This is the third in a series of reports on the American Diabetes Association (ADA) 61st Scientific Sessions held in Philadelphia, PA, in June 2001. It covers topics related to the treatment of type 1 diabetes.

Glucose monitoring and sensing

In a symposium at the ADA meeting, Charles M. Peterson, Bethesda, MD, gave an overview of noninvasive glucose monitoring, stressing the need to critically evaluate the differing technologies. Since 1995 there have been 8 new drugs, 8 new insulins, and 35 new meters introduced on the market; glucose monitoring is a huge industry that is growing by 15% annually. Peterson asked why there is no noninvasive meter, and answered, "because it's so difficult!" Wet chemistry, solid-phase reagent chemistry, and electrochemical sensing all require a sample as well as a reagent and therefore are invasive. Three general approaches exist for glucose enzyme electrodes, measuring consumption, or measuring production, with potential cross reactions from metals and ingested drugs. The latest approach has used a two-step enzymatic reaction in which glucose oxidase reduced by glucose is regenerated to its original form for further sample processing. Problems include sample size and preparation, complicated electronics and processing, response time versus sensitivity, sensor fouling, and effects of oxygen and oxidizing interfering substances, including ascorbic acid, uric acid, and acetaminophen. Humidity effects, stability, precision, accuracy, and membrane issues when the substrate is partitioned into a different compartment are additional factors to be addressed.

Satish K. Garg, Barbara Davis Center, Denver, CO, discussed clinical applications of continuous glucose monitoring, which can overcome the discomfort of multiple fingerstick glucose measurements and allow assessment of the peaks and valleys of glucose levels in patients with diabetes. He noted an important discrepancy between the conventionally treated and intensively treated groups in the Diabetes Control and Complications Trial (DCCT), so that at a given HbA1c, the risk of retinopathy of those in the intensive group was less than half of that in the conventional group. Thus, there are other mediators of complications, including perhaps glycemic excursions. Clearly, more frequent conventional home glucose monitoring improves HbA1c. Two commercial interstitial fluid glucose sensors are now available, the MiniMed continuous glucose monitoring system (CGMS) and the GlucoWatch Automatic Biographer. Interstitial glucose, Garg stated, is usually similar to the blood glucose, with a time lag of 2–3 min. When glucose levels are declining, however, interstitial results appear higher, and when levels are increasing, the interstitial levels are lower than actual blood glucose values, causing potential difficulties with these approaches (see notes below on similar findings with forearm capillary glucose monitoring). Leaving aside these difficulties during rapid changes in blood glucose, it is clear that conventional premeal monitoring misses much of the hyperglycemia and as much as 85% of the hypoglycemia, which can be recognized with interstitial glucose monitors. A potential safety issue is that patients may over-react to isolated high or low glucose readings. Issues with the GlucoWatch include a requirement for a 3-h warm-up period, a 20-min lag between readings, the fact that each sensor lasts only 12 h, skips in blood glucose (as can occur with sweating), changes in skin temperature (which can affect results), the size of the watch, and skin irritation (which is noted to at least some degree in all patients). The CGMS device is invasive (requiring placement of a subcutaneous catheter), has a lag of 13 min between readings, and currently has no glucose display, with data downloaded after 3 days. Calibration at least three times daily is required with this unit, and the device and sensor are quite expensive. Garg suggested that future glucose-monitoring goals are to narrow glucose excursions with devices that have better acceptability, thereby allowing easier implementation of intensive diabetes treatment, which will translate into better outcomes. The device should alert patients to hypoglycemia, show glucose trends, and allow physicians to fine-tune insulin doses.

Mark R. Burge, Albuquerque, NM, discussed novel strategies to obtain blood, recalling that supposedly therapeutic phlebotomy has been performed for at least 2,500 years, despite absence of evidence of benefit. Burge noted that George Washington died after a phlebotomy of 9 pints for a throat infection. Despite the proven value of home blood glucose monitoring, rates are suboptimal. Barriers to home glucose monitoring include inconvenience, pain, and cost. As of 1989, only 30% of type 1 diabetic patients and 20% of type 2 diabetic patients taking insulin reported home glucose monitoring more than once daily. Home glucose monitoring was more frequent with lower age, higher education, more visits to physicians, and Caucasian ethnicity (1). Data obtained in 1994 showed that among 1,480 insulin-treated patients with type 2 diabetes, 30% never tested and only 35% tested more than once daily (2).

The typical stainless steel lancet has a diameter of 0.3–0.8 mm and penetrates 0.7–1.3 mm, with depth of penetration directly related to pain. The Lasette eribium:YAG (yttrium-aluminum-garnet) laser skin perforator measures 14 × 8 × 3.5 cm and weighs 550 g. The device gives a single pulse of focused light that produces a 2-mm skin puncture (3). According to a survey of some 6,600 type 1 diabetic patients, to which 1,895 replied, actual testing frequency was less than that recommended, mainly because of soreness, pain, and inconvenience.
ence between the reported recommended and actual frequency of testing was proportional to the number of hospitalizations over the prior 2 years, so that a less painful device might be more useful. Burge also commented that the Needlestick Safety and Prevention Act passed by Congress in November 2000 requires that employers must provide safe alternatives to needlesticks, although an audience member who had used the device commented that it was uncomfortable for patients and that “the puff of smoke and the smell of burning flesh” are “a turn-off.”

Christopher D. Saudek, Baltimore, MD, discussed the status of implantable pump therapy. He noted that insulin delivery can be markedly improved, and that it is still painful, inconvenient, inaccurate, and in many respects unsuccessful. In the early 1980s the challenge was to design a variable rate pump that would deliver microliter pulses reproducibly and accurately with safe and effective surgical implantation. It was necessary to ensure that the insulin would last weeks to months, with the possibility of excess insulin delivery prevented by the storage of insulin in a reservoir at negative pressure. The implantation procedure itself is simple, and the pump becomes encapsulated in a thick fibrous capsule with little inflammatory reaction by use of a peritoneal catheter that rarely causes inflammation or becomes obstructed. The pump and telemetry system currently function well. From 1986 to 1990 these pumps were placed in 18 individuals with type 1 diabetes (4). The initial work was continued by Minimed, with a 3-year battery life expectancy, improved telemetry, and further design modifications. More than 600 of the devices were implanted, with 10–15% showing catheter blockage annually, infrequent skin breakdown, occasional pain at the implant site, and no severe adverse reactions or insulin overdelivery. A controlled trial comparing the device with multiple daily insulin injections in 121 subjects with type 2 diabetes (5) showed a 30 vs. 40 mg/dl standard deviation of blood glucose (pump vs. multiple dose, respectively), suggesting reduced glycemic variability; hypoglycemia was confirmed in 2 vs. 6 episodes per patient per year. Weight gain was decreased, and there was some evidence of improved quality of life.

From 1990 through 1994, more than 100 pumps were implanted annually, but in 1994, underdelivery of insulin became more common. A change in the manufacturing of the Hoechst insulin used in the pumps led to insulin aggregation. This has been addressed, and coming recombinant DNA insulin preparations may last 4–6 months. At the International Study Group on Innovative Insulin Delivery, 31 centers participated, 22 of which were located in Europe, with 1,381 pumps implanted into 737 patients as of 2000, although there were only 340 active patients at that time. A new model was introduced last year and has been submitted to the FDA. This pump has an 8-year battery life and a much smaller external pump controller, which uses a program similar to that in internal insulin pumps. The implant itself is ~10% smaller, with the size of the reservoir (which holds U400 insulin) limiting pump size. Saudek ended by commenting, “Our Holy Grail is closed loop insulin delivery.” The CGMS shows that, in principle, continuous interstitial glucose monitoring can be accomplished, and an intravenous sensor is also being developed to make this a potential option for patient treatment. In a study presented at the ADA meeting, Shah et al. (9-OR) described such a system, with an intravascular glucose sensor linked to an intraportaline insulin pump in insulin-dependent diabetic dogs (abstract numbers refer to the Abstracts of the 61st Annual Meeting of the American Diabetes Association, Diabetes 50 [Suppl. 2]:1–A649). Average blood glucose levels were 65–125 mg/dl, with <5% and <1% of readings >200 mg/dl using regular and fast-acting insulin, respectively, as compared with glucose levels of 135–400 mg/dl with 40% >200 mg/dl before initiation of the treatment. Steil et al. (533-P) described a similar approach using a subcutaneous glucose sensor and external pump administering subcutaneous insulin to insulin-dependent diabetic dogs showing preprandial glucose 75–125 mg/dl, although postprandial glucose increased to 250 mg/dl. Junghem et al. (10-OR) presented a CGMS with a subcutaneous microdialysis catheter and a portable miniaturized extracorporal electrochemical glucose sensor developed by Roche Diagnostics (Mannheim, Germany) in 23 ambulatory patients with type 1 and type 2 diabetes over 72 h, giving results comparable to capillary glucose values. Renard et al. (12-OR) implanted a long-term intravenous glucose sensor in two men with type 1 diabetes, showing high correlation with capillary glucose over 1- to 2-month periods.

Koschinsky et al. (214-OR) noted discrepancies between clinical symptoms of hypoglycemia and normoglycemic forearm capillary values. They studied six patients with type 1 diabetes who were given 75 g glucose orally, without insulin, to increase glucose to 300–400 mg/dl, after which insulin was given intravenously and both forearm and fingertip capillary glucose levels were measured every 5–15 min. The mean fasting glucose level was 124 vs. 121 mg/dl, but the measured glucose increase was 151 vs. 218 mg/dl, and the subsequent decrease was 213 vs. 293 mg/dl with forearm versus fingertip sampling. For two patients, fingerstick glucose decreased to 51 and 53 mg/dl when forearm glucose levels were 142 and 159 mg/dl, respectively. Hypoglycemic levels at the forearm were not reached until 27–34 min after being noted at the fingertip. Ellison et al. (444-P) compared fingertip, forearm, and thigh glucose at 0, 60, 90, 120, 150, and 180 min postprandial in 42 patients with diabetes. Fingertip glucose readings were higher, particularly at 60 and 90 min. Forearm sampling may only be desirable for use in situations during which rapid glucose changes are known to not be occurring, thus limiting its clinical value.

Desai et al. (13-OR) compared 3,060 transcutaneous glucose measurements with the Glucowatch Biographer (Cygnus, Redwood City, CA) with capillary glucose levels in 111 individuals with diabetes who used the device for 5 days, showing fairly good agreement. Kessler et al. (2298-PP) used the CGMS (Minimed, Sylmar, CA) to compare patients treated with islet or whole pancreas transplantation or by implanted intraperitoneal insulin infusion. The mean 3-day glucose level was 5.4, 6.1, and 8.1 mmol/l and the mean amplitude of glycemic excursions was 1.4, 1.4, and 3.5 mmol/l, respectively, suggesting the two transplantation approaches to be superior to insulin infusion in controlling glycemia and reducing blood glucose variability. Ratner et al. (517-P) reported use of this system in 42 patients with diabetes, finding that the peak postprandial glucose was typically similar with different meals for a given patient. There was greater variability of the time to maximal glucose after different meals, which occurred 93, 119, and 129
min after breakfast, lunch, and dinner, respectively, with considerable variability.

Bergenstal and Monk (4-LB) described an assay of glycated proteins in the lens of the eye by use of blue laser fluorescence measurement, thus not requiring a blood sample, showing specificity of 88.7% and sensitivity of 50% in comparison to fasting blood glucose in identifying patients with diabetes. March et al. (502-P) tested the Nefficon A disposable contact lens, which increases fluorescence with increasing glucose concentration, in 12 subjects, showing correlation between change in fluorescence and change in blood glucose.

**Strategies for insulin use**

Jay Skyler, Miami, FL, discussed the history and evolution of insulin therapy. Introduced 80 years ago by Banting and Best, initial insulin preparations were crude, but improvements in purification and duration of action continued through the decade of the 1950s. During that period of development, NPH insulin was considered to act in different fashions in different patients: some experienced shorter duration, others experienced normal duration, and others experienced late onset as well as long duration of action. Most likely, the early onset of action is the true pharmacologic pattern. U 100 insulin was introduced in 1972, with insulin available today in a highly purified form as biosynthetic human insulin.

The first publication on intensive insulin treatment was written by T. Donowski and appeared in the first issue of *Diabetes Care*. In Donowski’s study, regular insulin was administered before each meal, and NPH insulin was administered at bedtime with home glucose monitoring. Evening insulin was found to be more effective when NPH was administered at bedtime rather than before dinner. Glucose-controlled insulin infusion systems, though impractical for clinical use, provided many insights into optimal patterns of insulin administration. Insulin pumps, developed to provide continuous subcutaneous insulin delivery, have become smaller, allowing greater convenience. Skyler contrasted “intensive therapy of type 1 diabetes” with “intensive insulin therapy,” as the latter is a “quick and easy title but put too much emphasis on the insulin.” He stressed the need for a multicomponent insulin treatment program; careful balance among food intake, insulin, and exercise; home glucose monitoring; and planned alterations of insulin dose with improvements in diet and exercise to attain optimal glycemic outcome, all of which require a great deal of patient motivation and input by a variety of different health care personnel.

Human insulin and insulin pens became available in the late 1980s, the DCCT documented the importance of glycemic control in the 1990s, and the concept of flexible intensive therapy became important. Lessons from the DCCT included the importance of a management team with a dedicated nurse specialist, a flexible dietitian, and an involved patient and family. Monthly follow-up, the need for individualizing the diabetes treatment regimen, the concept of carbohydrate counting, and respect for hypoglycemia were important features of the DCCT regimens.

The use of the rapidly acting insulin analogs lispro and aspart allows patients to better reproduce a physiologic insulin profile and to maintain better control of postprandial glucose excursions. Five different devices are in clinical development for inhaled insulin for rapid-acting insulin, and other approaches are being assessed for buccal insulin delivery. Glycemic control in patients with type 1 diabetes treated with these approaches is similar to that seen with rapid-acting injected insulin, promising greater patient convenience. Basal insulin, however, remains important, and administering rapid-acting insulin without regular insulin before dinner often leads to a dip in insulin levels at bedtime, requiring additional NPH doses. Alternatives are the long-acting insulin analog insulin glargine and an analog in development, insulin detemir, which has a fatty acid side chain that allows albumin binding, thereby leading to prolongation of action. Comparing glargine, NPH, ultralente, and continuous subcutaneous insulin infusion (CSI), NPH shows an early peak of action; ultralente also has a peak, though broader, and CSI and glargine show flat and prolonged curves of insulin action. “Glargine and detemir,” Skyler predicted, “will be the [basal] insulins of the future.” Closed loop glucose regulation with CSI and a glucose sensor has been shown to produce “reasonable control throughout the day” in dog studies. Another approach is the use of implanted pumps with peritoneal insulin delivery, with implantable glucose sensors to eventually offer an artificial pancreas.

Sam Dagogo-Jack, Jackson, MS, further discussed basal insulin therapy, which mimics the postabsorptive insulin secretory profile of individuals without diabetes and is required for patients with type 1 diabetes and for many patients with type 2 diabetes who show progressive decline in β-cell function. Basal insulin leads to suppression of overnight hepatic glucose production and suppression of lipolysis. Insulin has many actions outside of its effect on metabolism, including effects on vascular biology, for which provision of basal insulin may be beneficial. The basal insulin requirement, Dagogo-Jack noted, is related to body weight and insulin secretory capacity. The increase in insulin requirement during the adolescent growth spurt and perimenstrual changes in insulin requirement are also well established. Nondiabetic individuals have basal plasma insulin levels of 10–20 μU/ml, but this insulin level may be insufficient in patients with diabetes. In most instances, the basal component of intensive treatment regimens is 40–50% of the total daily insulin requirement.

The administration of insulin lispro and regular insulin by CSI are ideal. When NPH is given twice daily, undesirable peaks are seen, which can be addressed by giving additional doses, although this increases the risk of hypoglycemia. Ultralente given once daily has unpredictable patterns of action. Insulin glargine has now been approved and promises to provide longer duration of action without a peak effect. Studies in patients with type 1 diabetes undergoing intensive treatment using lispro for bolus insulin have shown comparable reductions in fasting glucose but lower rates of nocturnal hypoglycemia with use of insulin glargine rather than NPH insulin. In type 2 diabetes, the addition of insulin at bedtime to oral agents with once or twice weekly insulin dose adjustments to achieve near normalization of fasting glucose has shown comparable degrees of glycemic control with NPH or glargine. Severe hypoglycemia is infrequent with such approaches in type 2 diabetes. In response to a question, Dagogo-Jack suggested that the data for use of insulin glargine at bedtime rather than before dinner or at other points are “not compelling.” Skyler pointed out that the mean
duration of action of insulin glargine is 
~22 h, so that “it doesn’t make 24 h, probably, in at least half of the patients.” He suggested that this may be particularly important in patients with type 1 diabetes treated with insulin lispro at dinner and, therefore, that some patients may need to take this insulin twice daily.

Richard Bergenstal, Minneapolis, MN, discussed bolus (‘‘prandial’’) insulin, which he described as a “critical part of optimizing control,” although he stated his belief that control of postprandial glucose is no more important than control of fasting glucose and HbA1c. The ADA consensus statement on postprandial glucose suggested using 2-h glucose in nonpregnant patients and 1-h glucose in pregnant patients. Patients with good fasting glucose and high HbA1c, patients being treated with drugs that are particularly effective postprandially, and patients involved in an exercise program particularly need to monitor blood glucose levels after meals. Bergenstal noted the poor correlation between frequency of monitoring and HbA1c, type 2 diabetic patients not treated with insulin; the poor outcomes have led to skepticism as to whether testing is important for these patients. Bergenstal suggested that “you have to know what to do with the data,” and that this implies the importance of postprandial rather than just preprandial testing. He reviewed a study of patients treated with glyburide in which NPH at bedtime was administered with or without resuspension, because it takes a longer time to resuspend the insulin or remove the needle too early, although this was not associated with significant difference in HbA1c or insulin dose requirement. Solvig et al. (531-P) compared four insulin injection techniques—90° into lifted skinfold, 90° direct, 40–60° into lifted skinfold, and 40–60° direct—in 48 patients with diabetes, using ultrasonography to track 384 injections of room air. With 12-mm-length needles, 16% of injections were intramuscular. The optimal technique with the 6-mm needle was the 90° insertion into a lifted skinfold, with 98% subcutaneous, while with the 12-mm needle, 94% of those administered at a 40–60° angle into a lifted skinfold were subcutaneous.

A number of studies gave information about the use of insulin glargine. Fonseca et al. (449-P) treated 100 patients with type 2 diabetes with NPH versus glargine insulin for 28 weeks. HbA1c decreased 0.4% in each group, with 60 vs. 46%, respectively, reporting at least one episode of hypoglycemia, 31 vs. 17% having hypoglycemic symptoms with glucose <50 mg/dl, and 31 vs. 17% experiencing nocturnal hypoglycemia. Hershon et al. (466-P) treated 394 type 1 diabetic patients with NPH twice daily or insulin glargine at bedtime. The fasting glucose decreased 0.8 vs. 1.4 mmol/l, respectively, with glucose <50 mg/dl reported by 82 vs. 73% and glucose <36 mg/dl reported by 46 vs. 37% of patients. Poccellati et al. (8-LB) evaluated 29 patients with type 1 diabetes randomized to treatment with either four daily NPH doses at each meal, in combination with insulin lispro, and at bedtime versus insulin glargine administered once daily at dinnertime and lispro at each meal, or to CSII, for 4 weeks. With NPH, plasma insulin peaked at 2:30 A.M., with a glucose nadir at 3:30 A.M., and with 3 of 10 patients having asymptomatic hypoglycemia between 2:00 and 4:30 A.M. After a 15% increase in the NPH dose at bedtime, seven patients required glucose infusion from 2:00 to 7:30 A.M. to prevent hypoglycemia. With insulin glargine and with CSII, overnight insulin and glucose curves were nearly flat, without hypoglycemia, and with 15% increases in the glargine and CSII dose overnight, there was no hypoglycemia. The intrapatient coefficient of variation of plasma insulin was 32 and 27% with the two NPH doses, 12 and 10% with the two glargine doses, and 8 and 10% with the two CSII infusion rates. The authors concluded that “NPH insulin is a suboptimal approach as compared to glargine insulin and CSII to near-normalize [glucose] [. . .] because of the high risk for nocturnal hypoglycemia,” and that “glargine insulin and CSII appear similarly suitable approaches to intensify blood glucose control.”
diabetes with lispro before each meal; NPH was given at bedtime only for 4 months, and an NPH dose was given before lunch and at bedtime for 4 months in a crossover trial. Predinner glucose was 0.8 mmol/l and postdinner glucose was 0.6 mmol/l lower with two NPH doses. However, HbA1c was similar at 7.2 vs. 7.1%, and evening hypoglycemia increased with the two-dose NPH regimen.

**Inhaled and oral insulin**

Hollander (34-LB) reported on an insulin regimen involving pulmonary delivery of rapid-acting dry powder insulin, which will be marketed under the name Exubera, plus a single bedtime dose of Ultralente in 149 individuals with type 2 diabetes compared with two injections of regular and NPH insulin in 150 patients for a 6-month treatment period. HbA1c decreased similarly in both groups. Of the patients, 21 vs. 3% complained of cough with inhaled insulin, but none discontinued treatment because of this, and pulmonary function tests were stable and similar in the two groups. Osborn et al. (7-LB) studied a similar rapid-acting inhaled insulin formulation using a small, breath-activated inhaler, showing somewhat greater 16–18% bioavailability with effects similar to those of insulin lispro and more rapid in onset than those of regular insulin. Mellén et al. (505-P) reported threefold higher peak insulin levels, seen at 32 vs. 54 min, and 58% greater total insulin absorption in smokers than in nonsmokers administered inhaled insulin with the AERX fine particle aerosol device. Pulmonary function did not change in either group.

Kipnes et al. (5-LB) reported on studies of 18 adults with type 2 diabetes treated with Hesyl-Insulin Monoconjugate 2 (HIM2), an insulin modified by attachment of polymeric oligomers and resistant to gastrointestinal enzymatic degradation, which showed postprandial glucose patterns similar to those seen with a corresponding dose of subcutaneous insulin lispro. Dandonia et al. (177-OR) studied 15 patients with type 1 diabetes using continuous subcutaneous insulin basal infusion, with HIM2 decreasing both fasting and postprandial glucose levels. Clement et al. (435-P) reported a study of HIM2 in 18 patients with type 1 diabetes, again showing a glucose-lowering effect. This preparation may lead to more physiologic portal delivery of insulin.

Cavallo et al. (431-P) administered the buccally absorbed RapidMist oral insulin spray to eight patients with type 1 diabetes, showing similar blood glucose and insulin patterns to those seen after subcutaneous insulin administration. Levin et al. (497-P) administered this insulin preparation to 24 patients with type 2 diabetes who were not receiving hypoglycemic treatment. Glucose levels before and 2 h after meals increased from 167 to 185 mg/dl with the oral insulin preparation but from 192 to 261 mg/dl without it. Lewin et al. (178-OR) reported a 53% increase in insulin levels with glucose increasing from 140 to 160 mg/dl 1 h after a standardized meal with the insulin preparation in 23 patients with type 2 diabetes treated with metformin; with a placebo spray, glucose increased from 157 to 204 mg/dl. Schwartz et al. (323-P) reported an HbA1c decrease at 90 days from 9.7 to 8.0% in patients with type 2 diabetes treated with the oral insulin before meals, but an increase from 8.5 to 9% in patients receiving a placebo spray, and Schwartz et al. (181-OR) reported that 33 patients treated with glyburide randomized to the preparation versus placebo showed a decrease in HbA1c from 9.9 to 8.7% vs. 9.3 to 8.9%. Lewin and Modi (278-OR), in a similar study of patients treated with pioglitazone 30 mg daily, showed a decrease in HbA1c from 9.0 to 7.9% with the insulin spray but an increase from 9.6 to 10.6% at 12 weeks with a placebo spray.

**Insulin pump therapy**

Differences in outcome of treatment of children with CSII were described in a number of reports. White et al. (267-OR) reported a study of 34 children under the age of 18 years with type 1 diabetes treated with usual care compared with 9 receiving CSII and 31 with multiple daily injection (MDI) therapy. The mean HbA1c was similar at 8.7, 8.5, and 8.1%, there were 0.58, 0.09, and 0.59 episodes of severe hypoglycemia per patient per year, and diabetic ketoacidosis (DKA) occurred in 35% of CSII patients per year; it was not seen with subcutaneous insulin. In another group of 48 children starting CSII, HbA1c did not change; severe hyperglycemia decreased from 0.37 to 0.07 episodes per patient per year, and DKA increased from 0.04 to 0.30 episodes per patient per year, suggesting a trade-off between considerably decreased hypoglycemia and increased DKA. Celona et al. (270-OR) reported results of CSII in 34 children with type 1 diabetes; there was no significant change in HbA1c, or hypoglycemia, but there was an increase in body weight and frequency of DKA. Ahern et al. (268-OR) reported experience with 76 school-age and 26 preschool children treated with CSII. HbA1c decreased at 12 months from 7.8 to 7.3% and from 7.1 to 6.5%, with 0.2 episodes of severe hypoglycemia per patient per year, and 2 episodes of DKA in 163 patient-years of follow-up. Laffel et al. (269-OR) reported results of CSII in 109 children with type 1 diabetes. HbA1c decreased from 8.5 to 7.8% at 3 and 6 months, respectively, but increased to 8.4% at 1 year, with decreasing frequency of home glucose monitoring and compliance with snack-bolus administration over time. After examining these reports, one may conclude that insulin pump therapy does not yet clearly offer benefit in the pediatric population, although it may play a role in the patient with difficult-to-manage hypoglycemia.

Chase et al. (365-P) administered an 829-kcal pizza, tiramisu, and sugar pop meal on four consecutive Saturdays to 9 patients with type 1 diabetes who were using CSII. Results showed a 9-mg/dl increase in glucose after administering 70% of the insulin dose as a bolus and 30% as a 2-h square wave, but increases of 33, 66, and 80 mg/dl with a single bolus, 2 boluses with 50% of the dose at 0 and 90 min, and the entire dose given as a square wave, respectively.

**Pediatric diabetes**

Stene et al. (159-OR) analyzed the 1,824 cases of type 1 diabetes before age 15 years among 1,382,602 persons born in Norway between 1974 and 1998. Diabetes was 18% less likely with each increase in birth order among children born to mothers aged 20–24 years at delivery, and among second or later-born children, there was a positive association between risk of diabetes and maternal age. Lipman et al. (158-OR) reported that there were 232 children <15 years of age who were hospitalized for diabetes requiring insulin treatment in Philadelphia from 1995 to 2000, an incidence rate of 14.5/100,000 per year. Black children aged 10–14 years had a rate of 25.3/100,000, more than double that of whites. Rewers et al. (13-
prevalence of non-Caucasian ethnicity and acanthosis nigricans than children with type 1 diabetes; obesity, blood pressure, and family history of type 2 diabetes were additional distinguishing characteristics. Moghaddas et al. (1591-P) reported on 31 children over 10 years diagnosed with diabetes in 1 year, noting that 7 patients had two or more features of type 1 diabetes, such as ketosis, and two or more features of type 2 diabetes, such as obesity. Therefore, it may be useful to classify some patients as having undetermined type to avoid errors in epidemiologic assessment and treatment. Maldonado et al. (1076-P) studied 76 adults with DKA, 47 with and 29 without β-cell response to glucagon within 2 weeks of the episode. Of those with β-cell response, 17% had GAD or IA-2 antibodies, 38% were able to discontinue insulin, and age at diagnosis was 41 years; 40% of those without β-cell response had antibodies, none were able to discontinue insulin, and age at diagnosis was 25 years.

Regarding the important topic of type 2 diabetes in the pediatric population, Katz et al. (223-OR) evaluated 180 children with new diabetes during the year ending July 2000. A total of 29 children had type 2 diabetes based on the absence of GAD65 antibodies, lack of insulin dependence, obesity, and family history of type 2 diabetes. Of the 180 children, 78% with type 1 diabetes vs. 35% with type 2 diabetes were white, 1 vs. 82% had acanthosis nigricans, onset at age was 9 vs. 14 years, and BMI was 17 vs. 34 kg/m². Urine ketones were higher in type 1 diabetes, fasting C-peptide was 0.4 vs. 2.1 ng/ml, and fasting insulin-like growth factor binding protein (IGFBP)-1 was 38 vs. 5 ng/ml, but glucose and HbA₁c were similar at presentation. Weinzierl et al. (274-OR) described 23 children with type 2 diabetes treated with metformin. Eight children received metformin as the initial treatment, resulting in HbA₁c <8.5%, absent ketosis, and normal renal and hepatic function. The other 15 children received metformin in combination with insulin. At the 18-month follow-up, 17 were treated with metformin alone, showing a mean HbA₁c of 6.3%; 3 were treated with metformin in combination with insulin, showing an HbA₁c of 6.8%; and 3 were treated with diet alone, showing an HbA₁c of 5.8%. Hardin et al. (225-OR) described 27 children with type 2 diabetes, again showing older age at onset and higher glycemic clamps at 93, 70, 61, and 53 mg/dl in 8 African-Americans without diabetes, in comparison with 15 Caucasians, showing that lower blood glucose levels were required for increases to occur in norepinephrine, growth hormone, and muscle sympathetic nerve activity.

Cersosimo et al. (219-OR) compared 12 patients with type 1 diabetes with 14 control subjects, showing decreased glucagon, epinephrine, and norepinephrine responses to hypoglycemia, with compensatory increases in total glucose production to 13.2 μmol·kg⁻¹·min⁻¹ and increases in renal glucose output to 4.5 μmol·kg⁻¹·min⁻¹ in control subjects. Yet, there was a lack of increase in total glucose production, with a particularly important factor being failure of renal glucose production to increase in the diabetic patients. Cheyne et al. (544-P) compared effects of mild alcohol intoxication, mild hypoglycemia, and the combination of both, showing the combination to markedly worsen cognitive performance and the total symptom score in nine type 1 diabetic patients. Sood et al. (561-P) further reported that low-dose ethanol delayed recovery from hypoglycemia in type 2 diabetic patients by reducing glucose production, delaying the epinephrine response, and leading to a requirement for lower glucose levels to be attained to cause epinephrine release, potentially predisposing to more severe hypoglycemia. Fanelli et al. (546-P) found greater decline in cognitive function in patients with type 1 diabetes during rapid than during slow decrease in blood glucose, seen primarily in patients showing hypoglycemia awareness, while those with hypoglycemia unawareness exhibited partial protection against this phenomenon. Ferguson et al. (547-P) reported that the presence of the apolipoprotein-E4 allele, which worsens outcome after a variety of cerebral insults, was associated with poorer intellectual performance and frontal lobe function in a group of 96 patients with type 1 diabetes, although this could not be correlated with history of severe hypoglycemia. Heller et al. (552-P) randomized 155 type 1 diabetic patients to human regular insulin or insulin aspart given preprandially for 16 weeks, showing 3.0 vs. 3.2 hypoglycemic events per month, with 0.017 vs. 0.036 severe nocturnal hypoglycemic episodes per month. There was no difference in HbA₁c.

Ford-Adams et al. (548-P) found an
association between prolonged QTc interval on electrocardiogram recorded every 30 min in association with spontaneous hypoglycemia in 18 children with type 1 diabetes having overnight studies for a total of 29 nights. Low potassium and high epinephrine were associated with both hypoglycemia and the prolonged QTc, suggesting potential mechanisms. Kern et al. (556-P) studied individuals without diabetes during insulin-induced hypoglycemia during the early period of sleep and again at the same time of the night while kept awake. The glucose level required for the onset of the counter-regulatory response was significantly lowered during sleep, from 3.3 to 2.7 mmol/l for epinephrine and norepinephrine and from 2.9 to 2.6 mmol/l for adrenocorticotropin and cortisol release, potentially explaining the increased risk of severe hypoglycemia during sleep in diabetic patients.

**Author’s correction**—In regard to the October 2001 article “Angiotensin II Receptor Blockers and Nephropathy Trials,” individuals with type 2 diabetes and microalbuminuria have a 5–10% annual (not lifetime) risk of progression to overt nephropathy. Our apologies to Dr. Parving.

**References**