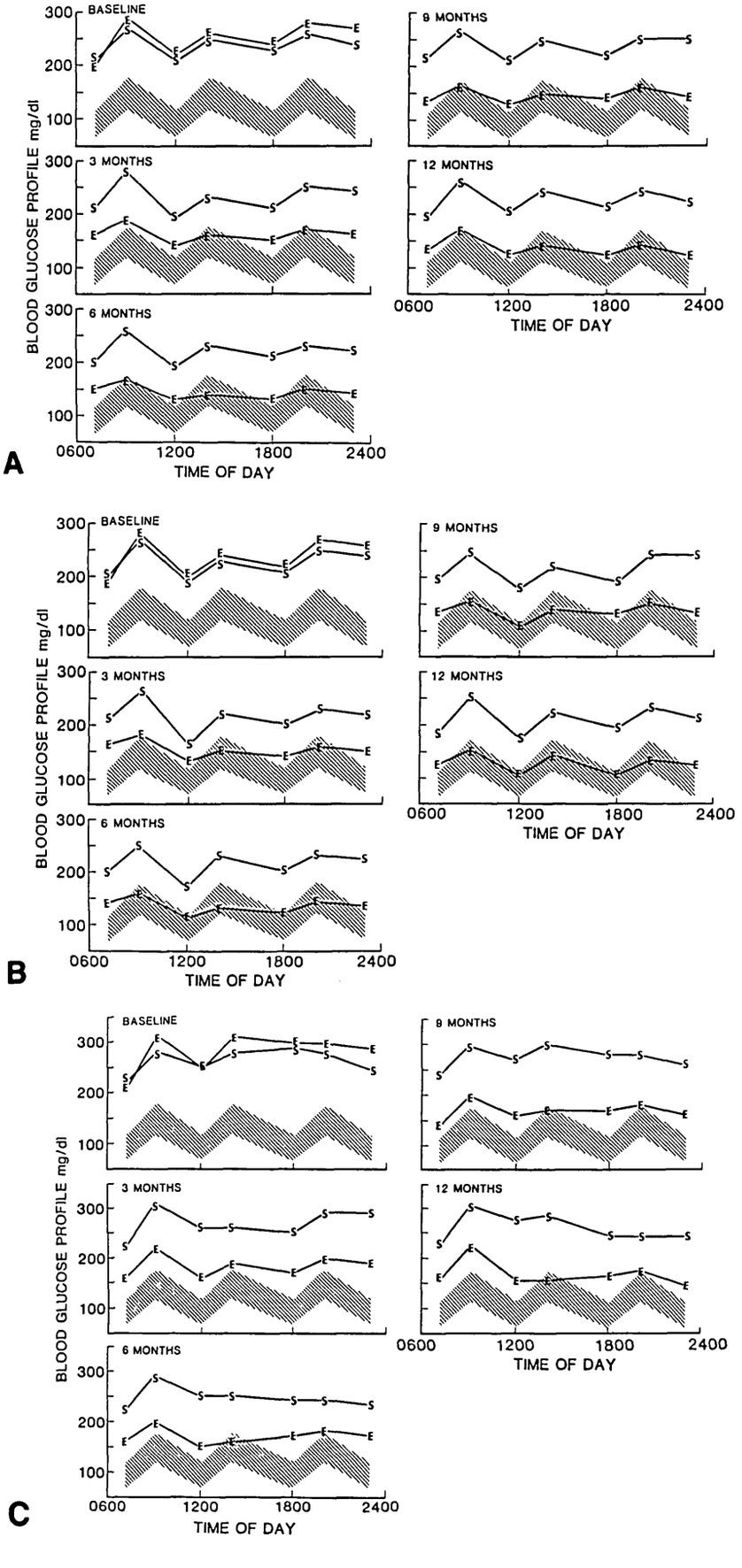

FIG. 2. Mean blood glucose profiles performed with Profilset (see METHODS) for standard- and experimental-group subjects. Differences between standard- and experimental-group results significant ($P < .0001$) at 3, 6, 9, and 12 mo. *Shaded area* represents target range for experimental-group subjects. A, all subjects; B, adults; C, adolescents.

TABLE 3
Mean glycemic control at 12 mo after entry

	All subjects		Adolescents (13–17 yr)		Adults (18–39 yr)	
	Standard (N = 132)	Experimental† (N = 146)	Standard (N = 42)	Experimental† (N = 45)	Standard (N = 90)	Experimental† (N = 101)
HbA_{1c} (%) (SEM)	8.88 (.14)	7.03 (.09)	9.60 (.24)	7.73 (.20)	8.56 (.15)	6.70 (.08)
Capillary glucose (mg/dl) (SEM)*	232 (7.2)	142 (3.9)	261 (13)	162 (9)	219 (5)	133 (4)

*Mean of self-monitored, 7-sample capillary blood glucose profile.
†P value for 2-sample (standard vs. experimental) 2-tailed t test = .00001.

at baseline in the experimental and standard groups at each center. A decrease in mean experimental HbA_{1c} from baseline to 12 mo (range 1.8–4.4) was achieved at every center. In contrast, among the standard groups there were only 2 centers in which the mean HbA_{1c} decreased by >1.0 at 12 mo. Conversely, the mean HbA_{1c} in the standard group rose in 7 centers, but the largest increase was only 0.46. A difference in mean HbA_{1c} between experimental and standard groups was achieved at each center, with a range of 0.8–3.2. Despite the small sample sizes, this difference was statistically significant ($P < .05$) at 15 of the 21 centers.

Blood glucose profiles. The capillary blood glucose profiles are shown in Fig. 2, A–C. At baseline, the blood glucose profiles for the experimental and standard groups were not significantly different (Fig. 2A). Blood glucose in the experimental-group adult subjects decreased rapidly and was essentially within the target range by 6 mo (Fig. 2B). Although blood glucose of the experimental-group adolescents also decreased, it did not reach the target range (Fig. 2C). These observations agree with the respective HbA_{1c} responses observed in the adult and adolescent experimental subgroups. In standard-group subjects, the capillary blood glucose profiles remained essentially unchanged from baseline to 12 mo. The means of the blood glucose profile for the total experimental and total standard groups were significantly different at all time points after baseline. This was also true for the adult and adolescent subgroups. At 12 mo the mean blood glucose values (mean of 7-point profile) were significantly different between experimental- and standard-group subjects for the study as a whole and for the adult and adolescent subjects ($P < .0001$ for all comparisons, Table 3).

The HbA_{1c} and blood glucose profiles were further analyzed to see how well these two measurements actually correlated. To minimize the time dyssynchrony between blood glucose levels and their effects on HbA_{1c}, the mean of all quarterly blood glucose profiles obtained over the 12 mo was plotted against the means of all quarterly HbA_{1c} values for each individual patient, regardless of treatment group (Fig. 3). A strong positive correlation was observed with a correlation coefficient of 0.80.

Clinical Well-Being and Safety

Clinical indices. The frequency of nocturia decreased from baseline in both standard- and experimental-group subjects. Nocturia occurred once per evening 1.4 times/wk in both standard and experimental groups at baseline and decreased to 1.0/wk in standard and 0.5/wk in experimental during the 1st yr. The occurrence of urinary frequency and ketonuria during the 1st yr was significantly greater in the standard than the experimental group (Table 4). HbA_{1c} exceeded the upper action limit (13.11%) in six standard-group subjects, and in four of these, this occurred just once. Self-treated hypoglycemia was more common in the experimental group.

In the experimental-treatment group, adults and adolescents of both sexes gained significant amounts of weight. The greatest weight gain was in adolescent men (6.8 ± 1.1 kg) and the least in adult women (3.9 ± 0.6 kg). In terms of ideal body weight, the increases ranged from 6.4 to 9.5% of ideal body weight. However, after 1 yr the mean ideal body weight exceeded 110% only in adult men. In the standard group, a significant weight gain was observed in the same subgroups, but in each instance, the gain was significantly less than that of corresponding experimental-group subjects. Height increased significantly in men and women adolescents without a significant difference between standard and experimental groups.

Psychologic state of well-being assessed with the SCL-90 questionnaire was not significantly different between treatment groups at baseline or 12 mo (results not shown). The QOL questionnaire results that measured the subjects' perception of their quality of life, particularly regarding diabetes therapy, revealed a small but significant improvement at 12 mo in the adult subgroups of each treatment regimen (data not shown). No significant differences were noted between the experimental and standard groups in either adults or adolescents. Thus, participation in the DCCT did not appear to have a negative impact on the subjects' perceived state of well-being and actually appeared to have a positive impact in the adult subjects.

Safety of Treatment

Death, ketoacidosis, and catheter infections. There were no deaths in either treatment group and no significant difference in the incidence of ketoacidosis between standard- and experimental-treatment groups. The incidence of ketoacidosis in the standard group was similar to that reported on the baseline history by the same patients in the year before entry into the DCCT (3.0 vs. 4.5 events/100 patient-yr, respectively,

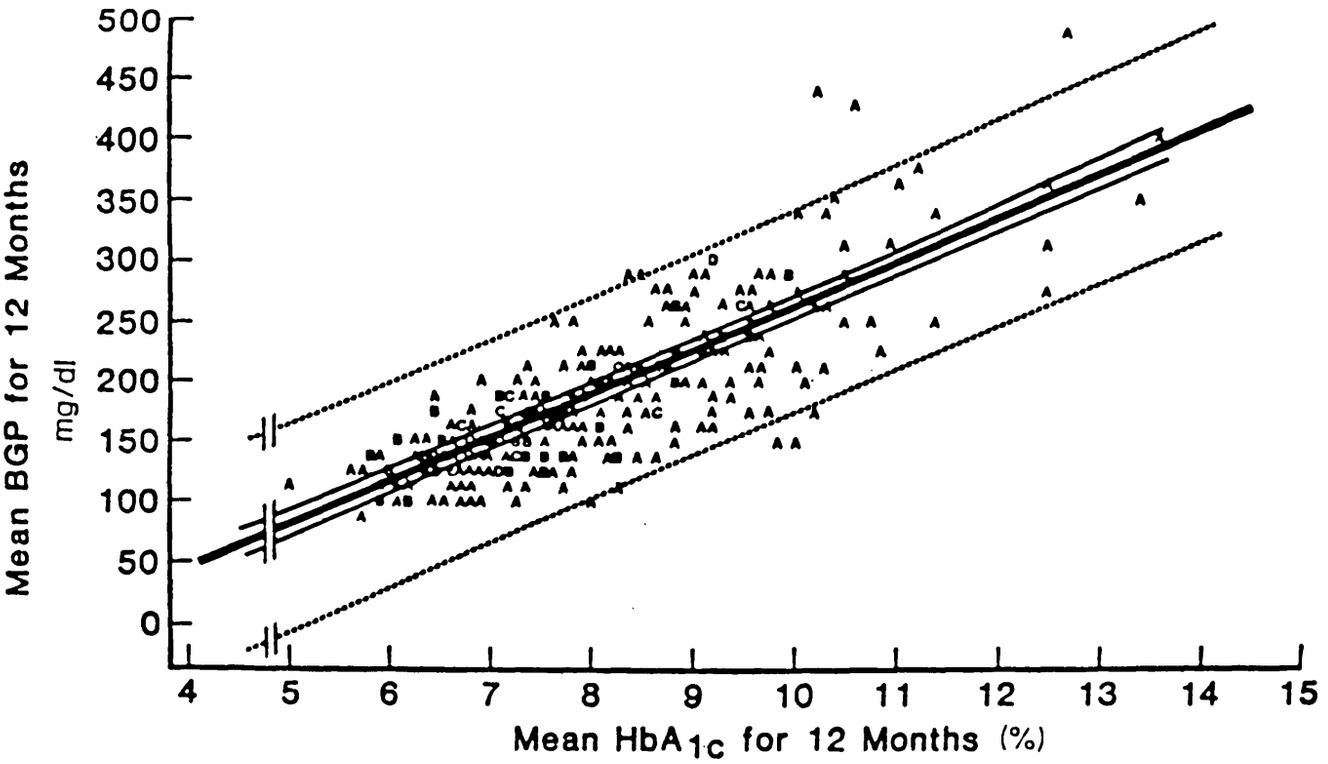

FIG. 3. Comparison of mean of all quarterly blood glucose profiles (BGP) with mean of all quarterly HbA_{1c} results. *Dark lines* represent mean regression line ± 2 SD. *Dotted line* represents 95% confidence interval for individual values. A = 1 point, B = 2 points, and C = 3 or more points. $r = .80$, $P < .0001$.

P=NS). In the experimental group, the incidence of ketoacidosis was lower, albeit not significantly, than that reported by the same individuals for the year before entry (2.7 vs. 6.8 events/100 patient-yr, P=NS). All episodes of ketoacidosis in the experimental group occurred in subjects who used insulin infusion pumps. Catheter infections occurred in 9.9% of experimental subjects, all of whom were on pumps. Adolescents experienced most of the episodes of ketoacidosis (3 adolescents vs. 1 adult) and catheter infections (4 adolescents vs. 2 adults). The incidence of diabetic ketoacidosis did not differ between experimental and standard groups (2.7 vs. 3.0 events/100 patient-yr, respectively, P = NS).

Hypoglycemia. The occurrence of severe hypoglycemia (see METHODS) and specifically of hypoglycemic coma are presented in Table 5. The number of subjects experiencing severe hypoglycemia or coma, as well as the respective event rates, was ~3 times higher in the experimental group than in the standard group. More experimental-group than stan-

TABLE 4
Indexes of clinical well-being over 12 mo

	Standard group	Experimental group	P value (standard vs. experimental)
Urinary frequency			
Nocturia once/night (mean days/wk)	1.0 (0.10)	0.5 (0.08)	.0008
Nocturia > once/night (mean days/wk)	0.1 (0.02)	0.1 (0.05)	NS
Fluid intake (mean glasses/day)	7.7 (0.24)	7.4 (0.27)	NS
Ketonuria (mean days/quarter)	1.6 (0.26)	0.3 (0.06)	.0001
Self-treated hypoglycemia			
(mean events/wk)	0.95* (0.07)	2.02* (1.41)	.0001
HbA_{1c} above action limit at least once (% of subjects)	4.55 (1.81)	0 (0)	.0001

Values shown are mean (SE) or % (SE).
*Consecutive means at 3, 6, 9, and 12 mo were 1.0, 0.9, 0.9, and 0.9 for standard patients and 1.5, 2.3, 2.1, and 2.3 for experimental subjects, respectively.

TABLE 5
Severe hypoglycemia and coma

	Subjects		Events	
	N	%	*N*	Per 100 subject-yr
Total severe reactions*				
Experimental	38	26.0†	79	54.1
Standard	13	9.8	23	17.4
Coma				
Experimental	29	19.9‡	49	33.6
Standard	8	6.1	16	12.1
Single episode of coma				
Experimental	17	11.6§	17	11.6*
Standard	5	3.8	5	3.8
Multiple episodes of coma				
Experimental	12	8.2‖	32	21.9
Standard	3	2.3	11	2.3

Total experimental subjects = 146; total standard subjects = 132.
*See METHODS section.
†P = .0009, ‡P = .0013, §P = .028, ‖P = .05 (standard vs. experimental x^2).

dard-group subjects experienced multiple episodes of coma (12 vs. 3). Two-thirds of all the episodes of coma in the experimental group occurred in the 12 subjects with multiple episodes. No subjects suffered permanent sequelae or injury from hypoglycemia.

Several baseline characteristics were examined in the group of subjects that experienced hypoglycemic coma versus the group that did not, regardless of subsequent DCCT treatment assignment. There were no differences in mean age, gender, percentage of adolescents, or mean baseline HbA_{1c} or fasting glucose levels. However, the duration of diabetes (101 ± 8 vs. 80 ± 3 mo, $P < .02$) and the occurrence of hypoglycemic coma in the year before entry (19 vs. 5%, $P < .005$) were significantly greater in the group experiencing coma during phase II of the DCCT.

Table 6 presents a more detailed examination of the relationship, within each treatment group, between the occurrence of prior hypoglycemic coma and the occurrence of hypoglycemia during the feasibility study. Ten percent of patients assigned to experimental treatment and 5 percent assigned to standard treatment had a history of coma before entry in the study (P = NS). Among those assigned to experimental treatment, 6 of the 13 (46%) patients who had a prior history of coma also had recurrent coma (13 total episodes), compared with 23 (17%) of the 133 patients with no prior history of coma (P = .02). Among those assigned to standard treatment, 1 of the 7 (14%) patients who had a prior history of coma also had recurrent coma compared to 7 of the 132 (5%) patients with no prior history of coma (P = .36). From the two two-by-two tables in Table 6, the combined odds ratio for prior coma versus no prior coma is 3.96, $P < 0.05$ (95% confidence interval 1.46–10.56), suggesting that the occurrence of hypoglycemic coma before the study was a risk factor for this event in the study. In the experimental group, associations between the susceptibility to hypoglycemic coma and the HbA_{1c} level or hypoglycemic coma and the insulin dose (U/kg) could not be established. There was no significant difference in the occurrence of hypoglycemia between CSII- and MDI-treated groups.

Acceptability of Assigned Regimens

Follow-up and adherence. None of the subjects refused treatment assignment, and all initiated the prescribed regimen. Ninety-seven percent of the 1112 scheduled visits were accomplished as scheduled, and only 0.4% were never held. This high level of follow-up was uniform in both treatment groups and across all 21 centers. The 12-mo HbA_{1c} value was obtained in 100% of the subjects and the final blood glucose profile in 99%. Ninety-nine percent of all fundus photographs and at least 96% of all end-point examinations (12 mo) were obtained. The subjects' adherence to self-monitoring schedules was high throughout the year; the results of 81% of requested urine tests and 91% of requested blood tests were reported. Three standard-group subjects who became pregnant were promptly changed to intensive regimens, as per protocol, and returned to standard treatment postpartum. Only two unmandated deviations from assigned treatment occurred. One standard subject changed to a multiple-dose insulin regimen, and one experimental subject changed to twice-daily mixed insulins.

Before signing the informed consent form, all volunteers' knowledge of the key elements of the trial was tested by questionnaire. The same test was administered again at 12 mo to evaluate retention (26). The initial average test score was 97%, and the 1-yr score was 91%. The data were similar when analyzed separately for adults and adolescents.

Precision and Accuracy of Measurements

Table 7 summarizes the external quality-control assessments of the CHL and the CBL. With one exception, the coefficient of variation and the coefficient of reliability for all listed

TABLE 6
Relationship between hypoglycemic coma during DCCT and prior history of hypoglycemic coma

		Previous year		Odds ratio*	*P* value†
		Coma	No coma		
Experimental group					
DCCT	Coma	6	23	4.1	.02
Experience	No coma	7	110		
	Total	13	133		
Standard group					
DCCT	Coma	1	7	3.7	.36
Experience	No coma	6	118		
	Total	7	125		

*Odds ratios were calculated with Woolf's method (ref. 25).
†*P* values were from Fisher's exact test.

TABLE 7
External quality assessment of DCCT central laboratories

Measurement	Period	*N*	Mean within-specimen C.V.	Coefficient of reliability
Hemoglobin A_{1c}	1	23	1.2	0.987
	2	115	2.2	0.981
	3	110	1.7	0.989
	4	126	2.1	0.981
Capillary blood glucose	1	0		
	2	34	8.8	0.954
	3	11	6.7	0.978
	4	46	9.4	0.955
Serum cholesterol	5	16	1.7	0.984
	6	22	2.3	0.976
Serum triglyceride	5	16	2.8	0.994
	6	22	3.9	0.995
Serum HDL cholesterol	5	16	4.6	0.959
	6	22	3.1	0.975
Serum LDL cholesterol	5	16	2.5	0.982
	6	22	3.4	0.967
Serum albumin	5	57	4.4	0.645
	6	23	3.1	0.850
Serum creatinine	5	57	6.6	0.855
	6	23	5.1	0.800
Urine albumin	5	57	16.4	0.760
	6	23	19.2	0.837
Albumin excretion	5	57	21.2	0.629
	6	23	14.6	0.917
Urine creatinine	5	57	4.3	0.995
	6	23	5.1	0.882
Creatinine clearance	5	57	8.4	0.851
	6	23	7.4	0.692

C.V., coefficient of variation.
The mean within-specimen C.V. is the average of the C.V.s for *N* split-duplicate specimen.
The coefficient of reliability is an estimate of the proportion of the total variability between patient values that is due to differences between actual patient values (and thus not due to measurement error).
Periods: 1 = 04/15/83 to 10/14/83; 2 = 10/15/83 to 04/14/84; 3 = 04/15/84 to 10/14/84; 4 = 10/15/84 to 05/24/85; 5 = 04/15/83 to 04/14/84; 6 = 04/15/84 to 05/24/85.

determinations were satisfactory. Measurement of albumin excretion at baseline yielded a coefficient of variation of 21% and a coefficient of reliability of .63. However, reevaluation and subsequent improvement of the albumin measurement led to improvement in the 12-mo samples to a coefficient of variation of 15% and a coefficient of reliability of .92.

Fundus photographs. The distribution of grades for quality of fundus photographs for phase II improved over the 1st yr of the study. At baseline, 1.3% of the photographs were judged to be excellent, 28.1% good, 35.3% fair, 35.4% acceptable, and 0% inadequate compared with 6.0, 38.6, 34.3, 21.1, and 0%, respectively, at 1 yr.

The reliability of the grading system was assessed by comparing classifications of the right and left eye and the overall retinopathy classification for each subject. In addition, the reproducibility of finding no retinopathy was evaluated as an important long-term outcome (Table 8). In classifying individual eyes, with only a four-level scale, perfect agreement was obtained at least 68% of the time, and agreement within one step virtually all the time. In classifying whole patients (two eyes), where a nine-level scale was used, perfect agreement was obtained only 55% of the time. If agreement within two steps on the scale was used as a criterion, reproducibility was 98%.

DISCUSSION

Recruitment and randomization. One of the major goals of the feasibility phase was to determine whether a suitable population of IDDM subjects, conforming to stringent eligibility criteria, could be recruited into a randomized trial. The selection process was intended to define a group of patients in whom differences in the effects of experimental and standard therapy on the rates of complications might be determined if such differences do in fact exist. Subjects with coexistent conditions that might confound the putative relationship between treatments and outcome were systematically excluded. In addition, the DCCT was designed to exclude patients who might be placed at increased risk. Finally, the selection of a group of volunteers who would likely comply with the demands of a long-term clinical trial was emphasized.

Phase II was effective in recruiting such a population, as judged by the adherence and results achieved. A few inappropriate subjects were included because of discrepancy between the grading of fundus photographs for the purposes of eligibility testing and for establishing baseline characteristics. This will be prevented in phase III by simultaneous assessments of eligibility and baseline characteristics. Only 3 of 108 comparisons of baseline characteristics were significantly different, a frequency that would be expected by chance alone. It is conceivable that when more subjects enter the study, the minor differences will disappear. Overall, the randomization procedure was effective in providing two comparable groups at baseline.

Efficacy of the treatment regimens. The ability to produce meaningful differences in metabolic control between the standard- and experimental-treatment groups was a central

TABLE 8
Analyses of repeat gradings of baseline fundus photographs

	Eye		
	Left (*N* = 60)	Right (*N* = 60)	Patient (*N* = 60)
Perfect agreement (%)	80	68	55
Agreement ±1 step (%)	100	97	92
Agreement ±2 steps (%)	100	100	98
Agreement on presence/absence of retinopathy (%)	90*	87*	85*

*P value ≤ .05 for test of agreement; significant from chance by κ.
κ (SE): left eye = .78 (.13), right eye = .72 (.13), patient = .66 (.13).

issue of the DCCT feasibility phase. Our data indicate that the two treatment regimens did result in substantial differences in metabolic control. At 12 mo, mean capillary blood glucose was 88 mg/dl (38%) lower in experimental- than standard-group subjects. Furthermore, these differences had been maintained steadily from 6 mo onward, an extremely important consideration for a long-term trial. Although the adolescent patients exhibited higher blood glucose and HbA_{1c} values than did the adult patients at all time points, the differences produced by the treatment regimens were similar in the two age strata. This suggests that adolescent subjects can be expected to contribute meaningfully to a long-term trial.

Given the multicenter nature of the DCCT, some variability in efficacy from clinic to clinic was to be expected, particularly because individual treatment groups were small (5–9 subjects). Therefore, the substantial fall in the mean HbA_{1c} levels of the experimental groups that occurred in all 21 clinics was gratifying. Furthermore, in 15 clinics, the difference between the means of the experimental and standard groups was statistically significant despite the small sample sizes in each clinic.

Unlike most other previous studies, experimental-group subjects in the DCCT could choose either CSII or MDI. The study was not designed to compare the efficacy of these two treatment modalities, and several subjects changed from one to the other during the course of the study. Therefore, no rigorous comparison can be made between the efficacy of these two methods of insulin delivery. However, there were two observations of interest. Fifty-one percent of the experimental-group subjects, started on CSII at baseline, and by 12 mo this figure had dropped to 37%. At that time, there were no substantial differences in mean HbA_{1c} or capillary blood glucose levels between the subjects on CSII and those on MDI.

In evaluating effficacy, the DCCT results may also be compared with previous randomized clinical trials (12–14) and cohort studies (27–29) employing intensive treatment similar to that of the experimental-group regimen. Because various methods for measuring glycosylated hemoglobin were used in these studies, such comparisons are facilitated by normalizing both the DCCT data and the literature data to the nondiabetic reference ranges for the respective laboratories. This method was chosen rather than the Z-transformation because means and standard deviations were not available for all studies. In the DCCT experimental group, the adult subjects' baseline HbA_{1c} was 1.83 times that of the mean value for nondiabetic individuals (9.24 ÷ 5.05). At 12 mo this normalized value had decreased to 1.33 times the nondiabetic value (6.70 ÷ 5.05). In the standard group, by contrast, the normalized HbA_{1c} of the adult subjects changed very little, 1.70 at 12 mo vs. 1.78 at baseline. The difference between the DCCT experimental-group and standard-group adults at 12 mo was 1.70 − 1.33 or 0.37 in normalized terms. As shown by a similar analysis, the difference between the normalized glycosylated hemoglobin levels of intensively treated and conventionally treated subjects in three previous randomized clinical trials ranged from 0.25 to 0.37 (12–14). In four previous nonrandomized cohort studies, differences in normalized glycosylated hemoglobin levels ranged from 0.23 to 0.77 (27–29). Thus, when expressed in comparable terms, the DCCT experience in creating two groups of IDDM subjects with substantially different levels of glycosylated hemoglobin has mirrored that of most other reports. Also note that the differences in HbA_{1c} levels achieved in the DCCT resulted only from a decrease in the intensively treated experimental group and not from an increase in the conventionally treated standard group.

Another important indicator of efficacy of the two treatment regimens was the degree of subject adherence to the trial. The absence of dropouts and the occurrence of only two unmandated crossovers attest to the acceptability of the two regimens, as well as to the quality of the recruitment process. This is further supported by the steadfastness with which subjects adhered to their visit schedules and the completeness of data collection. Thus, by all key indicators—acceptance of assigned treatment, faithful attendance, availability for outcome measurements, and maintenance of treatment regimens—adherence to the trial was considered excellent.

Safety of the treatment regimens. The low level of glycosuric symptoms and the paucity of ketonuria assures achievement of the principal goals of clinical well-being. Assessments of psychological status and of quality of life indicated no deterioration but modest improvement in both treatment groups. The gain in height of the adolescents appears reasonable, given the broad normal range of pubertal status and of growth rates in a group of subjects age 13–17 yr. Growth rates did not differ significantly in standard- and experimental-group subjects. The modest weight gain of standard-group subjects may be attributed to improved metabolic control accompanying the small decline in HbA_{1c}. The weight gain of experimental-group subjects was considerably greater. This has been noted previously with intensive insulin regimens (30) and may reflect a general difficulty, despite intensive dietary education, in controlling caloric intake as well as specific overeating in response to hypoglycemia.

The incidence of ketoacidosis in both treatment groups was below most published results (31,32). The CSII-treated subjects also had substantially lower rates of ketoacidosis and catheter infections than previously reported (33,34). Nonetheless, continued attempts to lower these event rates further, especially in adolescents, are necessary.

The other major risk of treating IDDM with insulin is hypoglycemia. Because the potential benefits of the two treatment regimens will ultimately be weighed against the risks of treatment, stringent ascertainment procedures were established before starting the study to ensure complete reporting of hypoglycemic events in both treatment groups. The frequency of severe hypoglycemic episodes in DCCT patients thus ascertained tended to be greater than previously reported for either standard or experimental treatment. In literature reports, the occurrence of severe hypoglycemia (variously defined) in intensively treated patients ranged from 5 to

30%, with event rates of 9.8–43.3 episodes/100 patient-yr (12,13,29,35–40). This compares with DCCT figures of 26% and 54 events/100 patient-yr. Similarly, an event rate of 17.4/100 patient-yr in standard-group patients is higher than that usually reported with conventional treatment (3.6–20/100 patient-yr) (12,13,29,33,41–43). The ascertainment procedures and the large sample sizes of the DCCT have provided the means to define more accurately the relative risks of hypoglycemia of the two treatment regimens, as well as to explore factors that might contribute to this risk.

At the inception of phase II, we correctly anticipated that hypoglycemia would be the primary adverse effect of the experimental regimen. In the standard group, the rate of occurrence of hypoglycemic coma was not significantly different than that reported by the same patients in the year before entry (6.1 vs. 5.3%). In contrast, experimental patients experienced more than twice the increase in incidence of severe hypoglycemia and coma (19.9 vs. 8.7%). The clustering of two-thirds of the total episodes of coma in 12 of 146 subjects suggests that a small subset of subjects may be at increased risk of hypoglycemia with intensive therapy.

Although no single patient characteristic reliably predicted the occurrence of an initial hypoglycemic event, a history of repeated hypoglycemic coma in the year before entry strongly predicted coma in the DCCT if experimental treatment was assigned. This observation is consistent with previous reports that a subset of IDDM patients with defective glucose counterregulation on standard treatment may be at greater risk for the development of severe hypoglycemia during intensified therapy (44). Exclusion of patients at greatest risk for severe hypoglycemia on the basis of a recent history of recurrent episodes should produce a reduction in the incidence of this complication without significantly diminishing the pool of volunteers for the study because this group only accounted for 4.5% of the total study population.

Experimental treatment increased the risk of hypoglycemic coma even in patients with no history of coma before entry in the DCCT. This may be due either to the stringent treatment goals or to an adverse effect of intensive treatment, per se, on counterregulatory hormone responses to hypoglycemia (45) or to other factors. Regardless of the mechanism, the greater incidence of severe hypoglycemia in the experimental group than in the standard group mandates continued efforts to identify prospectively vulnerable patients as well as to modify treatment goals for individuals in whom hypoglycemia occurs. It also reinforces the need to determine whether the potential benefits of intensive treatment (i.e., delaying or preventing early vascular complications) will outweigh the increased risk of hypoglycemia with which it is associated.

Relationship of metabolic control to microvascular disease. Although the standard and experimental regimens yielded statistically significant as well as substantial differences in the level of metabolic control, the critical question is whether such differences can be expected to affect the rate of development or progression of early microvascular disease in the long term. Currently there is insufficient data to assess any putative quantitative relationship between mean blood glucose levels and the risk of microvascular disease in humans. However, assuming such a relationship exists, there clearly is a high risk for the development of retinopathy at the prevailing mean blood glucose and HbA_{1c} levels of IDDM patients who are treated conventionally. If one hypothesizes that there is little risk of diabetic retinopathy when blood glucose and HbA_{1c} are within the normal range, then the risk must appear in IDDM patients somewhere above the upper limit of normal. Conversely, the risk may be significantly reduced somewhere below the usual level observed in conventionally treated IDDM patients. Without an understanding of these presumptive levels, we cannot assess the efficacy of the DCCT feasibility phase against absolute standards.

However, placing the 12-mo results in the perspective of three hypothetical models is interesting (Fig. 4). In the simplest case, a linear relationship is assumed to exist between mean blood glucose and the risk of retinopathy (Fig. 4, *line* A). For conventionally treated patients, e.g., the DCCT standard group, the mean blood glucose is 234 mg/dl. Epidemiologic studies suggest that the associated risk of developing retinopathy after 7 yr of diabetes is ~50% (46–48). If this risk of retinopathy were to fall linearly to near zero at the upper limit of normal for mean blood glucose (115 mg/dl), then the mean experimental-group values of the adults (133 mg/dl), of all the patients combined (146 mg/dl), and even of the adolescents (162 mg/dl) would be associated with a reduction in that risk to <35%. For the long-term (>5 yr) trial in phase III, a cohort size of ~700 has been calculated as sufficient to detect a change in prevalence of retinopathy from 50% to 35% with a power of at least 92%. If a threshold model is assumed (Fig. 4, *line B*), then blood glucose would have to rise to some level above normal limits before any risk of retinopathy appeared. In this case, the 12-mo mean

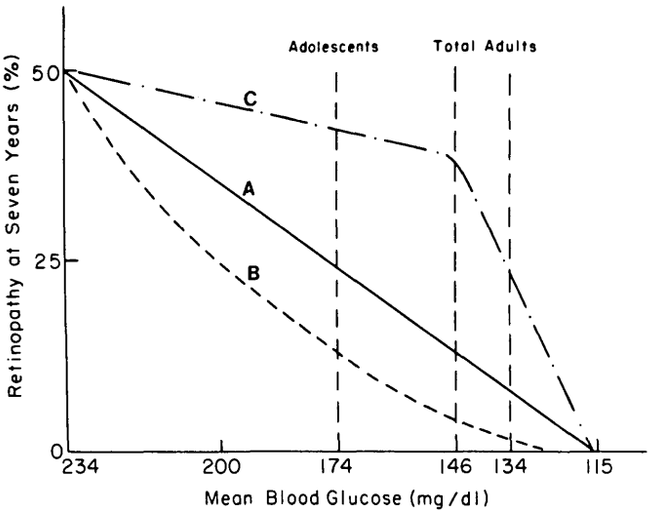

FIG. 4. Three possible models for relationship of retinopathy and mean blood glucose. *Line A* represents a linear model, *line B* a threshold model, and *line C* a nonlinear model (see text).

blood glucose results of the entire experimental group would be even more likely to be associated with a detectable risk reduction in phase III of the trial. Finally, as a worst-case scenario, a nonlinear model may be hypothesized (Fig. 4, *line* C) in which the risk of retinopathy rises steeply to 25% in 7 yr as blood glucose increases from upper-normal to the mean 12-mo level of the adult experimental-group patients (133 mg/dl). Even in such a situation, the mean blood glucose of the total experimental group (146 mg/dl) might be associated with reduced risk of retinopathy to 37.5%, a change detectable with a power of 80% in the projected cohort of 700. In this last model, adolescents in the experimental group could still be expected to contribute to testing the hypothesis of the trial, although to a lesser extent than the adults. These models and the power calculations for phase III were derived principally from a consideration of the primary prevention stratum of the DCCT. However, the limited longitudinal data available on the progression of nonproliferative retinopathy (20) suggest that they may also be reasonably applied to the secondary intervention stratum. The total cohort (primary prevention + secondary intervention) will be 1400.

CONCLUSIONS

The major feasibility objectives of phase II have been accomplished by the DCCT Research Group. *1*) Numerical recruitment targets have been met in a timely fashion, and patients of high-research quality have been enrolled. *2*) In both adults and adolescents, the two treatment regimens have yielded differences in mean blood glucose profiles and mean HbA_{1c} that are statistically significant and are maintained over time. These differences resulted from decreases in mean blood glucose profiles and HbA_{1c} levels with intensive treatment and not from increases with conventional treatment. Mean blood glucose and HbA_{1c} have been lowered by intensive treatment to levels that can reasonably be expected to reduce significantly the risk of microvascular disease, if that risk is in fact related to the degree of hyperglycemia. *3*) The clinical and psychologic well-being of all subjects has been either maintained or improved. With regard to safety, contemporary experience with ketoacidosis and infections has been duplicated or improved. With conventional treatment, the occurrence of severe hypoglycemia did not increase significantly and paralleled most contemporary reports. With intensive treatment, the occurrence of severe hypoglycemia did increase and was significantly greater than with conventional treatment. This observation has generated appropriate concern and protocol modifications. It also underscores the importance of determining the true risk-benefit ratio for intensive treatment regimens. *4*) Subject adherence to treatment assignments and follow-up procedures and the overall performance in both treatment groups were excellent. *5*) The methods used for biochemical measurements have proven to be reliable, reproducible, and precise. The methodology for assessing retinopathy, the major outcome variable of phase III, also appears very satisfactory regarding the quality of photography and grading.

With the satisfactory fulfillment of its objectives for phase II, the full-scale, long-term trial, phase III, has been initiated by the NIDDK and the DCCT Research Group.

A full list of investigators and members of the DCCT Research Group appears in the Appendix.

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APPENDIX

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