Prolongation of Near-Normoglycemic Remission in Black NIDDM Subjects With Chronic Low-Dose Sulfonylurea Treatment

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Microvascular and neuropathic complications of diabetes mellitus can be significantly decreased by long-term, near-normoglycemic regulation in patients with insulin-dependent diabetes mellitus. Prevention or delay of onset of hyperglycemia in non-insulin-dependent diabetes mellitus (NIDDM) patients should reduce morbidity and mortality from these complications. NIDDM can be nearly normoglycemic when diagnosed by screening before its symptomatic stage or when clinically hyperglycemic NIDDM goes into remission. One potential strategy to delay the onset of hyperglycemia in individuals at high risk is chronic low-dose sulfonylurea therapy. Thirty black NIDDM subjects who recently had developed near-normoglycemia were followed with no treatment or were randomly assigned to a 3-year, double-blind glipizide or placebo treatment. Baseline and follow-up parameters included fasting plasma glucose (FPG), HbA_{1c}, plasma insulin, and glucose responses to an oral glucose tolerance test and insulin action, as determined by the euglycemic insulin clamp. Baseline FPG and HbA_{1c} for all three groups were 107 mg/dl and 4.7%, respectively. Relapse to hyperglycemia was defined as an FPG level ≥140 mg/dl on several consecutive visits or an FPG level ≥140 mg/dl and symptoms of hyperglycemia. During the course of the treatment and follow-up, hyperglycemia occurred in 6 of 10 subjects in the no treatment group, 6 of 10 in the placebo group, and 2 of 10 in the glipizide treatment group. Prolongation of near-normoglycemia was significantly ($P < 0.05$) increased by low-dose (2.5 mg/day) glipizide compared with placebo treatment. Low-dose sulfonylurea therapy delays the onset of hyperglycemia in NIDDM subjects in remission and may be a useful method to delay the onset of NIDDM in high-risk individuals.
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Data from the Diabetes Control and Complications Trial demonstrate that both the rate of development and the rate of progression of microvascular and neuropathic complications in insulin-dependent diabetes mellitus (IDDM) patients are functions of the maintenance levels of glycemia, as assessed by serial HbA_{1c} levels and the length of time that hyperglycemia has been present (1). The obvious implication is that an intervention that either normalizes hyperglycemia or delays its onset should result in a significant decrease in morbidity and mortality from this disease (2,3). These data can be qualitatively extrapolated to patients with non-insulin-dependent diabetes (NIDDM), although the quantitative relationships are probably somewhat different. Since the hyperglycemic phase of NIDDM evolves over a period of years, an intervention that delays the onset of hyperglycemia would, in and of itself, reduce morbidity and mortality appreciably. This approach to treatment of NIDDM would be particularly useful in non-Caucasian populations, in whom the mean age of diagnosis of NIDDM is ~46 years (4,5), which is about a decade younger than Caucasians.

Strategies proposed to delay or prevent the onset of hyperglycemia in patients at high risk to develop NIDDM have included diet and increased physical activity and use of pharmacological agents, such as sulfonylureas or biguanides (6–13). The high-risk populations proposed for treatment have been those with impaired glucose tolerance (IGT) or with a history of gestational diabetes. Previous studies encountered difficulties, such as low rates of progression to NIDDM, long duration of treatment necessary, and lack of high compliance rates in a population that perceives itself as well.

During the course of investigating the pathophysiology of NIDDM in black Americans, we have observed that a significant number of patients go from marked hyperglycemia into a near-normoglycemic remission and discontinue all pharmacological therapy within the first few months of treatment (14). These patients have near-normal fasting plasma glucose (FPG) and HbA_{1c} levels, as well as oral glucose tolerance tests (OGTTs) that are normal (15%), impaired (40%), or diabetic (45%). Most patients relapse into hyperglycemia within 3 years. We have used this population to determine whether low-dose sulfonylurea therapy with glipizide can significantly delay the progression of their disease from near-normoglycemia to hyperglycemia.

RESEARCH DESIGN AND METHODS

The study population consisted of 30 black Americans who had originally presented with marked hyperglycemia (plasma glucose 635 ± 55 mg/dl [mean ± SD]) and, after several months of intensive glycemic regulation with either insulin or oral hypoglycemic agents, became near-normoglycemic and discontinued all pharmacological therapy. These patients were classified as having NIDDM on the basis of age at diagnosis, clinical course, insulin secretory reserve, and absence of both circulating islet cell and glutamic acid decarboxylase antibodies (14–

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BMI, body mass index; FPG, fasting plasma glucose; IDDM, insulin-dependent diabetes mellitus; IGT, impaired glucose tolerance; NIDDM, non-insulin-dependent diabetes mellitus; OGTT, oral glucose tolerance test.

TABLE 1
Baseline data on patients in near-normoglycemic remission

	No treatment	Placebo	Glipizide
n	10	10	10
Sex (M/F)	9/1	3/7	7/3
BMI (kg/m^2)	27.4 ± 1.4	27.5 ± 1.0	26.7 ± 0.8
FPG (mg/dl)	107 ± 3.9	107 ± 3.5	107 ± 2.9
Fasting plasma insulin (μU/ml)	11.0 ± 2	12 ± 2	14 ± 3
HbA_{1c} (%)	4.7 ± 0.17	4.7 ± 0.17	4.6 ± 0.18
Glucose area, OGTT 0–120 min ($mg \cdot min^{-1} \cdot dl^{-1}$)	21,544 ± 1,378	19,939 ± 717	20,618 ± 112
Insulin area, OGTT 0–120 min ($\mu U \cdot min^{-1} \cdot ml^{-1}$)	5,851 ± 1,101	5,464 ± 939	9,375 ± 2,361
Glucose disposal to 1 $mU \cdot kg^{-1} \cdot min^{-1}$ insulin infusion ($mg \cdot kg^{-1} \cdot min^{-1}$)	5.7 ± 0.65	6.2 ± 0.58	5.9 ± 0.53

Data are means ± SE. Normal value for HbA_{1c} is ≤4.9%.

17). Near-normoglycemic remission was defined as a mean FPG of ≤125 mg/dl with an HbA_{1c} within or at the upper limit of the normal range at least 3 months after the discontinuation of all pharmacological antidiabetic treatment. A detailed description of the phenomenon of near-normoglycemic remission has been previously published (14). Subjects who were in a near-normoglycemic remission were offered the opportunity to participate in a randomized double-blind, placebo-controlled trial to determine whether treatment with low-dose glipizide would prolong the development of their near-normoglycemic remission. All subjects were instructed on either an appropriate weight-maintaining or weight-reducing American Diabetes Association diet. After baseline studies, patients were assigned to either placebo or glipizide in a randomized double-blind design. Patients not wishing to participate in the pharmacological treatment program (untreated patients) were offered the opportunity to have the same baseline studies and be followed like the pharmacologically treated patients. Baseline studies included measurements of body mass index (BMI), FPG, and insulin; plasma glucose and insulin response to an oral glucose challenge; and insulin sensitivity, as assessed by the euglycemic insulin clamp. Clinical evaluations were made at monthly or bimonthly intervals in the pharmacologically treated patients and every 3 to 4 months in the untreated group to assess FPG and postprandial plasma glucose values, symptoms, and when applicable, drug tolerance. Subjects were treated for 3 ± 0.5 years or until relapse occurred. Relapse was defined as an FPG level >140 mg/dl on several consecutive measurements or an FPG level >140 mg/dl accompanied by symptoms of hyperglycemia. Baseline studies were repeated at yearly intervals and at the time of relapse. At the end of the study, FPG and OGTTs were performed 1 and 3 months after discontinuation of therapy in those patients who had remained in remission.

All patients were informed of the possibility of, and treatment for, hypoglycemic symptoms. The need to not skip meals was emphasized, and dosing was begun at one-quarter tablet daily (equivalent to 0.625 mg of glipizide) and increased at intervals of several days to one-half and, finally, one tablet (equivalent to 2.5 mg of glipizide) daily, as tolerated. Medication was usually administered before breakfast, but in a few instances, it was given before the patient's largest meal.

The study was approved by the institutional review board of the State University of New York Health Science Center at Brooklyn, and all patients signed informed consent forms. The study was conducted at the Clinical Research Center.

Insulin secretion. Plasma glucose and insulin responses to a 75-g oral glucose challenge were measured from blood samples obtained at 0, 30, 60, 90, and 120 min. Patients were instructed to consume at least 150 g of carbohydrate for at least 3 days before the test. The insulin and glucose areas were calculated using trapezoidal estimation. OGTT results were classified according to World Health Organization criteria (18).

Insulin action. Glucose disposal was measured in response to a euglycemic clamp with 3-^{3}H-labeled glucose (19,20) using a 1 $mU \cdot kg^{-1} \cdot min^{-1}$ insulin infusion, as previously described by us (21,22). Insulin resistance was defined as a glucose disposal of <5.5 $mg \cdot kg^{-1} \cdot min^{-1}$, which is <2 SD below the mean of our normal control subjects (23).

Assays. Insulin was measured using a double-antibody radioimmunoassay as previously described (15). Plasma glucose was measured by a glucose oxidase method with a Beckman glucose analyzer (Fullerton, CA). HbA_{1c} was measured using an automated high-performance liquid chromatography method (normal ≤4.9%).

Statistical analysis. Data were analyzed by an intention-to-treat design. Group means were compared using analysis of variance or Student's *t* test, as appropriate. A Kaplan-Meier estimated survival curve using the log-rank or Wilcoxon test was used to determine differences in duration of remission in the various treatment arms (24).

RESULTS

In all, 20 patients agreed to be randomly assigned to drug treatment, while 10 patients elected to be studied and followed but not to take a pharmacological agent. One subject in the placebo group and one in the glipizide-treated group had moderate postprandial hypoglycemic symptoms that antedated participation in the study. These were relieved, but not entirely eliminated, with smaller, more frequent meals. No serious hypoglycemic events occurred. Two patients (patients 9 and 3) in the glipizide-treated group stopped taking medication after 6 and 9 months; patient 9 discontinued for reasons not related to hypoglycemia and, for patient 3, it could not be ascertained whether hypoglycemic symptoms were involved in the decision.

Table 1 lists the baseline characteristics of the 10 patients who received no pharmacological therapy, the 10 patients who were placebo-treated, and the 10 who were glipizide-treated. No significant differences were noted in degree of obesity as estimated by BMI, glucose regulation as assessed by FPG, area under the OGTT glucose curve, HbA_{1c} level, or insulin action as measured by the euglycemic insulin clamp. Insulin secretion, as measured by the plasma insulin response to the OGTT, was not statistically different between the groups, based on parametric or nonparametric testing.

The mean duration of diagnosed remission before entry into the study was not different among the groups (no treatment, 3.5 months; placebo treatment, 2.1 months; and glipizide treatment, 2.2 months). All of these groups contained comparable numbers of insulin-sensitive and insulin-resistant patients (insulin-sensitive patients: 5 of 10 in the no treatment group, 6 of 10 in the placebo treatment group, and 6 of 10 in the glipizide treatment group).

To determine factors that might predict prolonged near-normoglycemic remissions, the baseline data for the untreated and placebo-treated patients who remained in remission for 3 years were compared with those who had relapsed during the study. As noted in Table 2, 12 of 20 patients (60%) relapsed during the study. No significant differences were found in baseline BMI, insulin response to oral glucose, or insulin action between those patients who remained in remission and those who relapsed into hyperglycemia. The only predictor was the baseline FPG. Of the 6

TABLE 2
Baseline data comparing untreated and placebo-treated subjects who relapsed into hyperglycemia with those who maintained the near-normoglycemic remission

	Patients who remained in remission	Patients who relapsed
n	8/20	12/20
Sex (M/F)	4/4	8/4
BMI (kg/m^2)	25.7 ± 0.9	28.6 ± 1.2
FPG (mg/dl)	97 ± 3.8	113 ± 2.0*
HbA_{1c} (%)	4.6 ± 0.19	4.9 ± 0.14
Glucose area, OGTT 0–120 min ($mg \cdot min^{-1} \cdot dl^{-1}$)	18,732 ± 1,224	22,082 ± 838†
Insulin area, OGTT 0–120 min ($\mu U \cdot min^{-1} \cdot ml^{-1}$)	5,535 ± 1,187	5,729 ± 894
Glucose disposal to 1 mU · $kg^{-1} \cdot min^{-1}$ insulin infusion ($mg \cdot kg^{-1} \cdot min^{-1}$)	6.6 ± 0.58	5.5 ± 0.59

Data are means ± SE. * $P < 0.005$. † $P < 0.05$.

patients with a mean FPG <99 mg/dl, all remained in remission, while 9 of 10 with a value >110 mg/dl relapsed.

Table 3 shows the individual data at the end of the study period in those subjects receiving placebo or no treatment who relapsed compared with those who remained in near-normoglycemic remission. The mean duration of remission in the 12 subjects who subsequently relapsed was 17.4 months with a range of 6–43 months. Three subjects (15%) relapsed within 12 months and 10 (50%) within 24 months. Five subjects (25%), who were still in near-normoglycemic remission at the last follow-up visit, had been in remission for >3 years. Relapse was characterized by a rapidly progressive, rather marked, deterioration of glycemic control. The mean FPG and HbA_{1c} levels at the onset of relapse compared with baseline were 209 ± 16 vs. 113 ± 2 mg/dl and 6.8 ± 0.31 vs. 4.9 ± 0.14% ($P < 0.001$). The relapse was not

TABLE 3
Untreated or placebo-treated patients: data at end of study

	Time (months)	FPG (mg/dl)	HbA_{1c} (%)	Change in BMI from baseline (%)
Relapse				
1	6	213	6.6	6.4
2	10	163	—	1.3
3	16	289	7.2	−3.2
4	14	189	5.2	−2.1
5	11	212	6.0	−3.9
6	20	259	7.1	−10.0
7 P	16	162	6.2	3.9
8 P	18	159	6.0	3.9
9 P	14	165	5.9	−0.5
10 P	43	330	8.0	0.8
11 P	16	162	8.2	3.3
12 P	27	209	8.1	5.3
Remission				
13	38	106	—	6.6
14	49	99	5.0	−1.5
15	35	122	4.8	−1.5
16	24	84	—	23.0
17 P	28	105	4.7	−2.5
18 P	43	103	4.6	11.2
19 P	43	104	4.3	5.5
20 P	49	113	3.7	9.4

P, patients in placebo-treated group.

TABLE 4
Data for patients receiving glipizide: end of study

	Duration of treatment (months)	Time at last follow-up (months)	FPG (mg/dl)	HbA_{1c} (%)	Change in BMI from baseline (%)
Relapse					
1	31	31	175	6.0	14.7
2	30	30	124	5.3	15.0
Remission					
3	9	46	123	5.2	10.4
4	52	52*	113	4.9	5.9
5	44	49	116	4.4	0.7
6	36	39	110	4.4	1.1
7	41	46	127	4.9	2.6
8	38	41	115	5.2	15.1
9	6	30	111	3.1	−1.1
10	40	53	91	4.2	5.8

Patient 2 relapsed at 36 months and was treated by his private physician. * Studies repeated 3 months later were unchanged.

associated with weight gain, since the change in BMI from the baseline to relapse was 0.6 ± 1.4%.

In the eight individuals who remained in near-normoglycemic remission, mean FPG and HbA_{1c} levels at the last follow-up visit (mean 38.6 months) compared with baseline values were 105 ± 8.8 vs. 97 ± 3.8 mg/dl and 4.5 ± 0.19 vs. 4.6 ± 0.19%, respectively. Mean BMI gain of those subjects during the same interval was 7.01 ± 2.8%.

The effect of glipizide treatment on patients in near-normoglycemic remissions is given in Table 4. Only 2 of 10 individuals (20%) relapsed into hyperglycemia during the course of the study and subsequent follow-up. Patients 3 and 9 discontinued glipizide treatment at 9 and 6 months, respectively, but remained in near-normoglycemic remission throughout the study and subsequent follow-up. Patient 2 continued glipizide treatment for 30 months but discontinued it when he moved to another state. He developed hyperglycemia 6 months later. After a mean follow-up time of 44.5 months, the patients who remained in near-normoglycemic remission had a slight increase in FPG level (114 ± 3 vs. 104 ± 3 mg/dl, $P < 0.05$) but no change in HbA_{1c} level (4.5 ± 0.1 vs. 4.5 ± 0.27%) compared with baseline values. The mean increase in BMI in the eight subjects who remained in near-normoglycemic remission was 5.1 ± 1.9% ($P < 0.05$). The two glipizide-treated patients who relapsed into hyperglycemia had gained ~15% in BMI.

A Kaplan-Meier estimated survival analysis (Fig. 1), using a log-rank test and Wilcoxon rank tests, compared the number of patients remaining in remission with the different treatments. This showed that the duration of remission among the three groups was statistically significantly different (log-rank test, $P = 0.056$; Wilcoxon's test, $P = 0.026$). Specific group comparisons showed that glipizide treatment was more effective than placebo treatment in prolonging near-normoglycemic remissions (log-rank test, $P = 0.05$; Wilcoxon's test, $P = 0.03$). Glipizide treatment significantly prolonged near-normoglycemic remissions compared with no treatment (log-rank test, $P = 0.024$; Wilcoxon's test, $P = 0.013$) or with placebo and no treatment combined (log-rank test, $P = 0.025$; Wilcoxon's test, $P = 0.015$). No differences in duration of near-normoglycemic remission existed between the no treatment and placebo treatment groups. At 30 months, none of the glipizide-treated group, five of the

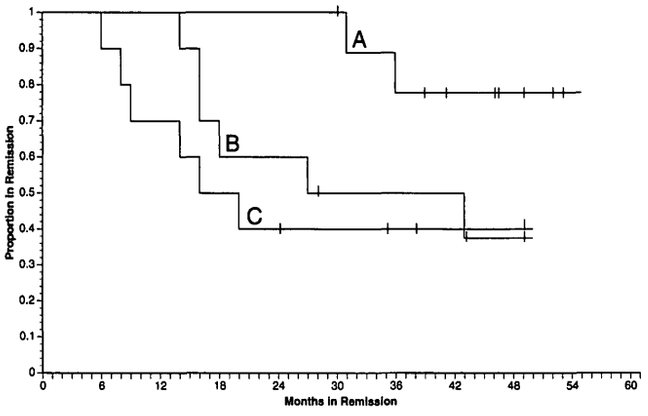

FIG. 1. The number of patients remaining in remission is plotted against months, using the Kaplan-Meier estimated survival analysis. *A*: glipizide treatment. *B*: placebo treatment. *C*: no treatment. Tick mark indicates last follow-up. Glipizide treatment prolongs near-normoglycemic remission compared with placebo treatment (log-rank test, $P = 0.05$; Wilcoxon's test, $P = 0.03$) and no treatment (log-rank test, $P = 0.024$; Wilcoxon's test, $P = 0.01$).

placebo-treated group (50%), and six of the no treatment group (60%) had relapsed into hyperglycemia.

DISCUSSION

Data on the effect of the level of glycemic control on primary prevention and the effect of secondary intervention on the chronic complications of IDDM patients provide quantitative information with which to formulate potential benefits of preventive and therapeutic strategies (1,25). For example, a recent analysis simulating the impact of primary and secondary interventions on the development of diabetic retinopathy estimated that a 6-year delay in the onset of diabetes (hyperglycemia) through primary intervention would result in a 50–70% decrease in proliferative retinopathy (2). While sufficient data are not available for NIDDM patients to ascertain the quantitative aspects of the benefit of primary prevention on microvascular and neuropathic complications, it is likely that it will be substantial. This is particularly true for non-Caucasian populations, such as African-Americans, who have a mean age at diagnosis of NIDDM of 46 years and who have a two to four times greater risk for microvascular diseases than do Caucasians (26).

Attempts to prevent or delay the onset of hyperglycemia in individuals who are at high risk to develop diabetes have been conducted using diet and exercise, sulfonylureas, and metformin (6–13). These studies have been fraught with numerous difficulties and generally have not shown positive results. The Malmo diet and physical exercise treatment showed a 50% reduction in the progression of IGT to NIDDM after a mean follow-up time of 6 years compared with a nonrandomized group, which was not followed, in the same health care environment (7). Sartor et al. (6) showed that chronic tolbutamide therapy for 10 years prevented progression of IGT to NIDDM in a small cohort. The interpretation of the data is somewhat tenuous because of the small number of patients, the necessity to combine several groups for analysis, and the uncertainty of whether a preventive or treatment effect was observed.

The availability of a somewhat unique population of black American NIDDM subjects who develop a near-normoglycemic remission after appropriate initial diabetic treatment afforded us the opportunity to investigate the potential of various therapeutic endeavors to delay the progression from normoglycemia to hyperglycemia. At the time of their near-normoglycemic remission, this group had mean FPG and HbA_{1c} levels at the upper level of normal, and >50% had normal glucose tolerance or IGT, with the remainder having 2-h postglucose challenge plasma glucose values <260 mg/dl. Thus, they may be considered comparable to a very high-risk, IGT population. Our data show that chronic low-dose sulfonylurea therapy can significantly delay the progression from near-normoglycemia to clinical hyperglycemia in NIDDM patients in remission. These data support the contention of Sartor et al. (6) that sulfonylurea therapy can delay or prevent progression of IGT to NIDDM.

The use of low-dose sulfonylurea therapy is not simply treating mild hyperglycemia. Discontinuation of the drug for 1–3 months at the conclusion of the study did not result in a rise in FPG or a poorer glycemic response to oral glucose. Furthermore, when relapse did occur, hyperglycemia was controlled with ordinary doses of sulfonylureas or insulin and not the low dose (2.5 mg glipizide) used in this study.

The maximal benefit of sulfonylurea therapy in delaying progression from normoglycemia cannot be determined from our study. We limited drug administration to 3 ± 0.5 years and followed our patients who were off therapy for only several additional months. Only one patient relapsed while taking glipizide. It is obvious from our no treatment and placebo-treated groups that at least 35% of our untreated patients experienced a remission that exceeded 3 years. The potential long-term benefits of chronic low-dose sulfonylurea therapy must be assessed by a 5- to 10-year treatment study. The form of sulfonylurea administration also needs to be evaluated. Our therapy was limited to a single daily low-dose administration to avoid potential hypoglycemic symptoms. A long-acting, slow-release form of a sulfonylurea may permit a more continuous effect with less risk of hypoglycemia.

The mechanism by which chronic low-dose sulfonylurea therapy may slow the progression from normoglycemia to hyperglycemia in NIDDM patients is not clear. Sulfonylureas bind to a receptor on the plasma membrane of the β-cell and increase its sensitivity to glucose as an insulin secretagogue (27–29). The progression from IGT to NIDDM has been shown to be due to a decrease in insulin secretion (30). One could speculate that chronic low-dose sulfonylurea therapy slows the deterioration of β-cell function (31). Preliminary analysis of insulin secretory and insulin action data in our patients is compatible with the concept that decreasing insulin secretion is associated with the development of hyperglycemia.

Glycemic control itself may be beneficial to β-cell function and recovery, regardless of the pharmacological agent used. Shah et al. (32) showed that short-term intensive insulin treatment early in the course of diabetes had a long-term protective effect on insulin secretion and improved glycemic control at 1 year. This suggests that brief glycemic control may have a future beneficial effect. This is consistent with the two subjects who remained in remission despite receiving glipizide for shorter durations.

The differences in baseline insulin response (area) to oral glucose and sex distribution in the glipizide- and placebo-treated groups (Table 1) were not statistically significant and were unlikely to account for the improved duration of remission in the glipizide-treated group compared with the placebo-treated group. A preliminary Cox hazard proportion

analysis of 64 black NIDDM subjects in remission who were followed long-term showed that neither baseline insulin response (area) nor sex predicted duration of remission. While the glipizide-treated group had more men compared with the placebo-treated group, it was similar to the no treatment group and not statistically different (7 of 10, 3 of 10, and 9 of 10). Reanalysis of our data, excluding the single individual in the glipizide-treated group with a very high insulin area (20,405 $\mu U \cdot min^{-1} \cdot ml^{-1}$), resulted in insulin secretory rates in the glipizide- and placebo-treated groups that were comparable (6,878 ± 1,347 and 5,464 ± 939 $\mu U \cdot min^{-1} \cdot ml^{-1}$). A survival analysis on this set also showed a significantly longer duration of remission in the glipizide-treated group ($n = 9$) compared with the placebo-treated group ($n = 10$) (Wilcoxon's test, $P = 0.03$).

In summary, our data show that chronic low-dose glipizide therapy prolongs near-normoglycemic remissions in black Americans with NIDDM. These data provide support for the concept that such therapy may be effective in delaying the progression from IGT to NIDDM.

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