Bariloche Foundation projection assigns 37.9 percent to renewables, with less oil and coal and little nuclear energy.

These strongly contrasting studies indicate that there may be considerable flexibility in developing the energy future of Latin America; it is likely that neither of them has given enough attention to improvements in the end uses of energy. It is clear, however, from the active search for new solutions and innovations that the oil crisis of the 1970's has had an impact. The search for new solutions will certainly lead to an energy future that will be different from the past, perhaps less than wished by many but more than predicted by some.

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RESEARCH ARTICLE

Effects of Cyclosporine Immunosuppression in Insulin-Dependent Diabetes Mellitus of Recent Onset

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Introduction

Type I diabetes mellitus occurs at an annual rate of approximately 15 per 100,000 people with a prevalence of 1 in 300 among those under the age of 20 years in North America. The incidence is increasing each decade with a clear genetic predilection and a strong association with the major histocompatibility complex (*1*). In particular, the disease is associated with DR antigens 3 and 4 of the HLA (histocompatibility) region with greater than 90 percent of patients under the age of 15 years having DR3 or DR4 or both. The etiology of the disease is not known. The possibility that viral infection has an etiological role is suggested by findings in animal models, but the occurrence of diabetes in the human as a direct result of a viral attack on the β cells appears to be a rare clinical event (*2*). That the disease can result from autoimmune processes is also suggested by studies in animals, particularly the BB rat, which serves as a telescoped model of type I diabetes (*3*). This animal develops gross abnormalities of the immune response including a T-cell lymphopenia preceding and accompanying the onset of the disease (*4*). The disease is genetically dominant and linked with the major histocompatibility complex (*5*). Although islet cell antibodies (*6*) have been described in association with diabetes in this rat model, the primary immunologic mechanism appears to be cell mediated. The disease in the BB rat can be prevented by a number of manipulations of the immune system (*7, 8*), including the administration of cyclosporine (Cy) prior to the onset of the disease (*9*). It was found that Cy completely prevented the acute isletitis, which destroys the β cells in 80 percent of untreated BB rats, while sparing the acinar tissue. If Cy was continued, the pancreas remained free of the cellular infiltrate. When Cy was discontinued at 120 days of age, diabetes occurred in less than 25 percent of the animals (*10*).

In the human, the evidence that type I diabetes is an autoimmune disorder is based largely on the histological appearance of the pancreas (*11*), the demonstration of cell-mediated immunity against islet cells (*12*), and an association of islet cell antibodies with the disease (*13*). Its association with a number of diseases where autoimmunity has been implicated such as Grave's disease, pernicious anemia, Hashimoto's thyroiditis, myasthenia gravis, and Addison's disease adds to the impression that it is immunologically mediated. The conviction that type I diabetes is mediated by immune mechanisms has already prompted a number of attempts to induce remissions in the human by the use of immunosuppressive agents early in the course, with inconclusive results to date (*14–17*).

The diagnosis of type I diabetes carries a sinister prognosis with an overall mortality of 60 percent four decades after the initial diagnosis is made. Uremia is the cause of death in over 30 percent of patients. It is expected that within this time, 16 percent will be blind, 21 percent will have a myocardial infarction, 12 percent will have gangrene or have undergone amputation, and 10 percent will have suffered a stroke (*18*). In recent reports it was estimated that the relative mortality in comparison to nondiabetics (*19*) is greater than ten times at any age, and that as many as 1.4 percent of patients with juvenile onset insulin-depen-

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dent diabetes mellitus (IDDM) may die within the first 5 years (*20*).

Although the loss of β cell mass at the stage of clinical expression of the disease is substantial (*11*), the capacity for partial recovery is demonstrated by the clinical remission phase of diabetes, which is apparent to varying degrees in most patients. During this phase there is partial recovery of endogenous secretion of insulin, so that good control of metabolism is relatively easily achieved with modest doses of insulin (*21*). This phase lasts for a few weeks or months, but is followed inevitably by increasing insulin requirement and lability of metabolic control associated with declining residual insulin secretion. Since it is believed that the complications of diabetes would be prevented or ameliorated by good long-term control of metabolism (*21*), the benefit that might follow enhancement or preservation of this remission phase is apparent.

The immunosuppressive qualities of Cy, a nonpolar cyclic oligopeptide (previously designated cyclosporin A) produced by the fungi *Cyclindrocarpon lucidum* and *Tolypocladium inflatum* Gams, were first described by Borel *et al.* (*22*). The drug has been used, alone or in combination with steroids, for more than 4 years to suppress graft rejection in humans. Compared with treatment regimens that include the standard immunosuppressant azathioprine, Cy with or without steroids has generally resulted in better graft survival in both animal and human studies (*23*). Cyclosporine arrests both the experimental uveitis of animals and clinical uveitis of man (*24*). It appears to act specifically at the level of the T-helper cell and inhibits the production of lymphokines. Its immunosuppressive effects appear to be reversible (*25*). It can be toxic to the liver and kidney, and although these effects appear to be reversible (*26, 27*), it is possible that persistent Cy therapy after the development of interstitial fibrosis may result in irreversible changes (*23*). It also induces gum hyperplasia and hypertrichosis (*28*). Because of its immunosuppressive action, it may be predicted that the incidence of infections and cancer in Cy treated patients will be increased over the general population. The incidence of these complications with Cy alone is not known, as very few subjects have received Cy therapy as the sole immunomodulatory agent prior to the present study. The incidence of lymphoma in 3900 kidney transplant patients receiving Cy alone or in combination with prednisone was 14 (0.4 percent); and in one subgroup with carefully monitored Cy blood concentrations there was one case in 618 subjects (*29*).

In November 1982, we initiated a pilot study in which patients with recent onset type I diabetes were treated with Cy for 6 to 12 months. The effect of the therapy was studied in regard to: (i) the development of adverse effects, (ii) the induction of remission (insulin independence), (iii) the preservation of β cell function (C-peptide secretion), and (iv) rate of disappearance of islet cell antibodies. Interim reports on the progress of this study have been published (*30*) and discussed (*31, 32*). We summarize here the results for 41 patients treated with Cy for 2 to 12 months. The incidence of recovery to a non–insulin dependent state was higher (50 percent) than expected (3 percent) (*33*). No untoward toxicity was observed.

Abstract. *Type I diabetes may be an autoimmune disorder, although the evidence is largely circumstantial. The natural history of the disease after diagnosis includes partial remission in most patients, but only about 3 percent achieve transient insulin independence. β Cell function, as indicated by the plasma concentration of C-peptide, is lost over 6 to 30 months and islet cell antibodies disappeared over 1 to 2 years. This article describes a pilot study in which 41 patients were treated with the immunosuppressive agent cyclosporine for 2 to 12 months. Of 30 patients treated within 6 weeks of diagnosis, 16 became insulin independent with concentrations of plasma C-peptide in the normal range and decreasing titers of islet cell antibodies. Of 11 patients who entered the study 8 to 44 weeks after diagnosis, two achieved this state. These results indicate that a controlled trial of the effects of cyclosporine in type I diabetes should be conducted.*

Clinical Protocol

Insulin-dependent diabetics between 8 and 49 years of age were recruited to the study after the diagnosis of IDDM had been made by their personal physicians. The diagnosis of IDDM was made on clinical grounds in nonobese subjects with confirmed hyperglycemia [National Diabetes Study Group criteria (*34*)]. All were required to have a serum immunoreactive C-peptide concentration within the normal fasting range, tested in the fasting state with and without glucagon stimulation (0.2 pmole/ml), and to have received insulin therapy for less than 12 months. Sixty-eight patients were considered eligible for the study, 47 were entered, and 41 have been observed for longer than 60 days of treatment (Table 1). The reasons for not entering were: (i) declined consent (18 subjects); (ii) not available for follow-up (three subjects). Predominant reasons for the lack of consent were the unknown long-term side effects of Cy in the diabetic, and the risk of lymphoma. Plasma C-peptide was determined by radioimmunoassay after extraction of plasma with polyethylene glycol (*35*). Fasting samples were drawn before breakfast and morning insulin administration, and 6 minutes after intravenous injection of 1 mg of glucagon. Glycosylated hemoglobin was measured with a colorimetric assay which does not detect the labile moiety (*36*). HLA typing was done, and serial blood specimens were obtained for assays for islet cell antibodies which were determined by an immunofluorescence technique at the Steno Memorial Hospital, Gentofte, Denmark.

Cyclosporine administration and monitoring. Patients were admitted to hospital for an average of 5 days at the beginning of the study. Baseline creatinine clearance, urinalysis, serum creatinine, blood urea nitrogen, serum glutamic-oxaloacetic transaminase (SGOT), and alkaline phosphatase were determined and found to be normal. Administration of Cy was then started at a dose of 10 mg per kilogram of body weight per day. It was given in divided doses every 12 hours; daily serum Cy concentrations were measured by radioimmunoassay and the dose was adjusted to maintain a serum concentration of 100 to 200 ng/ml at 12 hours (*37*). After they were discharged, most patients were seen weekly for 2 weeks and monthly thereafter. At each clinic visit blood was drawn for determination of Cy, creatinine, and electrolyte concentrations and for hematologic and liver function tests; basal and glucagon-stimulated plasma C-peptide concentrations were measured at 1 month and at 3-month intervals thereafter.

Management of diabetes. All patients were treated with purified pork insulin (Iletin II). They were encouraged to take insulin twice daily and to monitor their blood glucose concentrations using visual matching or reflectance meter methods with reagent strips. They were instructed in a diabetic diet appropriate for

maintenance of normal body weight and activity. The dosage of insulin was adjusted in an attempt to achieve a mean blood glucose of 140 mg/dl (7.8 mmole/liter) before the main meals and evening snack. The dose of insulin was reduced when control of glycemia was consistent with these targets or in order to avoid hypoglycemia. Subjects in whom insulin was completely withdrawn for at least 1 week without loss of target control or development of ketonuria and who did not resume insulin treatment during the study were classed as non–insulin-requiring (NIR). If subjects who had become NIR subsequently developed hyperglycemia exceeding the treatment goals, a trial of the oral hypoglycemic agent glybenclamide (up to 20 mg/day) was undertaken. Three such patients are included in the NIR subset and another three patients in the IR subset were also given glybenclamide to aid in metabolic control.

Results

The characteristics of the subjects are presented in Table 1. At 150 days into the study, it appeared that clinical responses were more frequent in patients entered soon after diagnosis of diabetes than in patients entered later. Two groups were identified: group 1 consisted of patients entered within 6 weeks of diagnosis; and group 2, patients entered from 8 to 44 weeks after diagnosis. Recruitment into group 2 was terminated at that point, after 11 patients had been entered. Nine patients were in group 1 and recruitment into that group continued. In Table 1 the groups are further subdivided into subsets; those destined to become NIR and those who continued to receive insulin. There were no major differences between the groups with respect to age or duration of diabetes, although both NIR subjects in group 2 were males. At entry, the mean dosage of insulin was similar in the groups and subsets. The mean glycosylated hemoglobin was elevated to a similar degree in the subsets of group 1, in which patients had received insulin treatment for only 15 ± 2 days [mean ± standard error of the mean (S.E.M.)]. In group 2, patients had been treated with insulin for 165 ± 23 days and the control of glycemia was relatively good as indicated by the glycosylated hemoglobin levels. There were no statistically significant differences between the groups with respect to initial mean basal C-peptide levels or between subsets in response to stimulation with glucagon. However, the stimulated C-peptide response was significantly greater in group 1 than group 2 patients. The islet cell antibody titers were comparable in the two groups, although both of the individuals who became NIR in group 2 were negative for these antibodies. Most of the subjects in both groups were positive for HLA DR antigens 3 or 4; only one subject lacked both of these antigens.

Table 1. Patient characteristics at time of entry into study. Groups 1 and 2 are differentiated by the mean days on insulin prior to this date, and further subdivided by response (NIR, non–insulin requiring; IR, insulin requiring; ICA, islet cell antibodies).

Subjects	Age (years)*	Number of		Time on insulin (days)*	Insulin dose (unit/kg-day)*	Glycosylated hemoglobin (%)*	C-peptide (pmole/ml)*		Number ICA positive (%)	Number positive for HLA antigens (%)			Number not positive for HLA antigens DR3 or 4 (%)	Not typed
		Males	Females				Basal	Stimulated		DR3	DR4	DR3 and 4		
Group 1														
Subject NIR	15.4 ± 1.6	8	8	14.6 ± 3.3	0.54 ± 0.06	13.6 ± 0.6	0.20 ± 0.02	0.42 ± 0.04	9 (56)	3 (19)	5 (31)	8 (50)	0	
Subject IR	15.5 ± 3.0	9	5	15.5 ± 3.1	0.59 ± 0.02	15.2 ± 0.8	0.21 ± 0.03	0.42 ± 0.08	2 (14)	2 (15)	6 (46)	4 (31)	1 (8)	1
Group 2														
Subject NIR	18.5 ± 8.0	2	0	102.0 ± 31.3	0.52 ± 0.09	12.0 ± 3.5	0.18 ± 0.04	0.30 ± 0.04	0	1 (50)	1 (50)	0	0	
Subject IR	16.3 ± 2.9	5	4	146.7 ± 27.5	0.51 ± 0.04	10.6 ± 0.8	0.18 ± 0.03	0.30 ± 0.05	6 (67)	4 (57)	1 (17)	2 (28)	0	2

*Data show means ± S.E.M.

In Table 2, the mean plasma C-peptide concentrations after stimulation with glucagon reflect maximum β cell responses. The basal values correlated significantly with the glucagon-stimulated values ($R = 0.83$, $P < 0.01$, not shown). In both groups 1 and 2 these stimulated values were significantly increased after 30 days of Cy administration, but the mean values were greater in group 1. The difference between the groups was significant at 195 and 285 days after initiation of insulin therapy. With discontinuation of immunosuppression in group 2 (after 180 days of Cy therapy), the mean stimulated C-peptide values declined from the peak level attained in most of the subjects (see also Fig. 1B). In subjects on Cy, the mean dose of insulin declined concurrently with these increases in the C-peptide response. In group 2, the two individuals who discontinued insulin therapy continued Cy and remained NIR through the remainder of the study, whereas those subjects who continued to receive insulin had their Cy discontinued at 180 days and took increasing doses of insulin with time.

The proportion of subjects who became NIR increased to equal or greater than 50 percent in the latter half of the period of Cy administration in group 1, and reached a maximum of 18 percent toward the end of the period of immunosuppression in group 2 (Table 2). The mean percentage of glycosylated hemoglobin approximated 10 percent in group 2 during Cy therapy, but began to increase, in spite of increasing dosage with insulin, after immunosuppression was withdrawn. The value of 10 percent approaches the upper limit of normal with the assay used, a result similar to that reported with this assay in patients receiving continuous subcutaneous infusion of insulin (*21*). These estimates of glycosylated hemoglobin represent the principal indices of glycemic control in this study. The mean values in groups 1 and 2 are shown in Table 3. Laboratory-determined plasma glucose concentrations in samples drawn before breakfast were also obtained, and the means of the averages of these for each patient are included in Table 3. Data from our labo-

ratories indicate that the observed glycosylated hemoglobin concentrations are consistent with mean diurnal plasma glucose concentrations in the range of 115 to 130 mg/dl (6.4 to 7.2 mmole/liter). Self-determined capillary blood glucose profiles of these patients were also concordant with their glycosylated hemoglobin levels (not shown).

In group 1, the IR and NIR subjects showed similar and significant increases in stimulated C-peptide levels by 30 days of immunosuppression (Fig. 1A). These concentrations leveled off, or increased slightly, through the period of Cy therapy. Insulin dosage leveled off by 90 days (0.3 U/kg-day) in subjects who continued to receive insulin, and declined in the NIR group until all had discontinued insulin therapy by 196 days. In the two subjects in group 2 who became NIR there was a rapid increase in mean stimulated C-peptide concentrations into the same range as in group 1 subjects, but in the nine subjects who remained IR there was only a relatively modest and delayed increase (see Fig. 1B). However, it is notable that this mean level did increase throughout the period of immunosuppression and began to decline only after discontinuation of Cy.

Islet cell antibodies were detected in 37 percent of the group 1 and 54 percent of the group 2 subjects prior to initiation of Cy therapy. Reciprocal titers of islet cell antibodies fell rapidly with means of 22, 8, and 2 at 0, 3, and 6 months, respectively. The initial titers were comparable with those of historical controls with type I diabetes, but the rate of decline was more precipitous than in newly diagnosed type I diabetes studied by the Steno group during conventional therapy (*38*).

Adverse Effects of Cy Therapy

The biochemical and hematological effects of Cy are shown in Table 4.

Renal function. Mean serum creatinine concentrations showed a 32 percent increase at 180 days of Cy therapy. In all patients in whom Cy was discontinued, the creatinine decreased to baseline (see Table 5). In 10 percent of these patients, there was also a transient rise in serum potassium of 30 percent and a reduction in bicarbonate of 9 percent. These values all returned to normal when Cy was discontinued.

Liver function. By 30 days, the serum bilirubin increased by 47 percent and alkaline phosphatase by 31 percent; both returned to baseline during Cy therapy (Table 4).

Anemia. An unexpected 15 percent decrease occurred in the mean serum

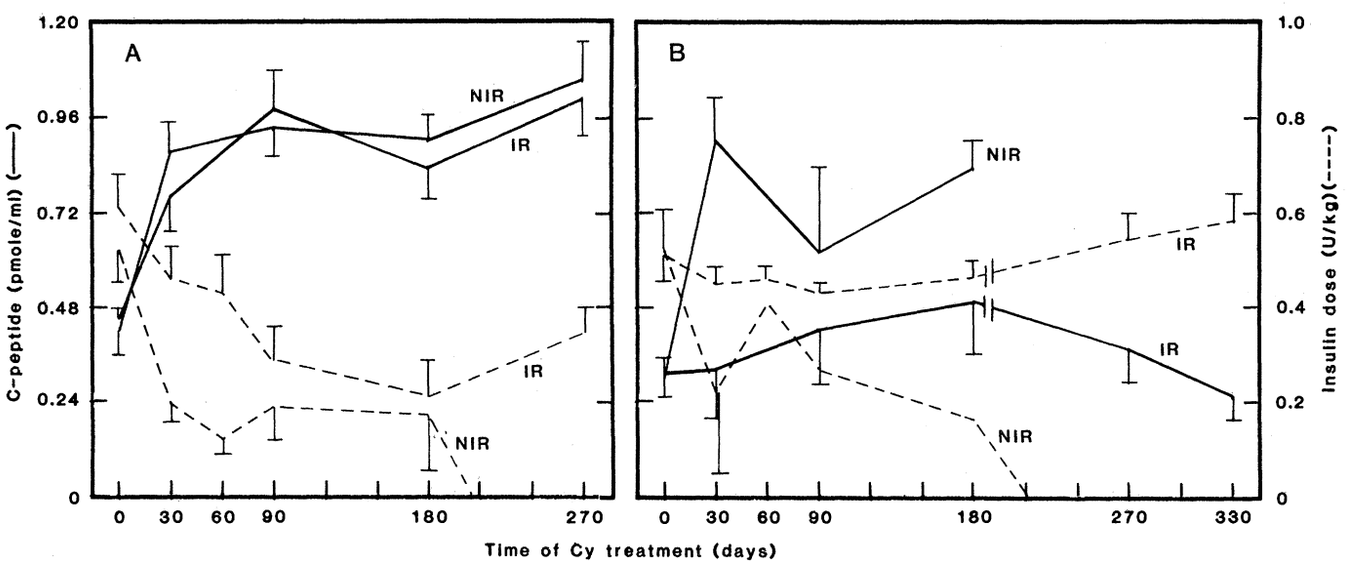

Fig. 1. Mean insulin dose and mean glucagon-stimulated C-peptide concentrations in the NIR and IR patients of (A) group 1 and (B) group 2. The data for insulin dosage are only for patients who were still taking insulin.

Table 2. Clinical and metabolic responses of the two groups of subjects in relation to duration of insulin treatment. At entry (1 to 5 days before initiation of Cy therapy), group 1 had received insulin for 15 ± 2 days and group 2 for 120 ± 28 days. Unless otherwise indicated, numbers in parentheses show number of patients tested. The glucagon-stimulated plasma C-peptide level in normal subjects was 1.41 ± 0.19 pmole/ml (N = 8). The percentage glycosylated hemoglobin in 95 percent of normal subjects was < 9.9.

Insulin treatment (days)	Glucagon-stimulated C-peptide (pmole/ml)*		Insulin dose for IR subjects (unit/kg-day)*		Number of NIR subjects/ number in study at date (percentage of group at date)		Glycosylated hemoglobin (%)*	
	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2	Group 1	Group 2
At entry	0.43 ± 0.05 (29)	0.31 ± 0.04 (11)	0.56 ± 0.05	0.51 ± 0.04	0/30	0/11	14.4 ± 0.5	10.9 ± 0.9
	Data for subjects who had received Cy therapy for more than 30 days							
45	0.81 ± 0.06 (21)		0.34 ± 0.05		6/30 (20%)		11.0 ± 0.3	
105	0.95 ± 0.06 (25)		0.25 ± 0.05		12/29 (41%)		9.9 ± 0.3	
195	0.82 ± 0.05 (20)	0.57 ± 0.11 (6)	0.20 ± 0.05	0.44 ± 0.05	10/20 (50%)	1/11 (9%)	9.8 ± 0.4	10.6 ± 1.0
285	1.04 ± 0.10 (7)	0.62 ± 0.12 (9)	0.33 ± 0.06	0.43 ± 0.05	7/12 (58%)	2/11 (18%)	10.1 ± 0.7	9.6 ± 0.4
375		0.45 ± 0.02 (9/3)†		0.47 ± 0.02				9.0 ± 0.6
465		0.20 ± 0.06 (5/4)†		0.56 ± 0.02				11.2 ± 0.6
555		0.27 ± 0.09 (4/4)†		0.69 ± 0.03				11.4 ± 0.6

*Data show means ± S.E.M. †Number of patients/number discontinuing therapy.

hemoglobin concentration during Cy therapy. This was not associated with iron deficiency or hemolysis (Table 4). The concentration returned to normal when Cy was discontinued (not shown).

Cosmetic effects. One hundred percent of the patients under age 15, and 50 percent over age 15, had some gingival hyperplasia as detected by careful dental examination with comparative photographs. Dental hygiene was thought to be a significant factor in reducing this effect and in no patient was gingival hyperplasia a major problem. Although some degree of hypertrichosis was seen in most patients, in no patient was this severe. Both the hypertrichosis and the gingival hyperplasia regressed on discontinuing Cy therapy.

Other effects. Peripheral hypersensitivity to extremes of temperature, nausea, and abdominal cramping, headaches, and leg cramps were noted in a number of patients, but they did not present serious problems or cause any of the subjects to discontinue therapy. One patient had generalized edema early in the course of her therapy and Cy was discontinued. This patient had a total of 76 days of Cy therapy with low serum levels (less than 100 ng/ml) and a mean daily Cy dose of 5 mg/kg. Six months later she was found to have early anterior and posterior subcapsular cataracts. There is no known association of this with Cy. One other patient developed a thyroid nodule that was excised and described histologically as "a papillary adenoma; without evidence of malignancy" (W. T. E. McCaughey, Canadian Tumour Registry). No relation of this with Cy has been described previously. One subject aged 17 developed labile hypertension during Cy therapy (diastolic blood pressure 90 to 95 mmHg).

One 10-year-old patient included in the IR subset of group 1, who did not comply with Cy administration, entered an NIR state with normal plasma C-peptide levels when his serum Cy concentration at 12 hours indicated compliance. Continued monitoring during a subsequent loss of metabolic control confirmed that he was not taking Cy (not detectable in serum) and he was then withdrawn from treatment on day 205. On this day his stimulated plasma C-peptide concentration was 0.94 pmole/ml; this level fell to 0.33 pmole/ml 30 days later.

Table 3. Mean percentage of glycosylated hemoglobin in patients on Cy. Group values after 120 and 250 days of Cy were correlated with average laboratory-determined concentrations of plasma glucose before breakfast. The percentage glycosylated hemoglobin was determined by a colorimetric method; 95 percent of the normal values were less than 9.9 percent. Data show means ± standard error. Numbers in parentheses show number of subjects tested.

Time of study	Group 1			Group 2
	Total	Subset IR	Subset NIR	
At entry	14.4 ± 0.5 (29)			10.9 ± 0.9 (11)
At 120 days		9.9 ± 0.4 (13)	9.9 ± 0.6 (9)	9.8 ± 0.5 (11)
At 250 days		9.7 ± 0.7 (5)	10.3 ± 0.9 (5)	10.2 ± 0.3 (9)
Mean plasma glucose*		8.9 ± 0.7 (14)	7.6 ± 0.6 (16)	7.6 ± 0.5 (11)

*Plasma glucose concentrations (in millimoles per liter) determined through the period of study were averaged for each subject.

Table 4. Biochemical changes with Cy therapy. Data show means ± S.E.M. Numbers in parentheses show number of subjects tested.

Time of Cy therapy (months)	Creatinine (μmole/liter)	K^+ (mmole/liter)	HCO_3 (mmole/liter)
Baseline	70.3 ± 2.8 (41)	4.8 ± 0.4 (36)	25.9 ± 0.5 (35)
1	78.7 ± 3.9 (41)	4.8 ± 0.09 (39)	24.5 ± 0.3 (37)
3	84.7 ± 4.5 (38)	4.8 ± 0.07 (37)	24.1 ± 0.3 (37)
6	93.0 ± 8.0 (29)	4.8 ± 0.6 (28)	23.6 ± 0.4 (28)
9	96.0 ± 12.4 (10)	4.7 ± 0.1 (10)	22.3 ± 0.8 (8)
Time of Cy therapy (months)	**Bilirubin (μmole/liter)**	**Alkaline phosphatase (unit/liter)**	**Hemoglobin (g/liter)**
Baseline	11.8 ± 1.2 (30)	242.1 ± 9.9 (35)	138.1 ± 1.4 (40)
1	17.4 ± 1.6 (38)	279.5 ± 28.9 (28)	128.1 ± 1.6 (41)
3	15.1 ± 1.3 (34)	317.2 ± 31.5 (36)	121.5 ± 1.7 (37)
6	13.0 ± 1.1 (25)	280.1 ± 28.6 (27)	118.2 ± 1.7 (29)
9	10.4 ± 1.7 (7)	215.3 ± 58.9 (7)	117.7 ± 3.1 (10)

Table 5. Serum creatinine concentrations. Number of patients tested are shown in parentheses. Data show means ± S.E.M.

Group	Before Cy therapy	Creatinine concentration (μmole/liter)		
		After 180 days of Cy therapy		At 90 days after Cy therapy stopped
		Total	Percent change	
1	57.7 ± 3.2 (6)	80.2 ± 13.4 (4)	39	52.2 ± 4.2 (5)
2	71.5 ± 5.9 (8)	82.0 ± 8.1 (6)	15	66.4 ± 5.1 (7)
1 and 2	66.6 ± 4.0 (14)	81.3 ± 6.8 (10)	24	60.5 ± 3.9 (12)

Discussion

In a group of more than 1000 juvenile diabetics in whom interventional therapy to induce remission was not attempted, the incidence of NIR remission in the first year after diagnosis was approximately 3 percent (*33*). In another group of diabetics, in whom the artificial endocrine pancreas was used to normalize glycemia, there was a high incidence of plasma C-peptide concentrations returning to normal (*39*). In a subsequent study, however, this effect was found to be short-lived (*40*). Although immunosuppressive therapy with steroids, azathioprine, antilymphocytic globulin (*17*), and antithymocytic globulin (*41*) has been attempted in type I diabetics, NIR remissions in the percentage and with the duration seen in this study have not been reported. Although partial recovery of β cell function usually occurs after metabolic stabilization, the Steno Hospital group has shown in unpublished studies that the mean C-peptide concentration declines progressively after approximately 3 months of diabetes. It appears that the maintenance of poststimulatory C-peptide concentrations within the normal range for up to 1 year (mean duration of Cy therapy 209 ± 15 days) in a group of patients with IDDM is unprecedented. Even in our group 2 subjects, where presumably a greater degree of β cell

destruction had occurred, the mean C-peptide levels (basal and poststimulatory) did not decline during the period of Cy therapy. A C-peptide concentration greater than 0.6 pmole/ml after stimulation has been recognized by the Steno Hospital group as the minimum response characteristic of the NIR diabetic receiving conventional management (*38*), and in the present study this appeared to be the critical concentration that permitted but did not predict the NIR state.

Our NIR patients remained carbohydrate intolerant. In three out of six patients, the use of oral hypoglycemic agents might have contributed to the attainment of target levels of glycemia. Intermittent hyperglycemia in NIR subjects was not associated with consistent reduction of plasma C-peptide levels and was sometimes related to infection or stress. However, after these data were analyzed and before submission of this manuscript, two of the patients became hyperglycemic and resumed insulin treatment, one transiently. It is not possible to determine under clinical conditions what proportion of the subjects would require insulin therapy under stricter conditions of management with diet and exercise. Thus the significance of the lack of a difference between the C-peptide values of the IR and NIR subjects in group 1 remains to be elucidated.

The results of our study support the theory of an autoimmune pathogenesis for type 1 diabetes mellitus. Whether the effects of Cy will be sustained is unknown, but the relapsing-remitting course of most autoimmune diseases suggests that relapse will occur in a significant number of the patients when Cy administration is discontinued. The optimum dosage and duration of therapy remain to be determined. It is also clear that methods for early detection of immune responses against islet cells would have to be developed in order to allow immunosuppressant intervention prior to irreversible β cell damage.

We conclude that a controlled trial of Cy should be conducted to confirm and quantify the effects observed in our study and to determine whether the benefits of Cy therapy exceed the risks. Cyclosporine is not a benign agent and its generalized use for the management of type I diabetes should not be initiated before clinical benefit has been demonstrated conclusively.

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