

Continuous Subcutaneous Insulin Infusion—An Historical Perspective

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INSULIN BECAME AVAILABLE for the treatment of diabetes mellitus in the early 1920s. From that time onward, as noted by Robert Tattersall in his historical review “The Quest for Normoglycemia,” there has been an ongoing struggle by diabetologists and their patients to maintain glycemic control as close to normal as possible.¹

For many years, it was uncertain what constituted normal insulin physiology. Our understanding of that really commenced after the development of the insulin radioimmunoassay by Yalow and Berson in 1960.² The radioimmunoassay permitted definition of normal insulin secretory dynamics and the division of insulin secretion into two phases: basal insulin secretion and meal-stimulated insulin secretion,^{3–8} as summarized in two classic reviews.^{9,10}

The 1960s and 1970s saw many advances in our understanding of insulin and glucose homeostasis. Several investigators provided the first observations and modeling of insulin kinetics.^{11–13} During the same era, other investigators reported the first studies of the pharmacokinetics of injected insulin.^{14,15} Meanwhile, several classical studies were being done with continuous intravenous insulin delivery in an attempt to mimic normal physiology.^{16–19} Development of methods for continuous glucose measurement permitted this to be combined with intravenous insulin infusion to develop glucose-controlled insulin infusion systems (GCIIS). This was first attempted by Arnold Kadish in Beverly Hills, CA in the 1960s.^{20–22} Success in developing GCIIS was achieved nearly simultaneously in the 1970s by groups in Toronto, Canada,^{23,24} Ulm, Germany,^{25–27} Montpellier, France,²⁸ Sydney, Australia,^{29,30} and Osaka, Japan.^{31,32} The Ulm GCIIS was commercialized by Miles Laboratories (Elkhart, IN) as the “Biostator.”

Over the course of many years, in the pursuit of the “quest for normoglycemia” several groups had devised approaches to subcutaneous insulin replacement therapy that took into account the separate components of insulin need: basal insulin secretion and meal-stimulated insulin secretion.^{33–36} In the late 1970s investigators first began to explore continuous subcutaneous insulin infusion (CSII) using insulin pumps. Parsons et al.³⁷ described the first infusion pump for subcutaneous delivery of hormones. Pickup et al.³⁸ in the United Kingdom and Tamborlane et al.³⁹ in the United States were the first groups to use CSII to treat patients with type 1 diabetes. Concomitantly, groups in Munich, Germany⁴⁰ and Vienna,

Austria⁴¹ used portable devices for continuous intravenous insulin delivery.

The pumps used in those early experiences with CSII provided a single basal rate of insulin delivery, providing basal insulinemia, the goal of which was to maintain hepatic glucose output equivalent to peripheral basal glucose utilization. The pumps were such that the insulin infusion rate could be altered preprandially to provide meal-related incremental insulin secretion in the form of an insulin “bolus” or “boost.” The initial pumps were relatively bulky (up to 400 g in weight, and as large as 18.3×7.3×6.4 cm) and required that batteries be recharged or changed on a frequent basis and that insulin be diluted. With time, the pumps became smaller, compatible with commercial insulin preparations (eliminating the need for dilution), had long-lived batteries (months to years) incorporated, were easier to use, and contained built-in alarms. The basic design of pumps remained that a syringe-driven pump uses a subcutaneously placed catheter to deliver insulin, controlled by electronics within the pump. Nonetheless, pumps have become more sophisticated—the sophistication permitting programming of multiple basal rates, profiling of boluses, suspension or temporary rate program of insulin delivery during exercise, memory display of historical insulin delivery, and softened catheters that do not require that an insertion needle be left in place. Indeed, now there are automated devices that facilitate insertion of catheters. A release mechanism has been developed so that it is also possible to disconnect pumps from infusion catheters, useful during such activities as showering, swimming, shopping (with multiple changes of clothes), and sexual intimacy. Some pumps have remote control devices. Others are waterproof or water resistant. More recently, “smart” features have been introduced into pumps, so that the pump’s computer can calculate recommended insulin doses for carbohydrate content of meals and/or recommended doses for correction of glycemic levels outside of target ranges.⁴² A new style of pumps has also been introduced, so-called “patch pumps,” in which the pump controller communicates with an infusion component that is attached to the skin directly rather than being connected by a catheter.⁴³

Initially, CSII was greeted with much enthusiasm by diabetologists. Pump manufacturers multiplied. There was much endorsement of the concept. Then problems arose. These included reports of (1) increased mortality in CSII patients,⁴⁴

a problem later refuted,^{45,46} and (2) increased risk of hypoglycemia and hypoglycemic coma, accelerated diabetic ketoacidosis (DKA) on CSII, and skin infections around the site of catheter insertion.⁴⁷ These observations triggered a wave of investigations that led to solutions that can prevent or minimize these problems. A meta-analysis of 52 studies, conducted in 2003, indicated that CSII therapy is associated with significant improvements in glycemic control (decreased glycosylated hemoglobin [A1c] and mean blood glucose), decreased insulin dose, decreased frequency of hypoglycemic episodes but potentially still an increased frequency of DKA (when pumps malfunction or dislodge), and an apparent lesser frequency of pump malfunction and of site infections.⁴⁸

Studies have been conducted evaluating the pharmacokinetics of insulin delivery via CSII.^{49,50} CSII may offer real advantages in terms of the pharmacokinetics of insulin delivery.⁵¹ For one thing, with CSII there is essentially no subcutaneous insulin depot.⁴⁹⁻⁵¹ Depots of insulin may be mobilized by increased blood flow with such things as exercise, sauna or other hot baths, or massage. The price may be unexpected hypoglycemia. Because CSII obviates the depots that routinely accumulate with subcutaneous injections, the risk of unexpected hypoglycemia is lessened. On the other hand, as implied above, the risk of DKA may be heightened by lack of a depot. Another pharmacokinetic advantage of CSII is that it uses only rapid-acting insulin. The absolute (minutes or hours) variation in day-to-day absorption of insulin is least in the shortest-acting insulins and greatest in the longest-lasting insulins.^{14,50} Therefore, CSII provides the greatest day-to-day reproducibility in insulin availability, and thus the least unexpected fluctuations in glycemic control.

In the late 1970s and early 1980s, with the then recent availability of CSII, coupled with the availability of self-monitoring of blood glucose (SMBG) and of A1c to assess glycemic control, several important developments were facilitated. One was the development of specific treatment approaches that combined CSII and SMBG with guidelines for patient management that facilitated attainment of glycemic control.⁵²⁻⁵⁴ Using these or similar approaches, it was possible to design randomized controlled studies to evaluate the impact of glycemic control on complications of diabetes. Several small studies were conducted,⁵⁵⁻⁵⁹ followed by the landmark Diabetes Control and Complications Trial.⁶⁰ All of these studies demonstrated that microvascular complications in type 1 diabetes can be reduced by attainment of meticulous metabolic control. Although CSII was not necessarily mandated in most of these studies, it clearly facilitated the attainment of meticulous metabolic control.

One question that exists is whether glycemic control is indeed better with CSII than with optimized insulin therapy using multiple injections. There have been a number of studies that have attempted to evaluate this, and as a consequence several meta-analyses have appeared to examine these collectively.⁶¹⁻⁷⁰ In general, these have shown that, compared to multiple daily injections (MDI), CSII results in better glycemic control in adults with type 1 diabetes,^{48,61-66} particularly in those with higher baseline A1c.⁶² On the other hand, there is lack of clear benefit on reduction of non-severe hypoglycemia.^{65,66} In addition, there is no firm evidence of benefit of CSII versus MDI, particularly with use of insulin analogs, in children,⁶⁷ in pregnancy,^{68,69} or in type 2 diabetes.⁷⁰

A review of CSII by the United Kingdom's National Institute for Clinical Excellence (NICE) in 2004 concluded "the trials to date have focused on easily measurable outcomes such as glycosylated hemoglobin. The main benefits may be in terms of flexibility of lifestyle and quality of life, and data on those would help with cost-effectiveness analysis. Some of the implications for patients such as the psychological impact of wearing a device for 24 hours every day have not been quantified."⁷¹ Their assessment then was "there appears to be no wholly satisfactory economic model for diabetes, which would allow improvements in diabetes control to be converted into a cost per quality-adjusted life-year."⁷¹ A subsequent analysis by NICE in 2010 concluded "based on the totality of evidence, using observational studies to supplement the limited data from randomized trials against best MDI, CSII provides some advantages over MDI in type 1 diabetes. For both children and adults, these are: [1] better control of glucose levels as reflected by A1c level, with the size of improvement depending on the level before starting CSII; [2] fewer problems with hypoglycemia; and [3] quality of life gains, such as greater flexibility of lifestyle."⁷² They noted, however, that the benefits of CSII come at an extra cost of about £1,700 (approximately U.S. \$2,600) per year. As with the meta-analyses cited above, they pointed out that there is no evidence that CSII is better than analog-based MDI in type 2 diabetes or in pregnancy.⁷² Given the respect placed in the NICE review process, this change in assessment is noteworthy.

The most recent excitement about CSII is its use in conjunction with continuous glucose monitoring (CGM). The Juvenile Diabetes Research Foundation (JDRF) CGM Study Group has demonstrated that, when used on a regular basis, CGM facilitates attainment of improved glycemic control.⁷³ In addition, in patients with type 1 diabetes already in good glycemic control, the JDRF CGM Study Group showed that CGM resulted in reduced hypoglycemia without sacrifice of glycemic control.⁷⁴ Most of the patients in these studies used CSII, although the benefits of CGM were also seen in those who used MDI. As a consequence, there has been much interest in development of portable GCIS. Some progress has been made in this regard in terms of initial pilot studies.^{75,76} It is anticipated that this field is likely to explode over the next several years.

In 2002, Pickup and Keen⁷⁷ reviewed the first 25 years of CSII therapy. Since that time, additional advances have been made. Thus, there has been much progress made in the "quest for normoglycemia."⁷¹ This observer believes that reliable systems of CGM and CSII will evolve further, to the point where automated achievement of glycemic control fulfills that quest.

References

1. Tattersall RB: The quest for normoglycaemia: a historical perspective. *Diabet Med* 1994;11:618-635.
2. Yalow RS, Berson SA: Immunoassay of endogenous plasma insulin in man. *J Clin Invest* 1960;39:1157-1175.
3. Cahill GF, Herrera MG, Morgan AP, Soeldner JS, Steinke J, Levy PL, Reichard GA Jr, Kipnis DM: Hormone-fuel interrelationships during fasting. *J Clin Invest* 1966;45:1751-1769.

4. Perley MJ, Kipnis DM: Plasma insulin response to oral and intravenous glucose; studies in normal and diabetic subjects. *J Clin Invest* 1967;46:1954–1962.
5. Malherbe C, De Gasparo M, De Hertogh R, Hoe JJ: Circadian variations of blood sugar and plasma insulin levels in man. *Diabetologia* 1969;5:397–404.
6. Lerner RL, Porte D: Acute and steady state insulin response to glucose in non-obese diabetic subjects. *J Clin Invest* 1972;51:1624–1631.
7. Goodner CJ, Conway J, Werrbach J: Control of insulin secretion during fasting hyperglycaemia in adult diabetics and in nondiabetic subjects during infusion of glucose. *J Clin Invest* 1969;48:1878–1887.
8. McCarthy ST, Harris E, Turner RC: Glucose control of basal insulin secretion in diabetes. *Diabetologia* 1977;13:93–97.
9. Kipnis DM: Insulin secretion in diabetes mellitus. *Ann Intern Med* 1968;69:891–901.
10. Cahill GF: The Banting Memorial Lecture 1971. Physiology of insulin in man. *Diabetes* 1971;20:785–799.
11. Williams RF, Gleason RE, Soeldner JS: The half-life of endogenous serum immunoreactive insulin in man. *Metabolism* 1968;17:1025–1029.
12. Sherwin RS, Kramer K J, Tobin JD, Insel PA, Liljenquist JE, Berman M, Andres R: A model of the kinetics of insulin in man. *J Clin Invest* 1964;53:1481–1492.
13. Insel PA, Liljenquist JE, Tobin JD, Sherwin RS, Watkins P, Andres R, Berman M: Insulin control of glucose metabolism in man: a new kinetic analysis. *J Clin Invest* 1975;55:1057–1066.
14. Binder C: Absorption of injected insulin. *Acta Pharmacol Toxicol* 1969;27(Suppl 2):1–84.
15. Berger M, Halban PA, Assal JP, Offord RE, Vranic M, Renold AE: Pharmacokinetics of subcutaneously injected tritiated insulin: effects of exercise. *Diabetes* 1979;28(Suppl 1):53–57.
16. Slama G, Hauteceuvre M, Assan R, Tchobroutsky G: One to five days of continuous intravenous insulin infusion on seven diabetic patients. *Diabetes* 1974;23:732–738.
17. Deckert T, Lorup B: Regulation of brittle diabetics by a preplanned insulin infusion program. *Diabetologia* 1976;12:573–579.
18. Genuth S, Martin P: Control of hyperglycemia in adult diabetics by pulsed insulin delivery. *Diabetes* 1977;26:571–581.
19. Hepp KD, Renner R, Funcke HJ, Mehnert H, Haerten R, Kresse H: Glucose homeostasis under continuous intravenous insulin therapy in diabetics. *Horm Metab Res Suppl* 1977;(7):72–76.
20. Kadish AH: A servomechanism for blood sugar control. *Biomed Sci Instrum* 1963;1:171–176.
21. Kadish AH: Automation control of blood sugar: a servomechanism for glucose monitoring and control. *Trans Am Soc Artif Intern Organs* 1963;9:363–367.
22. Kadish AH: Automation control of blood sugar. I. A servomechanism for glucose monitoring and control. *Am J Med Electron* 1964;3:82–86.
23. Albisser AM, Leibel BS, Ewart TG, Davidovac Z, Botz CK, Zingg W, Schipper H, Gander R: Clinical control of diabetes by the artificial pancreas. *Diabetes* 1974;23:397–404.
24. Albisser AM, Leibel BS, Ewart TG, Davidovac Z, Botz CK, Zingg W: An artificial endocrine pancreas. *Diabetes* 1974;23:389–396.
25. Pfeiffer EF, Thum C, Clemens AH: The artificial beta cell. A continuous control of blood sugar by external regulation of insulin infusion (glucose controlled insulin infusion system). *Horm Metab Res* 1974;6:339–342.
26. Kerner W, Thum Ch, Tamas JGY, Beischer W, Clemens AH, Pfeiffer EF: Attempts at perfect normalization of glucose tolerance test of severe diabetics by artificial betacell. *Horm Metab Res* 1976;8:256–261.
27. Clemens AH, Chang PH, Myers RW: The development of Biostator, a glucose controlled insulin infusion system (GCIS). *Horm Metab Res Suppl* 1977;(7):23–33.
28. Mirouze J, Selam JL, Pham TC, Cavadore D: Evaluation of exogenous insulin homeostasis by the artificial pancreas in insulin-dependent diabetes. *Diabetologia* 1977;13:273–278.
29. Kraegen EW, Campbell LV, Chia YO, Meler H, Lazarus L: Control of blood glucose in diabetics using an artificial pancreas. *Aust N Z J Med* 1977;7:280–286.
30. Kraegen EW, Whiteside R, Bell D, Chia YO, Lazarus L: Development of a closed-loop artificial pancreas. *Horm Metab Res Suppl* 1979;(8):38–42.
31. Shichiri M, Kawamori R, Yamasaki Y, Inoue M, Shigeta Y, Abe H: Computer algorithm for the artificial pancreatic beta cell. *Artif Organs* 1978;2(Suppl):247–250.
32. Kawamori R, Shichiri M, Goriya Y, Yamasaki Y, Shigeta Y, Abe H: Importance of insulin secretion based on the rate of change in blood glucose concentration in glucose tolerance, assessed by the artificial beta cell. *Acta Endocrinol (Copenh)* 1978;87:339–351.
33. McArthur JA, Jackson RL: Insulin treatment of juvenile diabetes; observations on the combined use of intermediate and regular insulins. *Diabetes* 1956;5:18–24.
34. Oakley W, Hill D, Oakley N: Combined use of regular and crystalline protamine (NPH) insulins in the treatment of severe diabetes. *Diabetes* 1966;15:219–222.
35. Gokal R, Harding P, Turner RC: Comparison between the plasma insulin and glucose responses to five different insulin regimes in diabetic patients. *Clin Endocrinol* 1977;7:301–305.
36. Phillips M, Simpson RW, Holman RR, Turner RC: A simple and rational twice daily insulin regime. Distinction between basal and meal insulin requirements. *Q J Med* 1979;48:493–506.
37. Parsons JA, Rothwell D, Sharpe JE: A miniature syringe pump for continuous administration of drugs and hormones: the Mill Hill infuser. *Lancet* 1977;1:77–78.
38. Pickup JC, Keen H, Parsons JA, Alberti KGMM: Continuous subcutaneous insulin infusion: an approach to achieving normoglycemia. *Br Med J* 1978;1:204–207.
39. Tamborlane WV, Sherwin RS, Genel M, Felig P: Reduction to normal of plasma glucose in juvenile diabetes by subcutaneous administration of insulin with a portable infusion pump. *N Engl J Med* 1979;300:573–578.
40. Renner R, Hepp KD, Mehnert H, Franetzki M: Continuous intravenous insulin therapy with a miniaturized open-loop system. *Horm Metab Res Suppl* 1979;(7):186–190.
41. Irsigler K, Kritiz H: Long-term continuous intravenous insulin therapy with a portable insulin dosage-regulating apparatus. *Diabetes* 1979;28:196–203.
42. Wolpert H, Block J: Hands-on demonstration and discussion of new pump software/hardware. *Diabetes Technol Ther* 2005;7:840–844.
43. Skladany MJ, Miller M, Guthermann JS, Ludwig CR: Patch-pump technology to manage type 2 diabetes mellitus: hurdles to market acceptance. *J Diabetes Sci Technol* 2008;2:1147–1150.
44. Centers for Disease Control (CDC): Deaths among diabetic patients using continuous subcutaneous insulin infusion

- pumps—United States. *MMWR Morbid Mortal Wkly Rep* 1982;31:80–82, 87.
45. Centers for Disease Control (CDC): Update: deaths among patients using continuous subcutaneous insulin infusion pumps—United States. *MMWR Morbid Mortal Wkly Rep* 1982;31:626.
 46. Teutsch SM, Herman WH, Dwyer DM, Lane JM: Mortality among diabetic patients using continuous subcutaneous insulin infusion pumps. *N Engl J Med* 1984;310:361–368.
 47. Mecklenberg RS, Benson EA, Benson JW, Fredlund PN, Guinn T, Matz RJ, Nielsen RL, Sannar CA: Acute complications associated with insulin infusion pump therapy. Report of experience with 161 patients. *JAMA* 1984;252:3265–3269.
 48. Weissberg-Benchell J, Antisdel-Lomaglio J, Seshadri R: Insulin pump therapy: a meta-analysis. *Diabetes Care* 2003;26:1079–1087.
 49. Lauritzen T, Pramming S, Deckert T, Binder C: Pharmacokinetics of continuous subcutaneous insulin infusion. *Diabetologia* 1983;24:326–329.
 50. Binder C, Lauritzen T, Faber O, Pramming S: Insulin pharmacokinetics. *Diabetes Care* 1984;7:188–199.
 51. Skyler JS: Lessons from insulin pharmacokinetics. *Diabetes Care* 1986;9:666–668.
 52. Skyler JS, Seigler DE, Reeves ML: Optimizing pumped insulin delivery. *Diabetes Care* 1982;5:135–139.
 53. Schade DS, Santiago JV, Skyler JS, Rizza R: *Intensive Insulin Therapy*. Princeton, NJ: Excerpta Medica, 1983.
 54. Howorka K: *Functional Insulin Treatment: Principles, Teaching Approach and Practice*, 2nd revised ed. New York: Springer-Verlag, 1996.
 55. Lauritzen T, Frost-Larsen K, Larsen HW, Deckert T; Steno Study Group: Effect of 1 year of near-normal blood glucose levels on retinopathy in insulin-dependent diabetes. *Lancet* 1983;1:200–204.
 56. Blood glucose control and the evolution of diabetic retinopathy and albuminuria. A preliminary multicenter trial. The Kroc Collaborative Study Group. *N Engl J Med* 1984;311:365–372.
 57. Dahl-Jørgensen K, Brinchmann-Hansen O, Hanssen KF, Ganes T, Bjoro T, Sandvik L, Aagaes O: Rapid tightening of blood glucose control leads to transient deterioration of retinopathy in insulin dependent diabetes mellitus: the Oslo study. *Br Med J (Clin Res Ed)* 1985;290:811–815.
 58. Feldt-Rasmussen B, Mathiesen ER, Hegedus L, Deckert T: Kidney function during 12 months of strict metabolic control in insulin-dependent diabetic patients with incipient nephropathy. *N Engl J Med* 1986;314:665–670.
 59. Reichard P, Bengt-Nilsson B-Y, Rosenqvist U: The effect of long-term intensified insulin treatment on the development of microvascular complications of diabetes mellitus. *N Engl J Med* 1993;329:304–309.
 60. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 1993;329:977–986.
 61. Pickup J, Mattock M, Kerry S: Glycaemic control with continuous subcutaneous insulin infusion compared with intensive insulin injections in patients with type 1 diabetes: meta-analysis of randomised controlled trials. *BMJ* 2002;324:705–710.
 62. Retnakaran R, Hochman J, DeVries JH, Hanaire-Broutin H, Heine RJ, Melki V, Zinman B: Continuous subcutaneous insulin infusion versus multiple daily injections: the impact of baseline A1c. *Diabetes Care* 2004;27:2590–2596.
 63. Jeitler K, Horvath K, Berghold A, Gratzner TW, Neeser K, Pieber TR, Siebenhofer A: Continuous subcutaneous insulin infusion versus multiple daily insulin injections in patients with diabetes mellitus: systematic review and meta-analysis. *Diabetologia* 2008;51:941–951.
 64. Pickup JC, Sutton AJ: Severe hypoglycaemia and glycaemic control in type 1 diabetes: meta-analysis of multiple daily insulin injections compared with continuous subcutaneous insulin infusion. *Diabet Med* 2008;25:765–774.
 65. Fatourehchi MM, Kudva YC, Murad MH, Elamin MB, Tabini CC, Montori VM: Clinical review: hypoglycemia with intensive insulin therapy: a systematic review and meta-analyses of randomized trials of continuous subcutaneous insulin infusion versus multiple daily injections. *J Clin Endocrinol Metabol* 2009;94:729–740.
 66. Misso ML, Egberts KJ, Page M, O'Connor D, Shaw J: Continuous subcutaneous insulin infusion (CSII) versus multiple insulin injections for type 1 diabetes mellitus. *Cochrane Database Syst Rev* 2010;(1):CD005103.
 67. Pańkowska E, Błazik M, Dziechciarz P, Szypowska A, Szajewska H: Continuous subcutaneous insulin infusion vs. multiple daily injections in children with type 1 diabetes: a systematic review and meta-analysis of randomized control trials. *Pediatr Diabetes* 2009;10:52–58.
 68. Mukhopadhyay A, Farrell T, Fraser RB, Ola B: Continuous subcutaneous insulin infusion vs intensive conventional insulin therapy in pregnant diabetic women: a systematic review and metaanalysis of randomized, controlled trials. *Am J Obstet Gynecol* 2007;197:447–456.
 69. Farrar D, Tuffnell DJ, West J: Continuous subcutaneous insulin infusion versus multiple daily injections of insulin for pregnant women with diabetes. *Cochrane Database Syst Rev* 2007;(3):CD005542.
 70. Monami M, Lamanna C, Marchionni N, Mannucci E: Continuous subcutaneous insulin infusion versus multiple daily insulin injections in type 2 diabetes: a meta-analysis. *Exp Clin Endocrinol Diabetes* 2009;117:220–222.
 71. Colquitt JL, Green C, Sidhu MK, Hartwell D, Waugh N: Clinical and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes. *Health Technol Assess* 2004;8(43):iii, 1–171.
 72. Cummins E, Royle P, Snaith A, Greene A, Robertson L, McIntyre L, Waugh N: Clinical effectiveness and cost-effectiveness of continuous subcutaneous insulin infusion for diabetes: systematic review and economic evaluation. *Health Technol Assess* 2010;14(11):iii–iv, xi–xvi, 1–181.
 73. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group, Tamborlane WV, Beck RW, Bode BW, Buckingham B, Chase HP, Clemons R, Fiallo-Scharer R, Fox LA, Gilliam LK, Hirsch IB, Huang ES, Kollman C, Kowalski AJ, Laffel L, Lawrence JM, Lee J, Mauras N, O'Grady M, Ruedy KJ, Tansey M, Tsalikian E, Weinzimer S, Wilson DM, Wolpert H, Wysocki T, Xing D: Continuous glucose monitoring and intensive treatment of type 1 diabetes. *N Engl J Med* 2008;359:1464–1476.
 74. Juvenile Diabetes Research Foundation Continuous Glucose Monitoring Study Group: The effect of continuous glucose monitoring in well-controlled type 1 diabetes. *Diabetes Care* 2009;32:1378–1383.
 75. Weinzimer SA, Steil GM, Swan KL, Dziura J, Kurtz N, Tamborlane WV: Fully automated closed-loop insulin de-

- livery versus semiautomated hybrid control in pediatric patients with type 1 diabetes using an artificial pancreas. *Diabetes Care* 2008;31:934–939.
76. Hovorka R, Allen JM, Elleri D, Chassin LJ, Harris J, Xing D, Kollman C, Hovorka T, Larsen AM, Nodale M, De Palma A, Wilinska ME, Acerini CL, Dunger DB: Manual closed-loop insulin delivery in children and adolescents with type 1 diabetes: a phase 2 randomised crossover trial. *Lancet* 2010; 375:743–751.
77. Pickup J, Keen H: Continuous subcutaneous insulin infusion at 25 years—evidence base for the expanding use of insulin pump therapy in type 1 diabetes. *Diabetes Care* 2002;25: 593–598.

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