Insulin Therapy in the Last Decade

A pediatric perspective

JULIO V. SANTIAGO, MD

The purpose of this review is to provide a personal perspective of changes in the treatment of childhood diabetes in the last decade. The commentary is based on the clinical and research experiences of our group at St. Louis Children's Hospital at the Washington University Medical Center in St. Louis, Missouri.

The current referral patterns in our region were influenced by Dr. Alexis Hartman, who served as the chief diabetologist at St. Louis Children's Hospital from 1930 to 1963. He felt strongly that all diabetic children should be trained and monitored by experienced pediatric diabetologists. Responsibility for diabetes care in children in our region has remained largely with one of two university-based diabetes teams and a limited number of diabetes specialists, rather than with the general pediatrician or family practice physician.

The introduction of human insulin was one of many changes in diabetes care made during the last decade in North America and western Europe. Consequently, daily self-monitoring of blood glucose replaced urine glucose monitoring, GHb assays were introduced to assess long-term metabolic control (2), sophisticated diabetes care teams were developed to provide individual, family-based training and follow-up care (3), and attempts were made to transfer an increasing proportion of the day-to-day responsibilities for diabetes care directly to the family (4). This commentary will focus on several practical issues in diabetes care directly related to the introduction of human insulin. Subsequently, specific examples of the increasingly complex nature of diabetes self-care will be discussed, with special emphasis on changes made as part of our effort to transfer increasing responsibility for daily care to the carefully trained and closely supervised family.

INSULIN ALLERGY— As recently as the early 1970s, ~30% of children treated with mixtures of beef and pork insulin developed areas of local reddening, itching, and inflammation within the first few months after initiating insulin treatment. Those who developed this complication often proceeded to develop lipoatrophy at insulin injection sites. With the introduction of more highly purified pork insulin preparations in the mid- and late-1970s, these localized skin reactions and less common systemic allergic reactions decreased rapidly. Indeed, preexistent lipoatrophy could be reversed simply by injecting any highly purified pork or human insulin directly into the margins of lipoatrophic skin (5). Insulin lipoatrophy and allergic reactions were attributable to impurities in the older insulin preparations rather than to the species of insulin used. We have not seen a single case of severe skin lipoatrophy in over five years, even among users of beef-pork insulins, and very few patients complain of reddening or itching at injection sites.

Infrequent, localized skin reactions occur occasionally and sometimes are associated with the failure to allow previously refrigerated insulin to warm to room temperature before injection. In the past decade, systemic, life-threatening insulin allergy has been a very rare finding. The most common skin reaction to insulin is lipohypertrophy, which occurs when any insulin is injected into the injection site repeatedly. This is an avoidable problem that is resolved by proper rotation of injection sites in patients who show early changes of lipohypertrophy.

INSULIN RESISTANCE— In the early 1970s, we would see a few children every year with unusually large total daily insulin requirements (>2.0 U/kg body weight) and high titers of insulin antibodies, often with highly labile diabetes. Some of these patients' apparent insulin resistance was attributable to binding of injected insulin to circulating antibodies. These antibodies blunted free plasma insulin increments after injection and, thus, contributed to postprandial hyperglycemia. However, high-affinity and high-capacity antibodies also served as functional reservoirs for insulin release hours or days after insulin injection. This resulted in nocturnal hypoglycemia or reduced nighttime insulin requirements

From the Division of Pediatric Endocrinology and Metabolism, Edward Mallinckrodt Department of Pediatrics and St. Louis Children's Hospital, and the Diabetes Research and Training Center, Washington University School of Medicine, St. Louis, Missouri.

Address correspondence and reprint requests to Julio V. Santiago, MD, Department of Pediatrics, St. Louis Children's Hospital, One Children's Place, St. Louis, MO 63110.

IDDM, insulin-dependent diabetes; DCCT, Diabetes Control and Complications Trial; DKA, diabetic ketoacidosis; CHO, carbohydrate.

in some patients. The diagnosis of insulin resistance caused by an excess of antibodies is now rare, presumably because of the introduction and exclusive use of highly purified pork, beef-pork, or human insulin preparations. Occasionally, we still see rare patients who require >2.0 U/kg of insulin daily. Most are on corticosteroid treatment or are obese. A few have severe learning disabilities or psychiatric problems with a mysterious disappearance of insulin resistance when hospitalized that raises doubts as to their true insulin administration at home.

We continue to monitor one patient who does not have elevated insulin antibody titers and who has shown an excessive clearance of both intravenously and subcutaneously injected insulin. However, as is the experience of others, most patients evaluated for the syndrome of excessive degradation of subcutaneously injected insulin do not have this syndrome at all (6–9). The syndrome of excessive insulin degradation may exist but is less common than brittle diabetes or apparent or real insulin resistance that is caused by recurrent infection, manipulative or self-destructive behavior, or insulin resistance from rare syndromes.

INSULIN DOSES DURING THE HONEYMOON PERIOD — During the first few weeks after diagnosis, insulin requirements commonly decrease substantially as endogenous insulin secretory capacity is restored during the honeymoon phase of IDDM. We observe this phenomenon more frequently now than in the 1970s. This may be attributable, in part, to earlier diagnosis of IDDM. However, it also may be a result of more intensive insulin treatment regimens, which help preserve endogenous insulin secretion for months to years after the initial diagnosis of IDDM (10,11). Long-term maintenance of this residual insulin secretory capacity is more pronounced in adults than in children. However, it still commonly results in dramatic reductions in the insulin need during the first year after diagnosis, even in the preadolescent child.

Persistence of endogenous insulin secretory capacity can be measured by assays for C-peptide after glucagon injection or meals. Persistent C-peptide secretion can be an important determinant of insulin requirements and metabolic stability during the first months or years after diagnosis of IDDM. Several practical consequences should be noted. First, endogenous insulin substantially facilitates the implementation of highly intensive treatment regimens. We inform families of this potential benefit to help motivate them to try to maintain optimal metabolic control during the months and first few years after diagnosis.

More importantly, we alert families to the consequences of waning endogenous insulin secretion so that they can anticipate having to increase insulin dosage at some undetermined time during the first two years after diagnosis. As the honeymoon period comes to an end, reviewing the fundamentals of insulin-dose adjustments and negotiating more realistic target blood glucoses for the posthoneymoon period is advisable. Although usually gradual, the end of the honeymoon period can be precipitated by an acute episode of severe hyperglycemia with ketosis, resulting from intercurrent infection or missed injections. Patients frequently present to us 6–24 mo after diagnosis of IDDM with several weeks or months of poor control that were not brought to our attention or attended to with appropriate upward adjustments in insulin dosage. Obviously, such instances represent communication failures that should be prevented simply by anticipating their occurrence.

The end of the honeymoon period often is frustrating for the family and staff, what worked at 1–6 months after diagnosis no longer works at 6–24 months. Patients, families, or staff mistakenly assume that all posthoneymoon deteriorations in metabolic control are solely attributable to reduced adherence to the assigned treatment regimen or that higher blood glucoses are ominous portents of bad times ahead. The child or adolescent with IDDM who continues to feel fine despite unexplained higher glucoses may be tempted to cheat or fabricate glucose monitoring test results during this period (12). Some patients fail to disclose results to avoid what they know, or intuit, will result if they report monitoring data that reflects deteriorating control. The posthoneymoon fabrication syndrome commonly presents as a patient with stable, rounded, and safe numbers (e.g., 120, 140, 160 mg/dl) but with an unexplained, paradoxical deterioration of GHb concentrations.

INSULIN DURING PUBERTY AND EXERCISE — Insulin doses often increase 20–30% during puberty. The relative insulin resistance that accompanies puberty is closely correlated with increased concentrations of sex hormones and growth factors (13,14). These changes occur about two years earlier in girls than in boys and coincide with pubertal increments in growth velocity. Cyclic variations in insulin requirements during the menstrual cycle are only occasionally noted by our patients, probably because they monitor less often and are less tightly controlled than older females using more intensive management methods.

Dramatic reductions in insulin dosage often occur during periods of markedly increased physical activity. This is especially apparent at summer camps for children with diabetes where insulin doses are often reduced 25–50%, despite a marked increase in food intake. These reductions in insulin needs are obviously attributable to markedly increased levels of physical activity in previously sedentary children. Increased insulin requirements often are seen when previously active children become less active during long trips, at the end of summer, or after the end of a sports season. Marked changes in insulin requirements

resulting from changes in physical activity require close attention, with added glucose monitoring and frequent insulin-dose adjustments for 1–2 weeks. Severe hypoglycemia often increases during the spring as activity levels increase.

TOTAL DAILY INSULIN REQUIREMENTS— Mean insulin dosages (expressed as U administered daily/kg body weight) were 0.93 and 0.96 U/kg in 1981 and 1991, respectively, among several hundred children followed in our center's diabetes registry. The failure to note a substantial decrease in total daily insulin doses, despite an increased use of pork and human insulin preparations of increased purity, is hard to interpret because mean GHb concentrations declined ~1.5% during this period. Insulin bound to circulating antibodies during the day may be released as free insulin during the night. Thus, lower insulin antibody titers may paradoxically increase nocturnal insulin requirements. Today, patients presenting with elevated GHb values that indicate mean blood glucoses >300 mg/dl frequently are given more insulin than they were a decade ago. Furthermore, we now know that daily insulin doses >1.0 U/kg are often required during puberty and in obese patients with sedentary life-styles. Thus, we often employ doses >1.0 U/kg if no evidence is found that these patients are experiencing recurrent hypoglycemia. This practice is at variance with recommendations made earlier by others; such advise created a functional barrier to giving adolescents the insulin they needed. However, we concur with the view that excessive insulin administration is a common cause of recurrent hypoglycemia in IDDM children treated by inexperienced physicians attempting to normalize blood glucoses or GHb concentrations.

SWITCHES TO HUMAN INSULIN: WHO, WHEN, AND THE CONSEQUENCES— We use human insulin in all of our newly diagnosed children and in many children still using beef-pork insulin who are in unsatisfactory metabolic control admitted to the hospital for reeducation or establishment of improved control. This is, in part, driven by economic realities that have reduced the costs of human insulin to near or below that of pork insulin. However, in view of the rarity of problems with insulin allergy or immunological insulin resistance with currently available pork insulins, children doing well on animal insulins (pork or beef-pork) are not routinely switched to human insulin in our practice. Unsupervised or poorly monitored switching between species or brands of insulin are discouraged.

When we do change brands or species of insulin, we advise patients and their families that the new formulation may have different absorption patterns. Generally, human insulins tend to be absorbed more rapidly than animal insulins and, thus, have a slightly shorter duration of action (15). These pharmacological differences result in common scenarios. First, prelunch hypoglycemia may increase because of more rapid absorption of NPH insulin injected before breakfast. This usually is apparent when breakfast and lunch are ≥ 4 h apart, and no midmorning snack is taken. Typically, these children end up taking a small dose of Regular insulin before breakfast rather than the frequently recommended 1 part Regular-to-2 part NPH mixture (16). Second, presupper or prebreakfast hyperglycemia may develop because of the more rapidly waning effects of NPH insulin given before breakfast or the previous evening. Third, some patients present with nocturnal hypoglycemia when the evening NPH is increased to lower elevated prebreakfast blood glucoses (17). Very rarely, patients switched to less-immunogenic forms of insulin may have to lower insulin requirements for several weeks after switching to human insulin.

COUNTERING ANTI-HUMAN INSULIN HYSTERIA— We stress to patients that differences in absorption characteristics among various insulin formulations are to be expected and that human insulin, of itself, does not cause hypoglycemia unawareness (18). We find this necessary because of the anxiety produced by recent claims that human insulin is inherently more dangerous than pork insulin (19). We point out to patients that symptoms of hypoglycemia frequently change with time, sometimes in unexpected or subtle ways. These changes can occur regardless of the species of insulin used (20,21). A reduction in symptoms or gradual evolution of warning signs of hypoglycemia from adrenergic to neurogenic presentations often occurs when mean blood glucose values are lowered or after repeated episodes of hypoglycemia (20–22).

We feel that regional epidemics of hypoglycemia unawareness and severe hypoglycemia in some countries in Europe during the 1980s may have resulted from overzealous treatment by well-meaning physicians (19). A high rate of severe hypoglycemia occurred in the DCCT in the mid-1980s and was greatly reduced in the late 1980s, even though the use of human insulin increased substantially during this time (22). The apparent reduction in severe hypoglycemia and hypoglycemia unawareness noted by some after transfer of patients from human to pork insulin may have been attributable to factors other than a switch in the species of insulin used. Such factors may have included raising glucose targets and increasing patient awareness and preventive measures to reduce severe hypoglycemia.

INSULIN ADMINISTRATION: FREQUENCY AND PATTERNS

The role of the predawn and dawn phenomena

In the early 1980s, 25% of our patients were prescribed one daily injection of

insulin, 74% with 2 daily injections, and <1% with 3 daily injections. Almost all of these patients were on Regular and NPH insulin. We have not used Lente insulins because of the concern that they are less compatible when mixing with Regular insulin. By 1991, <1% of our IDDM patients with >1-year duration of IDDM were on 1 daily injection of insulin, ~88% were on 2, and 11% were on ≥3 daily injections. Most of our patients are still on Regular and NPH insulin, except for ~4% who have begun using Ultralente human insulin in the last 3 years.

The most impressive trend in our center is an increased use of a third insulin injection at bedtime, either NPH or Ultralente insulin. At least two reasons have caused these changes. Because of the pharmacokinetics of NPH absorption, insulin levels frequently are higher at 2400–0200 than at 0600–0800. However, because the amount of insulin required to maintain normoglycemia is lower at 2400–0200 than at 0600–0800, simply increasing the presupper dose of NPH increases the risk of hypoglycemia in the early morning (23). Although many of these episodes of predawn hypoglycemia do not awaken the children, they sometimes result in nocturnal seizures. Indeed, we recommend that 0100–0200 glucoses be measured routinely whenever more insulin is given to reduce prebreakfast hyperglycemia or when children are suspected of having had silent, early-morning hypoglycemia because of the presence of frequent prebreakfast glucoses <100 mg/dl with ketonuria.

We and others have shown that many adult patients with recurrent nocturnal hypoglycemia have impaired glucose counterregulatory responses attributable to combined defects in glucagon and epinephrine responses during hypoglycemia (24). Increasing the bedtime snack will sometimes prevent this early morning hypoglycemia, especially if the snack is high in protein. Thus, a high-protein snack at bedtime usually is the first step when attempts to reduce prebreakfast hyperglycemia result in early morning hypoglycemia. Parenthetically, ingested proteins at bedtime may exert their benefit in adults by substantially increasing plasma amino acid and glucagon levels (25). Presumably, the same thing happens in children. Normal or exaggerated glucagon responses to amino acids and some nonhypoglycemic stimuli are common in IDDM, even after the ability to produce glucagon in response to hypoglycemia is lost.

When increasing bedtime protein intake is not enough to prevent early morning hypoglycemia, the presupper Regular insulin is maintained but the presupper NPH is moved and given as a third dose at bedtime. This NPH dose is titrated until satisfactory prebreakfast control is achieved and 0100–0300 blood glucoses are monitored to rule out hypoglycemia during the predawn period. In the 1980s, much attention was paid to dawn hyperglycemia. Today, we worry more about predawn hypoglycemia because >50% of all episodes of severe hypoglycemia occur during sleep (22).

Increasingly, we are turning to other alternatives to avoid predawn hypoglycemia and dawn hyperglycemia. One attractive, nondietary alternative uses Ultralente human insulin before supper or at bedtime. To avoid the need for a third injection, some centers have reverted to using pork NPH insulins in patients taking twice-daily human insulin injections who experience early morning hypoglycemia. Families are often reluctant to switch to a three-injection regimen as it disrupts their routine. Most accept it when the rationale and potential benefits are explained.

PENS, JET INJECTORS, AND PUMPS— Despite current widespread use in many European centers, pen injectors have not become popular in the United States and, currently, are used only occasionally in our center. Theoretically, pen injectors should increase both accuracy and convenience. The main disadvantage is that currently available pen injectors do not readily allow dose-to-dose modification of the proportions of rapidly absorbed and longer-acting insulins. Thus, we ask that most families continue to mix Regular and NPH insulin immediately before each injection. This choice is clearly driven by our goal to make the treatment regimen responsive to unexpected variations in individual glucose measurements and to encourage dose-to-dose adjustments in insulin in anticipation of meals or exercise. We do use pen injectors with premixed proportions of Regular and NPH insulin in specific situations. These include situations in which there is a threat of a major error in mixing or when it is thought impractical to expect poorly motivated or unreliable patients to titrate individual proportions of Regular and NPH insulin.

Use of pen injectors for injection of Regular insulin before each meal is more common in college age or adult patients who opt for more intensive or more flexible treatment regimens. Clearly, our current recommendations are likely to undergo modification if the DCCT and other studies show that more intensive regimens improve metabolic control and reduce early microvascular complications in IDDM or if pen injectors that allow adjustment of the proportions of different insulins become available. Scenarios where both quality of life and metabolic control can be improved with the use of pen injectors are not difficult to envision.

Various jet injectors have been developed during the last decade but are not commonly used in our center. Although jet injectors may have theoretical advantages associated with increased accuracy, wider subcutaneous dispersion, and somewhat faster absorption of insulin, they are cumbersome and often traumatize the skin. In our center, most of the few patients who have purchased these very expensive devices, against our

advice, do not continue to use them long term. We generally prefer to deal with injection phobias directly rather than resorting to jet injectors in younger children. Simply stated, in most cases, we do not view these gadgets as cost-effective or necessary.

Very few of our pediatric patients currently use subcutaneous insulin infusion pumps. In the early 1980s, we, like others, found that these devices were unnecessary for most children with difficult-to-control IDDM and were contraindicated in patients who could not be counted on to follow a highly complex treatment regimen because of poor adherence or emotional problems (26). Adequately controlled, more reliable children rarely expressed a preference for use of these devices, if they were free of coercion by their parents.

SPECIAL CONSIDERATIONS FOR SMALL CHILDREN — Of our patients, ~10% are diagnosed before age 3 and 17% before age 5. Among these, insulin-dose adjustments as low as 0.5 U often are used. In such patients, we routinely dilute insulin to concentrations of 10 U/ml using diluents provided by the manufacturers. Target glucose concentrations (i.e., the expected levels in the majority of samples at a given time of day) may be 60–180 mg/dl in the adherent older child without frequent severe hypoglycemia; however, these targets are often raised in preschool-age children and children at greater risk for severe hypoglycemia. Target glucoses may be raised (e.g., to 80–220 mg/dl) in these children.

PREMATURELY BAD INSULIN — In the mid-1980s, some of our patients developed DKA during the summer months apparently because their human insulin had gone bad before its expiration date. Formulations of human insulin distributed by all manufacturers of insulin seem to have been less stable during this period, possibly because of reduced zinc content. Instability seemed to increase at higher temperatures and with exposure to prolonged shaking or vibration.

These problems have become less common in recent years. Denatured or precipitated insulin is, however, still listed as a possible cause of DKA. Some of our families discard individual insulin bottles after 3 months of use, a practice we encourage if it does not cause a financial hardship. We ask families to watch for precipitation, clouding or clumping of insulin, or frosting of insulin vials before the contents of the vials are depleted. Problems with bad insulin are sometimes manifested by the gradual development of hyperglycemia at the end of a bottle or unexplained hypoglycemia when switching to a new bottle. These problems seem to be more common in smaller children taking <5 U/day of insulin from a single vial.

INSULIN CHANGES RELATED TO SELF-MONITORING OF BLOOD GLUCOSE — We began to employ self-monitoring of blood glucose in children in the 1970s soon after several European centers demonstrated the clinical efficacy of visually estimated blood glucose monitoring strips and the introduction of relatively painless finger-pricking devices. When our children first started to use these strips at a diabetes summer camp, a senior nurse educator, herself a long-standing diabetic, threatened to resign because of the physical abuse being perpetrated on innocent children by unethical university diabetologists. These and similar attitudes not withstanding, self-monitoring of blood glucose rapidly replaced urine glucose monitoring by the early 1980s. We soon stopped asking these patients to measure urine glucose and, today, <1% of our IDDM patients use urine to monitor their glucose control. Most have severe mental retardation or unique psychosocial situations that preclude use of self-monitoring of blood glucose.

We continue to instruct all patients on the use of reagent strips to measure urine ketones, especially when glucoses are >240 mg/dl for ≥2 readings or with any intercurrent illness. We often are frustrated when infrequently used urine ketone–measuring equipment is not available during illness or episodes of severe hyperglycemia.

During the early 1980s, it became obvious to us and others that the use of self-monitoring of blood glucose did not, of itself, result in reliable glucose measurements by patients or staff. Simply replacing urine glucose monitoring with blood monitoring would not necessarily improve glycemic control (2,27). One alarming realization was the fact that we were making insulin-dose adjustments based on unreliable measurements by inadequately instructed patients at home or poorly trained nurses in the hospital. This problem started at the hospital where nurses were overwhelmed by a wave of new products and inadequate training and quality-control measures (28). It deteriorated further when inadequately trained or poorly supervised families were left to their own resources to implement glucose monitoring at home.

Another problem was our need to protect our patients against the widely promulgated misconception that establishing near normoglycemia (i.e., blood glucoses 70–120 mg/dl before meals) was a reasonable and safe long-term goal of treatment in IDDM patients. We viewed this message as both unrealistic and unsafe in most IDDM children who had evolved past their honeymoon phase.

Perhaps the most pernicious problem during the last decade was the emergence of familiar patterns of fabrication of blood glucose test results. These false results replaced the fabrication of urine glucose–monitoring results ob-

Table 1—*Suggestions for more rational use of self-monitoring of blood glucose in children with IDDM*

1. Don't assume patients can measure blood glucose accurately without repeated instruction and retraining.
2. Avoid use of the term glucose testing. Use terms like checking, monitoring, and measuring instead.
3. Make monitoring meaningful, i.e., an action is required when a specific result is obtained. For example, you don't know how much insulin you need before a meal until you know your glucose reading.
4. Use monitoring behavior as a behavior trap that encourages desirable actions or habits in other areas (e.g., eating, insulin administration, and exercise).
5. Employ practical exercises so that families can experience and understand for themselves the effects of insulin dose/timing adjustments, exercise, and specific foods. Do this repeatedly after the stress of initial diagnosis has decreased and basic survival skills are mastered.
6. Transfer more responsibility for care to families using simple written agreements and frequent telephone contacts. Gradually increase patient independence, especially during adolescence. Encourage parental support appropriate for patient's age. Point out the long-term benefits to the patient (e.g., more responsibility, freedom, flexibility) and family.
7. Use a written log. Teach patients how to analyze and identify trends in data 1–2 wk at a time. Include criteria for insulin-dose adjustments or calls for assistance in the written log.
8. Beware of use of electronic logs if these reduce the review of patterns of glucose and the interpretation of data. Point out that recorded data will be validated by a HbA_1 measurement and that there is no gain in editing numbers.
9. Stress the use of bedtime monitoring as a safety measure to avoid nocturnal hypoglycemia.
10. Make written agreements. Use records both to review and teach.

served earlier in these same children. Unfortunately, fabrications of data were fueled by our enthusiastic, well-meaning, but unrealistic or impractical messages to our patients (27). One inadvertent message was that near normoglycemia was an easily achievable and beneficial goal. Any unexpected failures implied poor adherence or some type of personal imperfection, such as not caring enough about one's well-being. Children especially responded to this pressure in time-honored fashions. One such response was the tell-them-what-they-want-to-hear syndrome. For instance, if a child reported a 30 or a 300 mg/dl blood glucose result, "all hell would break loose." However, if the reported glucose was 100 or 140 mg/dl, no questions were asked and the patient was rewarded because he or she was a good person who followed expert advice. Not unexpectedly, glucose values became omitted, falsified, or otherwise edited so that real numbers were replaced with safe numbers that would not provoke inquisitions, accusations, or parental-physician hysteria. Curiously, these efforts could be viewed as logical efforts to protect the children's self-image and to reduce parental and medical harassment.

The patterns of behavior described above were more likely to emerge at the end of the honeymoon period. Brighter children and adolescents often would try to outsmart even the most diligent parent or health professional. This "theater of the absurd" was made evident (but not resolved) by the naive misuse of memory meters as modified lie detectors, rather than as tools to help record and rapidly analyze the large amount of data accumulated between visits to the doctor's office.

Even though such problems were very dramatic, they were not new, especially to those who had previously grown weary of fabricated trace glucose urine records. More importantly, it soon became evident that a main problem with blood glucose monitoring was that patients were simply not being taught how to accurately collect, interpret, and act on the massive amounts of data being requested (4). Memory meters could serve as a valuable data management and teaching tool when used by experienced personnel working with motivated and carefully trained patients. Too often, however, not enough time was allocated for competent use of these devices during routine follow-up visits. Gathering data, whether in a log book or computer memory, that never were used was correctly perceived by many children as an unimportant task, which required neither time nor serious effort.

Much of our current practice has evolved from research driven by behavioral and developmental psychologists and assorted diabetes educators at our center and others during the last decade. These methods are still imperfect and are undergoing modifications and ongoing research (27–36). Several practical recommendations are discussed briefly below and are outlined in Table 1.

We should not assume that a patient can learn how to measure blood glucose reliably simply by purchasing a glucose meter and reading a manual at home. Initial instruction by an experienced professional and repeated reassessment of basic skills are needed long after initial instruction. The patient's own monitoring system should be used.

Glucose monitoring should not be referred to or viewed as testing. In the minds of many children, taking a test implies that an unwanted result may be viewed as a failure. Parents should be asked to avoid overreacting or punishing a child who honestly reports unexpected results.

We try to develop a clear understanding that each glucose measurement

has a specific purpose and that the results obtained for each test may entail a patient's change in behavior or prenegotiated action. For example, the purpose of morning glucose measurements is to determine how much insulin to take and how long to wait between the injection and breakfast. If the blood glucose is 90 mg/dl, the morning injection is given 30 min before breakfast. This time may be increased by 15–30 min if the blood glucose is over a prearranged value. Extra rapidly absorbed insulin may be recommended with markedly elevated values. These increments are often modest (e.g., 1–2 U for glucoses 240–300 mg/dl and 3–4 U for values >300 mg/dl in a typical adolescent).

We advise patients to manipulate both the timing and dose of insulin, in lieu of manipulating the insulin dose alone, to more effectively correct post-breakfast hyperglycemia (37,38). Simply increasing the regular insulin dose by 5–10 U (referred to by some as the sliding scale approach, but, by me, as the orthopedic approach) increases the risk of hypoglycemia before lunch. The sliding waiting time approach requires that we encourage patients to monitor as soon as they awake and before they bathe and dress for school. This allows the insulin dose to be given, if needed, 30–60 minutes before breakfast. Use of waiting times is often unpopular and impractical with children, particularly boys, who prefer to dress before bedtime, roll out of bed, and be on their way to school 20 minutes later.

Our overall rationale is to maintain a simple procedure that is based on what psychologists refer to as a behavior trap, in which changes in one behavior (e.g., glucose monitoring) trigger changes in another (e.g., adjusting insulin, diet, or exercise) (34). If a glucose value is required to determine a premeal insulin dose, fabricating it is less rational than if it is simply recorded with no change in insulin required or expected. At each office visit, we should try to find at least one example where the patient or family has used the results of monitoring to change some behavior. These are praised extensively. Also, it helps if patients and families can negotiate options, e.g., a reduction in CHO rather than an increase in insulin dose to help correct a high glucose value.

We should not expect families to become experts in self-care or insulin-dose adjustments during their initial hospitalization or the first few instruction sessions. Follow-up calls, visits, and continuous review are essential. We have shown that a 7-session training course in blood glucose monitoring, given as a supplement to expert physician, nurse, and nutritionist education, significantly improves long-term diabetes control (4). This course stresses practical didactic exercises during the first 6 months after diagnosis. Specific exercises focus on how to measure glucose accurately, how to interpret results, what one can do to raise or lower blood glucose, what options are available to help maintain blood glucoses between practical, readily attained ranges, and when and how to seek assistance. The benefits of this form of training become evident after the honeymoon period and persist for at least 2 years. Attempts to implement most of the basic principles of this method are made routinely for all of our patients and many have been incorporated into this commentary. These methods do not work well without strong parental support or in dysfunctional families (29,30,36).

A long-term goal of glucose monitoring should be to help patients and families not only cope but to gradually accept more responsibility in making their own insulin-dose adjustments between visits by following specific, written instructions. For example, it may be written that a family should increase the evening NPH by 1 or 2 U if 3 successive morning glucoses are over a given value (e.g., 200 mg/dl) or 5 out of 7 values are >200 mg/dl and no values are <100 mg/dl. Similarly, insulin doses are lowered by 1–3 U or a dietary modification is introduced if symptomatic hypoglycemia or measured glucoses <60 mg/dl occur at similar times ≥2 times in a given week. The main goal is to have patients view themselves as part of the decision-making process rather than as mere pawns. Initially, these changes are supervised by an experienced nurse or physician, through phone calls or, more recently, fax communications to the office and a return call to the patient. This type of care encourages small, gradual adjustments at 1- to 2-week intervals between office visits. The long-term goal is a growing sense of independence and self-confidence and a general transition beyond the earlier coping phase of management. The system deteriorates when patient calls for assistance are not answered promptly and consistency or continuity in care is not present. The effort required for this type of care is both demanding and time consuming. Unfortunately, such care is often poorly reimbursed by third-party health-care providers. Reimbursement is more likely if services are billed as management of poorly controlled diabetes rather than diabetes education.

A few families overuse the system and call several times a week for prolonged periods. An attempt should be made to determine the cause of such abnormal or unwarranted client-provider dependency relationships and corrective measures taken. By the time they reach adolescence, children can assume much of the responsibility for more complex types of diabetes self-management. However, a common mistake is made to think that all adolescents can make their own insulin adjustments or reliably call for help without family and professional support.

An important feature of glucose monitoring in our center is our insistence on the use of a written log, preferably with negotiated goals of treatment written on the cover. Glucose goals or targets should be broad and readily achieved. Thus, after the honeymoon period, a typical IDDM patient may be taught that we expect the majority of (not all) glucoses

before breakfast and supper to be between 60 and 180 mg/dl. This analysis is conducted separately for the morning and evening results. The results are arranged in overlapping columns and analyzed for periods of 1–2 weeks. When the family properly collects and arranges the data, results of 4 weeks of monitoring can be reviewed in less than 2 minutes by an experienced patient or health professional. If buried in a memory meter or dictated over the telephone as 100 bits of scattered data that must be transcribed by a physician or nurse, this type of periodic review soon becomes a tedious chore.

Because patients may be seen in the office or clinic only every 3 months or so, the family must be encouraged to seek interval assistance if problems arise between visits. If goals are not met, the family must make adjustments on their own or call or fax a message for assistance. Criteria for who and when to call should be clear and in writing. Entries over or below broad targets should trigger a brief notation as to any unusual exercise, food intake, illness, or irregularity in the schedule. Such entries should be praised and used to revise the treatment regimen, adjust goals, and to teach. Goals of treatment may be broader or more liberal (e.g., 100–280 mg/dl) for very young or less reliable patients or those predisposed to severe hypoglycemia. Keeping an electronic log book is fine but not if it is used as an excuse not to analyze the data regularly at home. Prior arrangements should be made to allow time for downloading and analysis of data during the next visit. All long-term goals should be the result of negotiations that allow the patient to initiate modifications and allowances.

We emphasize to our patients that the main purpose of bedtime and 0100–0200 glucose monitoring is safety, i.e., prevention of severe hypoglycemia. Prebedtime readings <100 mg/dl may require an increased protein intake with the usual bedtime snack. Measurements at bedtime and at 0100–0200 are particularly important when evening NPH doses are being adjusted, on nights after days of unusually severe or prolonged physical activity, and in patients at increased risk for nocturnal hypoglycemia. Extra Regular insulin is given at bedtime only during illness or with close professional supervision in well-trained, reliable families.

In most patients, we recommend 3 blood glucose measurements per day (before breakfast and supper and at bedtime). However, additional glucose measurements may be needed, for example, at 0200, if nighttime NPH or Ultralente is being adjusted or hypoglycemia is likely attributable to a low bedtime reading or prolonged exercise the previous day. Extra measurements should be praised when performed.

The majority of our patients do not measure their blood glucoses before lunch while at school. We realize that this is suboptimal but make allowances because many children are concerned about becoming stigmatized if they are seen measuring blood glucose in front of their school peers. Measurements before lunch are encouraged on weekends or whenever the morning insulin is being adjusted. One disadvantage of this system is that doses of morning Regular insulin are frequently lowered because of prelunch hypoglycemia but less frequently raised for undetected prelunch hyperglycemia. To counter this tendency, we sometimes increase the prebreakfast Regular insulin by 1 U for every 2- to 3-U increase in prebreakfast NPH, provided no hypoglycemia is detected before lunch.

GHB ASSAYS

Impact on care

In the early 1980s, we demonstrated that switching patients from urine to blood glucose monitoring was associated with 1.4% lower mean HbA_1 values, even when little was done to instruct patients what to do (1). Elevated HbA_1 values indicating mean glucose values >300 mg/dl prompted interventions that commonly resulted in higher insulin doses and more intensive care. Subsequently, as HbA_1 assays, self-monitoring at blood glucose, and greater self-management were incorporated in our practice, mean HbA_1 values declined from 11.4 to 9.0% between 1979 and 1989 (39). The nondiabetic mean for this assay is 6.0%, and the upper limit of normal is ~7%. Values of 9.0% are associated with mean premeal and bedtime glucose values of 210–220 mg/dl over the previous 2 months.

We routinely intensify management in any patient developing HbA_1 values >11% (40). High values are usually seen when mean blood glucose levels approach or exceed 300 mg/dl. This often results in more insulin being given or renewed efforts to have previously prescribed insulin given more effectively by the patient or a responsible family member. We also make an effort to identify patients at increased risk for poor outcome, as defined by higher HbA_1 values or need for recurrent hospitalization. A model was created by Auslander and Anderson at our center that identified, at diagnosis, 5 specific risk factors for future IDDM problems (29–32). These factors include: single parent, one parent not attending instructional classes, coma on admission, psychiatric disorder in the household, and family requiring social assistance because of low income. The presence of ≥3 of these 5 largely interactive factors placed children at a substantially increased risk for a poor outcome during the next 2 years. Providing preventive care and assigning high-risk patients to a specific doctor or nurse reduced admissions for DKA more than twofold. In our practice, many of these children were from single-parent, African-American households. Assignment of a social worker or psychologist as part of the treatment team was viewed as advisable, as was the involvement of local

health and protective government agencies.

Perhaps the greatest contribution of HbA_1 assays is their use as a feedback and overall evaluation tool for patients. This requires telling patients what the numbers mean and what the goals are. Patients should be encouraged to call for results. Recently, we have begun to give patients the results of rapidly performed assays obtained during the same office visit. This method is promising but will require further study to assess efficacy.

MEAL PLANS AND FOOD INTAKE DURING HYPOGLYCEMIA

— Because of the negative connotations often associated with dieting, we have preferred to use the term meal planning rather than diet in our center. The idea is that most IDDM patients can select foods that are normally consumed by the rest of the family. A nutritional assessment is conducted by an experienced nutritionist and an emphasis is placed on incorporating foods that are normally eaten by the family into a meal plan. The plan emphasizes educating patients to group types of foods into 6 categories (i.e., meat, bread, fruit, fat, milk, and vegetable) that allow for the exchange of different foods at a given meal. The goal is to provide variety while maintaining fairly consistent CHO and protein intake from one day to another. We follow recent recommendations by the American Diabetes Asssociation and the American Heart Association, which distribute calories as 15–20% protein, 30- 35% fat, and 45–55% from CHO. Cholesterol intake is limited to 300 mg/day and the P:S fat ratio at least 2:1.

Several areas are emphasized. First, meals and snacks have to be eaten on time. Second, increased food intake is encouraged when vigorous physical activity that lasts more than 15 minutes is anticipated. Third, children <8 years of age are usually prescribed a midmorning snack, particularly if this is the custom of nondiabetic peers. Midmorning snacks are also sometimes needed when the time between breakfast and lunch is ≥4 h. With the introduction of human NPH insulins and their more rapid absorption, an increasing proportion of older children have been developing prelunch hypoglycemia, which necessitates lowering the morning dose of Regular insulin or adding a morning snack. An added morning snack, or a reduced Regular insulin dose, is particularly important when there is a gym or exercise period before lunch. Fourth, although families are taught how to estimate quantities of food, they are not expected to weigh portions of food. Indeed, the total caloric content of food is estimated rather than measured precisely. If weight gain or loss is unsatisfactory, attempts are made to adjust caloric intake or exercise. In general, children should not leave the table hungry and should not need to cheat to obtain their desired caloric intake. Often, the content of a given meal can be modified according to the child's appetite and eating preferences. An extra meat, fruit, or bread exchange, for example, can be added to a given meal at the family's discretion. The majority of patients do not gain excessive weight when they are given some flexibility in the amount of food they eat. Fifth, the nutritionist should help the patient cope with special needs such as attending a birthday or special celebration, dining out with the family and friends, and eating while traveling, during unusual exercise, or on sick days. Sixth, the bedtime snack, used by almost all of our patients, requires special attention. One of the main purposes of this snack is to avoid nocturnal hypoglycemia. This will occur in about 25% of nights in which the prebedtime blood glucose is <100 mg/dl, but in <2% of nights when the concentration is >150 mg/dl (17). When prebedtime, presnack blood glucoses are ~≤100–120 mg/dl, extra protein is added to the bedtime snack. Low-fat milk, cheese, peanut butter, and lean luncheon meats are added, usually as one meat exchange or more. The CHO content of the bedtime snack can also be reduced if presnack bedtime glucoses are >200 mg/dl.

The use of food to compensate for hypoglycemia also requires special attention. Most health professionals who have not lived with an IDDM patient fail to grasp the anxiety and fear associated with an episode of seizure or severe neuroglycopenia attributable to hypoglycemia. Four factors should be considered. First, the amount of food needed will depend on the prevailing level of insulinemia and the amount of exercise before the event. For example, in a patient who exercises at 1100 and has had a dose of NPH at 0700 or 0800, the amount of CHO needed may be considerable; one 12-oz can of soda that contains 40 g of CHO is not unusual. This may have to be repeated in 30–60 min if lunch cannot be provided early. Lesser amounts of CHO may be needed if there is no antecedent exercise and the prevailing level of insulinemia is lower, as would occur before the evening meal or in the early morning in a patient being given 2 doses of a Regular/NPH mixture daily.

Second, the amount of increased food intake needed to compensate for strenuous physical activity is often underestimated. Just 60 min of strenuous sports (bicycling, racquetball, hiking, running) can increase glucose disposal to rates exceeding 14 $mg \cdot kg^{-1} \cdot min^{-1}$. For a 50-kg adolescent this will require 50 g CHO/h, more than the 160 calories found in a typical 12-oz can of cola. Severe, prolonged exercise (e.g., long bike trips, 2 h of soccer practice) can have glucose lowering effects for ≥8–12 h. This is an important consideration because early morning hypoglycemia can be attributable to afternoon physical activity. Extra food may be required at bedtime in these instances.

Third, the amount and type of food given during hypoglycemia is best determined by trial and error. Blood glucose monitoring logs should be reviewed

with this in mind and the patients own experience used as a guide for future management. The goal is to determine how many glucose tablets, sugar packets, or fruit juices are needed to correct hypoglycemia under different circumstances.

Fourth, families should be instructed that when there is doubt, treatment should be initiated immediately. For example, preschool-age children should be fed whenever the parents or sitters notice bizarre behavior or subtle signs of neuroglycopenia. Blood glucoses can be done immediately afterwards and discrepancies or unexpected results discussed with an experienced nurse or physician as needed.

Hypoglycemia unawareness (i.e., no symptoms with blood glucoses of 50 mg/dl or no warning before neuroglycopenia) is common in younger children and in children with a longer duration of diabetes. Rapidly absorbed CHO should be available to correct hypoglycemia, even if no symptoms are present. Family members should be encouraged to initiate treatment when early signs of hypoglycemia are evident. Recurrent hypoglycemia with or without coma unawareness requires more intense glucose monitoring, upward adjustments in target glucoses, and education of the entire family, teachers, and close friends. This is particularly important in smaller children in whom recurrent hypoglycemia may be associated with defects in neurobehavioral function later in life. Glucagon should be available for use by the family, school nurse, or roommates.

Finally, we, and others, have noted that adherence to a meal plan is an excellent predictor of long-term glucose control. This association may be attributable to several factors. First, patients who more closely follow the details of meal plans may be the same ones who are more likely to pay more attention to other aspects of their treatment regimen. Second, patients who follow a more reasonable meal plan may experience less severe fluctuations in glycemic control from excess CHO intake or mixed or late meals. Third, those who know that they have deviated from their diet may note the consequences during glucose monitoring. Those who make this observation and use it to change their dietary behaviors may be likely to have better glucose control than those who do not.

THE FUTURE— We feel that mean HbA_1 values should and can be lowered <9.0% in two-thirds or more of our patients because studies such as the DCCT demonstrate a clear benefit with an acceptable risk from severe or recurrent hypoglycemia (40). This will require more frequent glucose monitoring and insulin injections, more aggressive treatment goals, and more frequent office visits by the 30–50% or so patients with current HbA_1 values >9.0% who are now seen every 3–4 months. Such intensive care will likely require widespread use of a team approach to implement more effective patient training and supervision. We have found that this is best done in tertiary care specialty settings by an experienced staff using standardized evaluation and treatment guidelines (41). These measures are likely to increase health-care costs and, thus, may be resisted by some third-party health-care providers and government agencies. Ultimately, the hope is that paying for these services now will save eyes, kidneys, hearts, and legs of young adults in the future.

New monomeric insulin formulations that produce more rapid increments in plasma insulin concentrations soon after meals should help reduce postprandial hyperglycemia. These designer insulins may also reduce hypoglycemia before the next meal. More slowly absorbed insulins, such as human Ultralente, should gain increased popularity as sources of basal and nocturnal insulin replacement (42). Measures to prevent and detect nocturnal hypoglycemia are clearly needed, as are methods for less traumatic measurement of blood glucose levels. Development of techniques to enhance rational interpretation and use of information derived from self-monitoring also are necessary. Implantable pumps probably will not gain acceptance in children unless they can be coupled with reliable glucose sensors for more or less continuous closed-loop control. Less invasive measurement of blood glucose with bloodless monitors could be of enormous benefit, as would implantable sensors to allow automated insulin delivery and alarms during hypoglycemia. An initial step in this direction may be the use of noninvasive monitoring of blood glucose during the night, particularly in those predisposed to severe nocturnal hypoglycemia.

Overall, the good news is that things have improved considerably in the last decade and that IDDM patients who get expert care seem to be doing better. The bad news is that hypoglycemia and inconvenience remain major problems and that a cure is not just around the corner for diabetic children. Moreover, large numbers of children with IDDM deserve better quality of care, and they are not getting it because of deficiencies in current health-care delivery systems worldwide. The next decade promises to be better than the last, with enormous challenges for health professionals and IDDM patients and their families.

Acknowledgments— This study was supported by the Diabetes Research and Training Center National Institutes of Health Grant P-60-DK-20579; and the Clinical Research Center National Institutes of Health Grant 5M-01-RR-00036.

The author acknowledges the insights and collaboration of many hundreds of families and health-care professionals who have educated him in pediatric diabetes care over the last quarter century. Special thanks are extended to Drs. Philip Cryer, Neil White, Barbara Anderson, Wendy Auslander, Alan Dela-

mater, and Sharon Pontious; and to Susan Green Davis and Jeanne Bubb for collaboration and enthusiasm.

References

1. Carney RM, Schecter K, Homa M, Levandoski LA, White NH, Santiago JV: The effects of blood glucose testing vs. urine sugar testing on the metabolic control in insulin-dependent diabetic children. *Diabetes Care* 6:378–80, 1983
2. Santiago JV, Wolff PB, Davis JE, Brother MA, Ratzan SK, Weldon VV, Haymond MW, Schoenfeld G: Effect of blood glucose control and a lipid lowering diet on blood lipids in diabetic children. *Pediatr Adolesc Endocrinol* 7:241–48, 1979
3. Bubb J, Daughaday WH, Davis SG, Fisher EB Jr, Flavin KS, Gavin JR III, Haire-Joshu D, Heins J, Hopper SV, Lange M, Santiago J: Professional education in diabetes care: beyond the physician and back. *Diabetes Educator* 12: 210–14, 1986
4. Delamater AM, Bubb J, Davis SG, Smith JA, Schmidt L, White NH, Santiago JV: A randomized, prospective study of self-management training with newly diagnosed diabetic children. *Diabetes Care* 13:492–98, 1990
5. Levandoski LA, White NH, Santiago JV: Localized skin reactions to insulin: insulin lipodystrophies and skin reactions to pumped subcutaneous insulin therapy. *Diabetes Care* 5:6–10, 1982
6. Schade D, Santiago J, Rizza R, Skyler J: *Intensive Insulin Therapy*. Amsterdam, Excerpta Medica, 1988
7. White NH, Santiago JV: Clinical features and natural history of brittle diabetes in childhood. In *Brittle Diabetes*. Pickup JC, Ed. Oxford, Blackwell Scientific Publications, 1985, p. 19–28
8. Friedenberg GR, White NH, Cataland S, O'Dorisio TM, Sotos JF, Santiago JV: Diabetes responsive to intravenous but not subcutaneous insulin: effectiveness of aprotinin. *N Engl J Med* 305:363–68, 1981
9. Schade DS, Drumm DA, Duckworth WC, Enton RP: The etiology of incapacitating, brittle diabetes. *Diabetes Care* 8:12–20, 1985
10. Shah SC, Malone JI, Simpson NE: A randomized trial of intensive insulin therapy in newly diagnosed insulin-dependent diabetes mellitus. *N Engl J Med* 320:550–54, 1989
11. DCCT Research Group: Effects of age, duration and treatment of insulin-dependent diabetes mellitus on residual β-cell function: observations during eligibility testing for the Diabetes Control and Complications Trial (DCCT). *J Clin Endocrinol Metab* 65:30–36, 1987
12. Drash AL, Becker DJ: Behavioral issues in patients with diabetes with special emphasis on the child and adolescent. In *Ellenberg and Rifkin's Diabetes Mellitus: Theory and Practice*. 4th ed, Rifkin H, Porte D, Eds. New York, Elsevier, 1990, p. 922–34
13. Blethen SL, Sargeant DT, Whitlow MG, Santiago JV: Effect of pubertal stage and recent blood glucose control on plasma somatomedin C in children with insulin-dependent diabetes mellitus. *Diabetes* 30: 868–72, 1981
14. Amiel SA, Sherwin RS, Simonson DC, Lauritano AA, Tamborlane WV: Impaired insulin action in puberty: a contributory factor to poor glycemic control in adolescents with diabetes. *N Engl J Med* 315:215–19, 1986
15. Galloway JA: Treatment of NIDDM with insulin agonists or substitutes. *Diabetes Care* 13:1209–39, 1990
16. White NH, Santiago JV: Diabetes mellitus in children and adolescents. In *Conn's Current Therapy*. Philadelphia, WB Saunders, 1988
17. Shalwitz RA, Farkas-Hirsch R, White NH, Santiago JV: Prevalence and consequences of nocturnal hypoglycemia among conventionally treated children with diabetes mellitus. *J Pediatr* 116: 685–89, 1990
18. Hepburn DA, Eadington DW, Patrick AW, Colledge NR, Frier BM: Symptomatic awareness of hypoglycemia: does it change on transfer from animal to human insulin? *Diabetic Med* 6:586–90, 1989
19. Teuscher A, Berger WG: Hypoglycemia unawareness in diabetics transferred from beef/pork insulin to human insulin. *Lancet* ii:382–87, 1987
20. Reichard P, Berglund A, Britz A, Levander S, Rosenqvist U: Hypoglycemic episodes during intensified insulin treatment: increased frequency but no effect on cognitive function. *J Intern Med* 229:9–16, 1991
21. Clarke WL, Gonder-Frederick LA, Richards FE, Cryer PE: Multifactorial origin of hypoglycemia symptom awareness insulin-dependent diabetes mellitus. *Diabetes* 40:680–85, 1991
22. The DCCT Research Group: Epidemiology of severe hypoglycemia in the diabetes control and complications trial. *Am J Med* 90:450–59, 1991
23. Clarke WL, Haymond MW, Santiago JV: Overnight basal insulin requirements in fasting insulin-dependent diabetics. *Diabetes* 29:78–80, 1980
24. White NH, Skor DA, Cryer PE, Bier DM, Levandoski L, Santiago JV: Identification of type I diabetic patients at increased risk for hypoglycemia during intensive therapy. *N Engl J Med* 308:485–91, 1983
25. Cryer PE: Alanine nocturnal hypoglycemia. *Diabetes Care*. In press
26. White NH, Santiago JV: What can be achieved with and what are the complications of the insulin pump? In *Diabetes Mellitus: Achievements and Skepticism*. Paptis S, Church J, Eds. London, The Royal Society of Medicine, 1984, p. 111–25
27. Dellameter AM, Kurtz SM, White NH, Santiago JV: Effects of social demand on reports of self-monitored blood glucose in adolescents with type I diabetes mellitus. *J Appl Soc Psychiatry* 18:491–502, 1988
28. Davis SG, White NH, Stoverock LS, Santiago JV: In-hospital bedside blood glucose monitoring: the importance of a quality control program. *J Pediatr Nursing* 4:353–56, 1989
29. Auslander WF, Anderson BJ, Bubb J, Jung KC, Santiago JV: Risk factors to health in diabetic children: a prospective study from diagnosis. *Health Soc Work* 15:133–42, 1990
30. Anderson BJ, Miller JP, Auslander WP, Santiago JV: Family characteristics of diabetic adolescents: relationship to metabolic control. *Diabetes Care* 4:586–94, 1981

31. Anderson BJ, Auslander WF, June KC, Miller JP, Santiago JV: Assessing family sharing of diabetes responsibilities. *J Pediatr Psychol* 15:477–92, 1990
32. Auslander WF, Haire-Joshu D, Rogge M, Santiago JV: Predictors of diabetes knowledge in newly diagnosed children and parents. *J Pediatr Psychol* 16:213–28, 1991
33. Delamater AM, Bubb J, Kurtz SM, Kuntze J, Smith JA, White NH, Santiago JV: Physiologic responses to acute psychological stress in adolescents with type I diabetes mellitus. *J Pediatr Psychol* 131: 69–86, 1988
34. Delamater AM, Davis SG, Bubb J, Smith JA, White NH, Santiago JV: Self-monitoring of blood glucose by adolescents with diabetes: technical skills and utilization of data. *Diabetes Educator* 15:56–61, 1988
35. Delamater AM, Kurtz SM, Bubb J, White NH, Santiago JV: Stress and coping in relation to metabolic control and adolescents with type I diabetes. *Dev Behav Pediatr* 8:136–40, 1987
36. Kuttner MJ, Delamater AM, Santiago JV: Learned helplessness in diabetic youth. *J Pediatr Psychol* 15:581–94, 1990
37. Witt MF, White NH, Santiago JV: Roles of site and timing for the morning insulin injection in type I diabetes. *J Pediatr* 103: 528–33, 1983
38. Dimitriadis GD, Gerich JE: Importance of timing of preprandial subcutaneous insulin administration in the management of diabetes mellitus. *Diabetes Care* 6:374–78, 1983
39. Arfkin C, Schmidt L, White NH, Santiago JV: Temporal trends in glycemic control of insulin treated patients with diabetes mellitus (DM). In *Abstract for 1992 ADA Meetings*, 1992. In press
40. The DCCT Research Group: The effects of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 329:977–86, 1993
41. Santiago JV, White NH, Pontious SL: Diabetes in childhood and adolescence. In *International Textbook of Diabetes Mellitus*. Alberti KGMM, DeFronzo RA, Keen H, Zimmet P, Eds. London, John Wiley and Sons, 1992, p. 1025–57
42. Zinman B: The physiologic replacement of insulin. *N Engl J Med* 321:363–70, 1989