Glucose Counterregulation in Pre-School-Age Diabetic Children With Recurrent Hypoglycemia During Conventional Treatment

P. BRAMBILLA, P. F. BOUGNERES, J. V. SANTIAGO, J. L. CHAUSSAIN, A. POUPLARD, AND L. CASTANO

SUMMARY

To determine whether immature or defective glucose counterregulation was responsible for the severe recurrent hypoglycemic episodes (3.6 per patient per year) observed during conventional therapy (CT) in six pre-school-age diabetic children, we investigated their metabolic and hormonal responses to insulin infusion (40 mU/kg i.v. for 60 min). Counterregulation was considered adequate because no patient experienced symptoms requiring discontinuation of the test, and blood glucose (BG) nadirs averaged 42 ± 5 mg/dl. Glucose production rate decreased from 4.2 ± 0.2 to 2.6 ± 0.6 mg · kg^{-1} · min^{-1}. Blood 3-hydroxybutyrate levels were elevated (~ 3 mM) and did not change during insulin infusion. The responses of epinephrine (from 137 ± 37 to 393 ± 143 pg/ml), norepinephrine (from 145 ± 33 to 347 ± 152 pg/ml), and growth hormone (from 6.0 ± 1.5 to 20.3 ± 5.1 ng/ml) were normal for this age group. As previously observed in diabetic adults, glucagon response was deficient (from 117 ± 30 to 114 ± 18 pg/ml). The six children were subsequently treated with continuous subcutaneous insulin infusion (CSII), which resulted in a 20-fold decrease in the number of severe hypoglycemic reactions. Predisposition to severe hypoglycemia in this subset of diabetic children, which remains a refractory problem even after considerable efforts have been made to decrease them, may thus be sharply decreased with CSII therapy. During this therapy, a significant inverse correlation appeared between the individual frequency of BG values <40 mg/dl and BG nadir during the insulin infusion test (r = .94, P < .001). We conclude that the glucose counterregulatory status evaluated by a simple standardized insulin-infusion test can predict the risk of developing hypoglycemia during CSII in young diabetic children, as proposed previously in adults. *Diabetes* 36:300–304, 1987

From the U.188 INSERM et Service d'Endocrinologie Pédiatrique, Hôpital St. Vincent de Paul, Paris, France, and the Division of Endocrinology and Metabolism, Department of Pediatrics, Washington University School of Medicine, St. Louis, Missouri.

Address correspondence and reprint requests to P.F. Bougneres, U.188 INSERM, Hôpital St. Vincent de Paul, 74, avenue Denfert Rochereau, 75014 Paris, France.

Received for publication 13 May 1986 and accepted in revised form 23 September 1986.

Marked lability of blood glucose concentrations is common among children treated for insulin-dependent diabetes (IDDM) (1). In a few, recurrent episodes of severe hypoglycemia remain a major clinical problem even after standard efforts directed at achieving more stable blood glucose control (1,2). Although there are many potential causes for severe hypoglycemia among insulin-treated diabetic subjects, a subset of adult diabetic subjects has been defined who demonstrate defective glucose counterregulatory responses during sustained hyperinsulinemia (3,4). Subjects with this defective response, when placed on highly intensive treatment regimens, develop severe hypoglycemia 10–20 times more often than subjects with normal glucose counterregulatory responses (3–5).

Hormonal counterregulatory responses to insulin-induced hypoglycemia have not been studied in detail in pre-school-age children with IDDM. Glucagon and epinephrine secretion during hypoglycemia have been proposed as the predominant mechanisms that defend against insulin-induced hypoglycemia (6,7). In adults and adolescents, defective glucagon and epinephrine responses are associated with a longer duration of diabetes and autonomic neuropathy (8,9). Our study was designed to determine whether defective glucose counterregulatory responses during sustained moderate hyperinsulinemia could partly account for the occurrence of recurrent severe hypoglycemia in six pre-school-age children with overt IDDM of ~1–2 yr duration.

METHODS

Subjects. Six 18- to 57-mo-old children (3 boys, 3 girls) with known IDDM for 13–27 mo were studied. All had plasma glucose levels >150 mg/dl and simultaneous plasma C-peptide values <0.1 pmol/ml after an overnight fast.

TABLE 1
Clinical characteristics of the six diabetic children at time of insulin-infusion test

	Mean ± SE	Range
Age (mo)	37 ± 6	18–57
Weight (% ideal body wt)	103 ± 2	98–108
Duration of treatment (mo)	43 ± 4	29–53
CT	19 ± 4	13–27
CSII	24 ± 3	13–30
Insulin dose ($U \cdot kg^{-1} \cdot day^{-1}$)		
CT	0.99 ± 0.2	0.7–1.3
CSII	0.97 ± 0.1	0.8–1.2

After the insulin-infusion test, children were switched from conventional therapy (CT) to continuous subcutaneous insulin infusion (CSII).

Four age- (34 ± 7 mo) and sex- (2 boys, 2 girls) matched nondiabetic controls without family histories of diabetes were also studied. All studies were performed after informed parental consent under a protocol approved by the medical ethics committee of INSERM.

Clinical characteristics of the patients are summarized in Table 1. All had a history of severe recurrent hypoglycemia (loss of consciousness, seizure, and need for intravenous glucose or glucagon) despite repeated efforts to achieve clinical improvement. These efforts included hospitalization on a metabolic ward, use of two daily insulin injections adjusted on the basis of three or more daily capillary blood glucose measurements, individually calculated diets, and extensive training and motivation of patients and family members. All were treated with highly purified pork insulin (Actrapid and Monotard, Novo, Copenhagen, Denmark), and none had any other known medical problems.

Insulin-infusion test protocol. Each subject underwent a modification of a previously described insulin-infusion test to assess glucose counterregulatory status (3). Briefly, the test calls for withdrawal of longer-acting insulin preparations and rapidly absorbed insulin at least 24 and 12 h, respectively, before each study. Blood glucose was maintained between 60 and 100 mg/dl throughout the night and early morning with an intravenous infusion of insulin adjusted every 30–60 min based on bedside capillary blood glucose measurements. At 0730 h (t_0), a continuous infusion of 6,6-[$^2H_2$]glucose tracer was begun and maintained to achieve a 1–3 mol percent excess enrichment of plasma glucose and permit measurement of glucose utilization and production rates.

At 0900 h (t_{90}), the feedback-controlled intravenous insulin infusion was interrupted, and a constant intravenous infusion of regular pork insulin at an hourly rate of 40 mU/kg body wt was begun and continued for 1 h until the end of the study. All syringes and tubings were rinsed previously with the insulin and diluting medium supplied by the manufacturer (Novo). Arterialized blood (0.5 ml) was obtained every 15 min for immediate plasma glucose analysis at the bedside and for later measurement of isotope enrichment and β-hydroxybutyrate concentrations. An additional 5-ml baseline blood sample was obtained at 0900 h and at the end of the study for measurement of plasma free-insulin and fatty acid concentrations and the counterregulatory hormones glucagon, cortisol, growth hormone, epinephrine, and norepinephrine. Anti-insulin and antiadrenomedullary cell antibodies in the plasma were also measured in each subject.

The infusion test was carried out under the supervision of a physician who constantly monitored each subject's neurologic status. Subjects who remained well oriented and alert during the infusion and who also maintained blood glucose levels >30 mg/dl were considered to have adequate glucose counterregulation. The 30-mg/dl value is the lower limit of the range in normal children. This value is lower than the 35 mg/dl used by White et al. (3) in adults and reflects the lower fasting glucose concentrations normally seen in 3- to 6-yr-old children (10). Subjects who became disoriented or lethargic, who exhibited abnormal behavior at any time, or whose blood glucose levels fell to or below 30 mg/dl without a rise during the subsequent 15 min were considered to have defective glucose counterregulation; when this occurred, the insulin infusion was stopped immediately and glucose was given intravenously.

Follow-up intensive treatment with continuous subcutaneous insulin infusion (CSII). After completion of the insulin-infusion test, the children were placed on pump therapy. The protocol used to initiate CSII has been described elsewhere (11). Briefly, pump therapy (Microjet MC 20, Ames, Elkhart, IN) was begun at the usual total daily dose used during conventional therapy. The basal rate was initially set at 40%, and four equal premeal boluses were given at 15% of the daily dose 15 min before the meals. Basal rates and bolus doses were adjusted as necessary on the basis of seven blood glucose concentrations, mea-

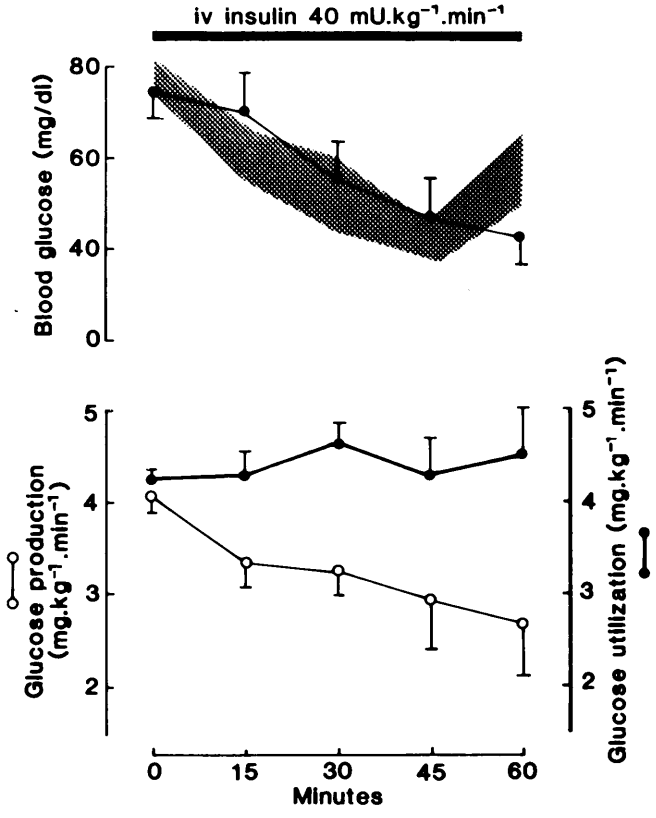

FIG. 1. *Top*: time course of blood glucose concentration in diabetic children during insulin-infusion test. *Hatched area*, ± 1 SD from mean in normal controls. *Bottom*: responses of glucose production and utilization rates to insulin-infusion test in diabetic children.

sured at 0730, 1000, 1200, 1600, 1930, 2200, and 0300 h during the hospital stay.

The children were discharged from the hospital after 6–12 days, as soon as both the blood glucose profile and parental training appeared to be satisfactory. During the first 2 wk, we requested the parents to measure and record the capillary blood glucose concentration before each meal and every day at 0300 h. If the blood glucose concentration was <60 mg/dl at these times, the basal rate of CSII was decreased by 10% and then readjusted. They were instructed to call the physician in charge of the program once weekly for adjustment of the insulin dose. The initial return visit was scheduled in 2 wk, with subsequent visits every 4–6 wk. After stabilization, two daily measurements of capillary blood glucose were requested at varying hours, and one monthly measurement of nocturnal blood glucose was required. At monthly outpatient visits, long-term metabolic control was assessed by measurement of glycosylated hemoglobin levels. At these visits, episodes of severe hypoglycemia and clinical circumstances surrounding any adverse events were recorded, and logs recording all home glucose measurements were reviewed. Severe hypoglycemia was defined as any episode causing seizure or loss of consciousness or requiring glucagon injection or intravenous glucose.

Analytical methods. Blood glucose concentrations were determined with a glucose dehydrogenase method. The rates of production and disposal of blood glucose were calculated from the non-steady-state approximation equation of Steele et al. (12), as modified by De Bodo et al. (13), with extracellular volume estimated from the pediatric data of Widdowson and Dickerson (14). The baseline rate of glucose production was calculated from the mean of 80- and 90-min values of plasma [$^2H_2$]glucose enrichment (15). Plasma insulin concentrations were measured by radioimmunoassay, and free insulin was measured after polyethylene glycol precipitation with intra- and interassay coefficients of variation <10% (17). Plasma concentrations of cortisol, growth hormone, and glucagon were measured by radioimmunoassays, and plasma epinephrine and norepinephrine were determined by a single-isotope derivative assay (18).

Serum samples were tested for antiadrenomedullary cell antibodies by indirect immunofluorescence with human adrenal tissue as antigens (16). After a first incubation step of the patient's serum with 5-μm cryostat sections, fluorescein isothyocyanate–labeled anti-human IgG was added (16). Insulin antibody binding was determined by a modification of the method of Kuzuya et al. (17).

Glycosylated hemoglobin concentrations (HbA_{1c}) were measured by an automatic chromatographic technique giving a normal value of 4.7 ± 0.7% (19). Data are expressed as means ± SE. Paired and, when appropriate, unpaired Student's *t* tests were used for evaluation of statistical significance. Correlation coefficients were calculated by the least-squares method. The average rate of decrease of blood glucose during hypoglycemia was calculated by dividing the differences between baseline and nadir blood glucose values by the time interval.

TABLE 2
Counterregulatory hormone responses to insulin-induced hypoglycemia in diabetic children and nondiabetic age-matched controls

	Diabetics (N = 6)	Controls (N = 4)
Glucagon (pg/ml)		
Basal	117 ± 30	89 ± 21
At 60 min	114 ± 18	128 ± 42
Epinephrine (pg/ml)		
Basal	137 ± 37	217 ± 72
At 60 min	392 ± 143	533 ± 227
Norepinephrine (pg/ml)		
Basal	145 ± 33	103 ± 44
At 60 min	347 ± 152	405 ± 169
Growth hormone (ng/ml)		
Basal	6 ± 1.5	6 ± 4
At 60 min	20 ± 5	19.5 ± 5
Cortisol (μg/dl)		
Basal	21 ± 2	13.5 ± 3
At 60 min	20 ± 2	13 ± 3

RESULTS

Baseline observations. After the overnight variable-rate insulin infusion in the diabetic subjects, plasma glucose during the baseline period (0730–0900 h) was almost identical in the diabetic (75 ± 6 mg/dl) and normal (76 ± 4 mg/dl) children. Similarly, the rates of glucose utilization and production were stable during the baseline period (Fig. 1) and within the normal range for normal children of this age group (15).

At baseline, plasma free fatty acids were similar in the normal (0.41 ± 0.07 mM) and diabetic (0.49 ± 0.07 mM) children. Blood 3-hydroxybutyrate was higher in the diabetic (3.4 ± 0.3 mM) than in normal (1.8 ± 0.2 mM) children ($P < .001$). Baseline concentrations of epinephrine, norepinephrine, growth hormone, cortisol, and glucagon were similar ($P > .10$) in the diabetic and control subjects (Table 2).

Baseline free-insulin levels in the diabetic children averaged 11 ± 4 μU/ml. Insulin binding of diabetic serum was 40 ± 6% in the diabetics (range 16–60%). Five of the six diabetic subjects, but none of the controls, had circulating antibodies that bound to human adrenal medullary membranes.

Response to insulin infusion. During the infusion of insulin at 40 mU · kg^{-1} · h^{-1}, plasma glucose declined at similar rates in both diabetic (0.95 ± 0.16 mg · dl^{-1} · min^{-1}) and nondiabetic (0.93 ± 0.09 mg · dl^{-1} · min^{-1}) subjects (Fig. 1). In the nondiabetic children, the mean nadir glucose of 38 ± 3 mg/dl occurred at 45 min and then rose to 57 ± 8 mg/dl at 60 min despite continued insulin infusion. In the diabetic children, the mean nadir glucose was similar (42 ± 5 mg/dl) but occurred at 60 min, 15 min later than in the controls. The only difference between the two groups was that three of the diabetic children had a continuous gradual decline in plasma glucose concentration throughout the test, whereas the normal children all had a postnadir rise in plasma glucose. Overall, the decline in plasma glucose was primarily due to a decrease in hepatic glucose release into plasma (Fig. 2).

None of the diabetic or normal children demonstrated any signs of neurologic impairment during the constant insulin infusion. Two diabetic subjects had plasma glucose concentrations <30 mg/dl (one was 21 and the other was 22 mg/dl). These values were increased in the next sample and were 59 and 37 mg/dl, respectively, at the end of the study.

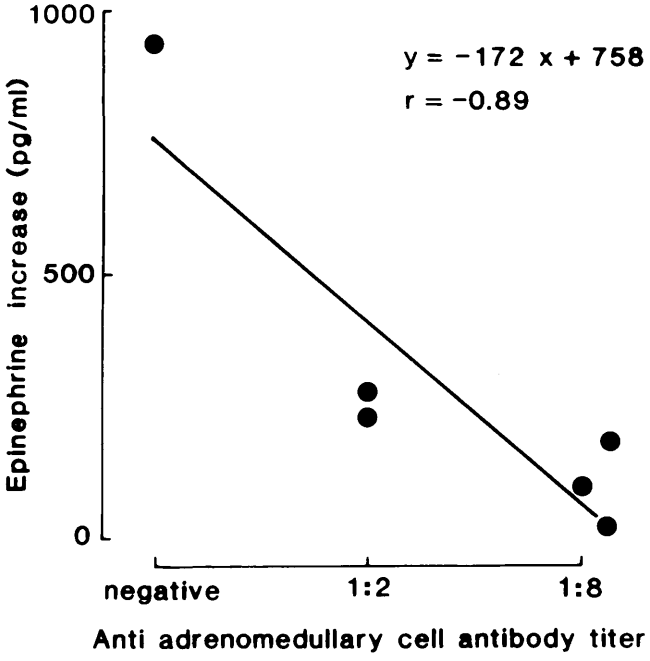

FIG. 2. Relationship between individual plasma epinephrine increase and titers of circulating antiadrenomedullary cell antibodies.

Blood 3-hydroxybutyrate levels did not change substantially in either the diabetic (2.7 ± 0.2) or control (1.8 ± 0.1 mM) subjects during the constant insulin infusion. Epinephrine, norepinephrine, and growth hormone concentrations increased in both the diabetic and control subjects at the end of the insulin infusion (Table 2). Cortisol remained unchanged in both groups. Glucagon increased only in the controls. At the end of the insulin infusion, concentrations of plasma free insulin were similar in the normal (25 ± 4 μU/ml) and diabetic (23 ± 3 μU/ml) subjects. A significant negative correlation ($r = -.89$, $P < .01$) was observed between the titer of antiadrenal medullary antibodies and the plasma epinephrine responses to insulin-induced hypoglycemia.

Response to intensive therapy. During a 13- to 32-mo follow-up, while on highly intensive therapy with an insulin infusion pump, there was a substantial fall in mean glycosylated hemoglobin concentrations from 9.0 ± 0.2 to 6.4 ± 0.3% ($P < .01$). The frequency of severe hypoglycemia decreased from a mean of 3.6 episodes per patient per year the year before the onset of pump treatment to 0.19 per patient per year during pump treatment. Less severe reactions, requiring family administration of carbohydrates or food by mouth were common during CSII. Furthermore, an average of 3.8 ± 1.6% of all recorded glucose values performed at home were ≤40 mg/dl, but treatment of suspected or obvious reactions without prior measurement of blood glucose was common. The frequency of measured blood glucose values <40 mg/dl was highly correlated with the nadir plasma glucose value during the insulin infusion test ($r = -.94$, $P < .001$), a result similar to that observed in adults by Bolli et al. (4).

DISCUSSION

Three observations made during this study merit special consideration. First, a subset of pre-school-age IDDM patients selected because of severe recurrent hypoglycemia responded favorably when changed from conventional treatment to a regimen employing CSII. Several factors could have contributed to this favorable response. *1*) The closer-to-physiologic patterns of insulinemia achieved with CSII probably reduced substantially the frequency of unphysiologic hyperinsulinemia that occurs commonly with twice-daily insulin injections. *2*) CSII probably results in less erratic insulin absorption and inadvertent hyperinsulinemia than does conventional treatment. *3*) Perhaps most important, patients treated with CSII commonly measure their blood glucose levels and adjust their insulin and diet more frequently than do patients treated conventionally, thus potentially reducing the hazards of hypoglycemia due to day-to-day and hour-to-hour fluctuations in insulin need and erratic plasma insulin levels.

Although CSII has resulted in excellent responses in carefully selected and closely supervised adults, the results in adolescents are mixed. Schiffrin et al. (20) obtained excellent results in carefully selected adolescents, whereas others have reported poor results in adolescents with serious emotional and behavioral problems (21) and in poorly motivated nonadherent adolescents (22). The excellent results obtained in our patients were partly related to the extraordinary efforts made by highly motivated, cooperative, and resourceful parents who assumed direct responsibility for day-to-day management of their children's blood glucose monitoring, diet regimen, and insulin adjustments. Obviously, this method of treatment may not be as effective in older children or in less cooperative families.

The second point that merits discussion is that the recurrent hypoglycemic episodes seen during conventional treatment could not be explained by any detectable defect in glucose counterregulation in the diabetic children studied. All children tested tolerated moderate sustained hyperinsulinemia well without the development of severe biochemical hypoglycemia. As expected, the fall in glucose concentration was due primarily to decreased hepatic glucose release. The data indicate that, as in adults (8), deficient glucagon responses are common during insulin-induced hypoglycemia, even in pre-school-age children with diabetes of short duration. Adrenergic mechanisms can largely compensate for glucagon's absence, as they did in all of the children tested (6). Furthermore, counterregulatory hormone status clearly does not predict the occurrence of hypoglycemia during conventional therapy. This point has been made previously in adults (4,5,23).

Third, the results of the insulin-infusion test predicted well the relative risk of hypoglycemia during intensive therapy employing CSII. This confirms the results of others (3,4). A practical consequence of this observation relates to the potential clinical utility of the insulin-infusion test in diabetic children. If a highly intensive regimen employing CSII is being contemplated for a given patient, the results of the test can be used to predict its potential risks. This would apply not only to children in whom CSII is being considered as a therapeutic option designed to reduce hypoglycemia, but also to those in whom this type of therapy is being used in the hope that it will reverse or prevent one or more of the long-term complications of diabetes.

Several additional comments can also be made based on

the results of this study. The absence of neurologic symptoms among the diabetic children during the test, even in those with the lowest glucose values, may partly be related to the higher than normal β-hydroxybutyrate concentrations during the test, because ketone bodies have been reported to be an excellent fuel for brain metabolism (24). The failure of insulin doses that normalize plasma glucose overnight to normalize midmorning β-hydroxybutyrate concentrations has been observed previously (25). Whether this is due to decreased ketone body utilization, increased production, or a combination of the two is not clear from this study. The data suggest, however, that a major difference in fatty acid availability does not account for the higher ketone bodies in the diabetics whose blood glucose levels have been normalized overnight with insulin.

Finally, the apparent correlation between antiadrenomedullary antibody titers and plasma epinephrine responses during hypoglycemia is interesting and requires confirmation in larger studies. The presence of these antibodies did not appear to cause a major inhibition of epinephrine release in our patients, but it could result in impaired glucose counterregulation in some patients with IDDM.

ACKNOWLEDGMENTS

We thank Dr. F. Landier for help in the preparation of the experimental protocol.

P.B. is a Research Fellow from Clinica Pediatrica (G. Chiumello) Ospedale L. Sacco (Milano).

REFERENCES

1. Baker L, Stanley CA: Diabetes in childhood. In *Endocrinology*. DeGroot LJ, Ed. New York, Grune & Stratton, 1979, p. 1057
2. Golden MP, Russell BP, Ingersoll GM, Gray DL, Hummer KM: Management of diabetes mellitus in children younger than 5 years of age. *Am J Dis Child* 139:448–52, 1985
3. White NH, Skor DA, Cryer, PE, Levandoski LA, Bier DM, Santiago JV: Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. *N Engl J Med* 308:485–91, 1983
4. Bolli GB, De Feo P, De Cosmos S, Perriello G, Ventura MM, Massi Benedetti M, Santeusanio F, Gerich JE, Brunetti P: A reliable and reproducible test for adequate glucose counterregulation in type I diabetes mellitus. *Diabetes* 33:732–37, 1984
5. Santiago JV, Clarke WL, Shah SD, Cryer PE: Epinephrine, norepinephrine, glucagon, and growth hormone release in association with physiological decrements in the plasma glucose concentration in normal and diabetic man. *J Clin Endocrinol Metab* 51:877–83, 1980
6. Gerich J, Davis L, Lorenzi M: Hormonal mechanisms of recovery from insulin-induced hypoglycemia in man. *Am J Physiol* 236:E380–85, 1979
7. Cryer PE, Gerich JE: Relevance of glucose counterregulatory systems to patients with diabetes: critical roles of glucagon and epinephrine. *Diabetes Care* 6:95–99, 1983
8. Bolli GB, De Feo P, Compagnucci P, Cartechini MG, Angeletti G, Santeusanio F, Brunetti P, Gerich JE: Abnormal glucose counterregulation in insulin-dependent diabetes mellitus: interaction of anti-insulin antibodies and impaired glucagon and epinephrine secretion. *Diabetes* 32:134–41, 1983
9. White NH, Gingerich RL, Levandoski LA, Cryer PE, Santiago JV: Plasma pancreatic polypeptide response to insulin-induced hypoglycemia as a marker for defective glucose counterregulation in insulin-dependent diabetes mellitus. *Diabetes* 34:870–75, 1985
10. Haymond MW, Karl IE, Clarke WL, Pagliara AS, Santiago JV: Differences in circulating gluconeogenic substrates during short-term fasting in men, women, and children. *Metabolism* 31:33–42, 1982
11. Bougneres PF, Landier F, Lemmel C, Mensire A, Chaussain JL: Insulin pump therapy in young children with type I diabetes. *J Pediatr* 105:212–16, 1984
12. Steele R, Wall J, De Bodo C, Altszuler N: Measurement of size and turnover rate of body glucose pool by the isotopic dilution method. *Am J Physiol* 187:15, 1956
13. De Bodo R, Steele R, Altszuler R, Dunn A, Bishop J: On the hormonal regulation of carbohydrate metabolism: studies with ^{14}C glucose. *Recent Prog Horm Res* 19:445–61, 1963
14. Widdowson EM, Dickerson JWT: The chemical composition of the body. In *Mineral Metabolism*. Vol. 2A. Comar C, Bronner F, Eds. New York, Academic, 1964, p. 1
15. Bier DM, Leake RD, Haymond MW, Arnold KJ, Gruenke LD, Sperling MA, Kipnis DM: Measurement of "true" glucose production rates in infancy and childhood with 6,6-dideuteroglucose. *Diabetes* 26:1016–23, 1977
16. Schopfer K, Matter L, Tenschert R: Anti-glucagon cell and anti-adrenalmedullary cell antibodies in islet cell autoantibody positive diabetic children. *N Engl J Med* 310:1536–37, 1984
17. Kuzuya H, Blix PM, Horwitz DL, Steiner DF, Rubenstein AH: Determination of free and total insulin and C-peptide in insulin-treated diabetics. *Diabetes* 26:22–29, 1977
18. Cryer PE, Santiago JV, Shah S: Measurement of norepinephrine and epinephrine in small volumes of human plasma by a single isotope derivative method response to the upright posture. *J Clin Endocrinol Metab* 39: 1025–29, 1974
19. Wacjman H, Dastugue B, Labie D: Quantitation of hemoglobin A_1C: a rapid automated precision chromatography technique. *Clin Chim Acta* 92:33–37, 1979
20. Schiffrin A, Desrosiers M, Moffatt M, Belmonte MM: Feasibility of strict diabetes control in insulin-dependent diabetic adolescents. *J Pediatr* 103:522–27, 1983
21. Riley WJ, Silverstein JH, Rosenbloom AL, Spillar R, McCallum MH: Ambulatory diabetes management with pulsed subcutaneous insulin using a portable pump. *Clin Pediatr* 16:609–13, 1980
22. Daneman D, Epstein DH, Siminiero L, Beck S, Farkas G, Figueroa J, Becker DJ, Drash AL: Effects of enhanced conventional therapy on metabolic control in children with insulin-dependent diabetes mellitus. *Diabetes Care* 5:472–78, 1982
23. Polonsky K, Bergenstal R, Pons G, Schneider M, Jaspan J, Rubenstein A: Relation of counterregulatory responses to hypoglycemia in type I diabetics. *N Engl J Med* 307:1106–12, 1982
24. Settergren G, Lindblad BS, Persson B: Cerebral blood flow and exchange of oxygen, glucose, ketone bodies, lactate, pyruvate and amino acids in infants. *Acta Paediatr Scand* 65:343–53, 1976
25. Griffin NK, Spanos A, Jenkins PA, Turner RC, Werther G, Baum JD: 24-Hour metabolic profiles in diabetic children. *Arch Dis Child* 55:112–17, 1980