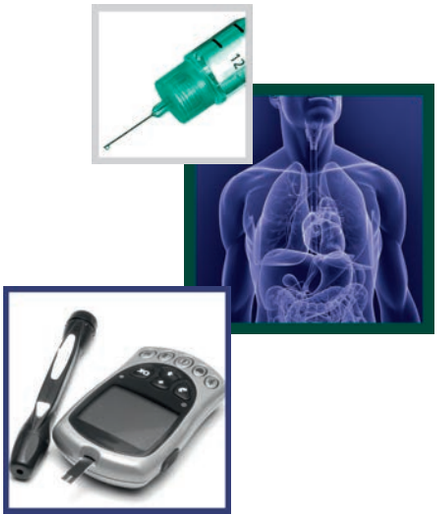
FOREWORD



Unfulfilled promises: a call to action

Denis Daneman*[1] David B Dunger[2]

"...hypoglycemia remains the 'elephant in the room' – the central impediment to achievement and maintenance of near normoglycemia for all."

In June 2011, the James Lind Alliance Type 1 diabetes (T1D) Priority Setting Partnership generated their top ten list of T1D unresolved treatment issues for research as agreed upon by both patients with T1D and clinicians [101]. **Box 1** provides this list. While the novice (patient and clinician) might be tempted to dismiss the list as much too simplistic, the most experienced will simply say: they got it right! Being in the latter category (each of us has more than 35 years of experience in the field of T1D in children and youth), we interpret the questions to be a call-to-action to make the major clinical discoveries/developments in T1D of the past 30 years more accessible to those with T1D and their careproviders.

What then do we see as those pivotal developments? No doubt, they include the development of assays for HbA1c (A1c), purer and biologically altered insulin preparations that have the potential to better mimic the rhythms of the nondiabetic pancreas, methods to self-monitor blood sugar levels outside of the hospital or clinic setting, followed by continuous monitoring systems and the rapid evolution of insulin pump therapy and the ability to track early markers of diabetes-related complications (retinal fundus photography and albumin excretion rates). However, there has been an increasing awareness that hypoglycemia remains the 'elephant in the room' – the central impediment to achievement and maintenance of near normoglycemia for all. Also of critical importance has been the recognition of psychological and/or psychosocial factors as playing crucial roles in outcomes, and the increasing evidence of the impact of the so-called social determinants of health across many important child (and adult) healthcare indicators [1–3].

Let's start at the top of the 'Lind list' and work down. The participants agreed that the overarching goal or aspiration of T1D research was for an 'effective' cure [4]. On this front, basic science has considerably advanced our understanding of the immune mechanisms inherent in the pathogenesis of T1D, epidemiology and laboratory studies of immune and genetic markers have combined to define the natural history leading to expression of

"The first fruits are likely to be technological with a closed loop, implantable pump, followed at some stage ... by stem cell cures and, eventually, safe and effective prevention by application of targeted immune modulation."

[1]Department of Paediatrics, University of Toronto, The Hospital for Sick Children, 555 University Avenue, Toronto, ON, M5G 1X8, Canada
[2]University Department of Paediatrics & University of Cambridge Metabolic Research Laboratories, Level 8, Box 116 Addenbrooke's Hospital, Hills Road, Cambridge, CB2 0QQ, UK
*Author for correspondence: Tel.: +1 416 813 6122; Fax: +1 416 813 7479; denis.daneman@sickkids.ca

Future Medicine part of fsg

Box 1. Ten top unanswered questions in Type 1 diabetes according to the James Lind Alliance.

Overarching research aspiration for T1D: an effective cure

1. Is it possible to constantly and accurately monitor blood sugar levels in people with T1D with a discrete device (invasive or noninvasive)?
2. Is insulin pump therapy effective (immediate vs deferred pump, and comparing outcomes with multiple injections)?
3. Is an artificial pancreas for T1D (closed loop system) effective?
4. What are the characteristics of the best type of T1D patient education programs (from diagnosis to long-term care) and do they improve outcomes?
5. What are the cognitive and psychological effects of living with T1D?
6. How can awareness of and prevention of hypoglycemia in T1D be improved?
7. How tightly controlled do fluctuations in blood glucose level need to be to reduce the risk of developing complications in people with T1D?
8. Does treatment of T1D by specialists (e.g., doctors, nurses, dietitians, podiatrists, ophthalmologists and psychologists) trained in person-centered skills provide better glucose control, patient satisfaction and self-confidence in management of T1D, compared with treatment by nonspecialists with standard skills?
9. What makes self-management successful for some people with T1D and not others?
10. Which insulin preparations are safest and have the fewest (long-term) adverse events?

T1D: Type 1 diabetes.

T1D, and well developed and executed multinational, randomized control trials have studied key candidates for diabetes prevention/intervention: TRIGR is an ongoing birth cohort study to understand the role of cow's milk protein in the expression of T1D in the genetically predisposed; DPT-1, then TrialNet sponsored by the NIH in the USA, have studied, and continue to study those high-risk relatives of probands with T1D: among the failed candidates are nicotinamide, insulin, glutamic acid decarboxylase and a host more. In addition, the number of agents attempting to alter the early course of the disorder once expressed now easily exceeds 20. That leaves islet transplantation and stem cell manipulation: islet transplantation has retracted into a protective shell since the early claims of massive success, while stem cells continue to be 'the low hanging fruit', they ought to be the solution, just not yet! Stem cell biology of the islets is developing steadily, but is nowhere near ready for clinical application. One can only hope for breakthroughs in this technology.

"...of critical importance has been the recognition of psychological and/or psychosocial factors as playing crucial roles in outcomes, and the increasing evidence of the impact of the so-called social determinants of health."

Although the aspiration of the 'Lind list' was for a cure, its top ten unanswered questions in T1D read rather like a plea to make the existing developments more accessible and to make significant inroads into our understanding of the factors, both biological and psychological/psychosocial, that support successful delivery of care to people with T1D. For our current purposes, we clumped the top ten into three main groups: the 'promise of technology' – questions 1, 2, 3 and 10; the 'context of care' – questions 4, 6, 7 and 8; and 'individual variation' – inter- and intrapersonal variables implied in questions 5 and 9.

Each wave of new technology has brought with it an expectation of improved metabolic control, and yet when meta-analyses or systematic reviews were performed a few years after their introduction, most came up wanting. Do insulin analogs really make a difference? Do insulin pumps allow sustained improvements in A1c levels? In some, the answer is a definite yes: collectively the data show only small, if any, improvements. Closing the loop with preprogrammed algorithms for insulin delivery by pump in response to glucose sensor-measured changes in blood sugar levels seems to be the most imminent hope for the next breakthrough. Then what is the delay? No doubt the manufacturers are reluctant to introduce these devices until they are absolutely certain of the accuracy and dependability of their sensor technology. The closed loop system is certainly a way to finally bring the issues of hypoglycemia under control.

What then is the current context of T1D care? The Diabetes Control and Complications Trial (DCCT) that started in 1982 and ended in 1993, reported the tight relationship between control and complications, providing the highest grade of evidence for the recommendations that inform the intensive management philosophy of T1D today [5]. However, there have been two or three unrelenting findings of the DCCT and its long-term follow-up study, the Epidemiology of Diabetes Interventions and Complications, which continue to frustrate all of us involved

in diabetes care. First, only a small number of subjects treated intensively during the DCCT achieved normal A1c levels, and during the more than 11 years of follow-up in the Epidemiology of Diabetes Interventions and Complications, the average A1c of the group was approximately 8% (regression to the same mean as very many large diabetes clinics report for longer duration T1D) [5]. Second, there is metabolic (or hyperglycemic) memory, implying a significant disadvantage to those experiencing long periods of poorer control before 'getting their act together,' specifically here we refer to adolescents with T1D [6]. Third, the adolescent cohort within the DCCT achieved and maintained A1c levels approximately 1% higher than the adult cohort in both intensive and conventional treatment groups [7]. This was in the face of similar approaches to therapy, higher prescribed insulin dosages in the adolescent group and the challenges of biological (e.g., insulin resistance of puberty) and psychological/psychosocial (adolescent noncompliance, risk-taking behavior, depression, and eating and weight psychopathology) factors in this age group [8].

With respect to the Lind questions on context of care, there will probably never be a randomized control trial comparing care of children and youth with T1D by experienced multidisciplinary healthcare teams and care by an inexperienced healthcare professional practicing in isolation: we have all invested too heavily in the former for good reasons. What we urgently need, however, are careful analyses of what works (and for whom) and what does not. Attempts to do this through the Hvidore International Study Group in Childhood Diabetes have failed, with the exception of lower and clearly elucidated glycemic targets enabling children to achieve lower A1c readings [9].

The final category then refers to 'individual variation,' those characteristics that might help define why some patients with T1D do better than others. For many years now, one of us, at least, has asked teenagers who seem to get great A1c levels without breaking a sweat, how they do this. The answer is inevitably a shrug of the shoulders and a look of perplexity: "why do you ask? Doesn't everyone do as well as or better than me." The roles of the social determinants of health and its close associate income equality, the discrepancy in income between the richest and poorest in society cannot easily be dismissed, nor for that matter, easily modified. What becomes increasingly obvious, is that as technology becomes more sophisticated and able to overcome some of the barriers described, the costs of diabetes care will rise. The result is predictable: an increasingly wide gulf between the 'haves' and 'have nots' with respect to access to and use of these technologies. In a world where the next surges in T1D incidence and prevalence are likely to be in the emerging economies of the so-called BRICK nations, the demands of increased healthcare costs, not just for T1D but across the entire spectrum of chronic diseases of both childhood and adulthood, threaten to derail, or at least slow, the pace of change.

"What we urgently need ... are careful analyses of what works (and for whom) and what does not."

In this edition of *Diabetes Management*, we have drawn together a selection of articles that specifically address the issues of managing diabetes in children and youth, some more biological in focus, others psychological/psychosocial, and some a blend of both. It is our distinct hope that the pace of change in management of diabetes in children and youth moves ahead in the years to come, as the fruits of basic and applied science no longer require that we give the wrong amount of insulin in the wrong place at the wrong time, nor that we apply guesswork in closing the loop, nor that behavior plays such a pivotal role in treatment success. The first fruits are likely to be technological with a closed loop, implantable pump, followed at some stage, not yet foreseeable, by stem cell cures and, eventually, safe and effective prevention by application of targeted immune modulation. Until then it behooves our multidisciplinary healthcare teams to do their best for their patients with diabetes: we know the look of what is best when viewed from 40,000 feet above the ground. The problem is that things get murkier as we confront the individual with T1D not able or, in some cases, perhaps not willing to do the work needed to meet their treatment goals.

This special edition begins with editorials addressing three very different issues: barriers to care in adolescents with diabetes, by Barbara Anderson from TX, USA [10]; optimizing sensor augmented pump therapy in young children, by Margaret Lawson from ON, Canada [11]; and then to a seldom considered issue in this age group, namely fertility, which is addressed by Ethel Codner's group from Chile [12]. While unrelated to each other, each editorial sets the stage for one or more of the pieces that follow: expert responses to questions as to when primary care physicians ought to consider the diagnosis of diabetes (Juliet Usher-Smith, UK),

"...as technology becomes more sophisticated ... the costs of diabetes care will rise."

when insulin-sensitizing agents could or should be considered as adjunctive therapy in T1D (Jill Hamilton, ON, Canada), and when should screening for celiac disease be performed in people with T1D, and who should be treated (Farid Mahmud, ON, Canada) [13]. The thoughtful responses of Silva Arslanian (PN, USA) introduce the issues of insulin resistance and Type 2 diabetes [14]. Trang Ly and Tim Jones (Australia) [15], and Fergus Cameron and Liz Northam (Australia) address two of the major limiting factors in achieving and maintaining good control, namely hypoglycemia and psychological/psychological disruption [16]. Then come a series of peer reviewed papers on diagnostic dilemmas in diabetes in childhood, transitions of care, complications and comordibities, and finally, the ever-present threat of diabetic ketoacidosis [17–21]. Each of these contributions addresses one or more of the top ten unanswered questions in **Box 1**. They do not, however, promise an end to diabetes in children and youth. That remains a challenge for the next phase of the 21st century.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

1 Hovorka R. Closed-loop insulin delivery: from bench to clinical practice. *Nat. Rev. Endocrinol.* 7(7), 385–395 (2011).

2 Shulman R, Palmert M, Daneman D. Insulin pump therapy in children and youth: uptake, efficacy and discontinuation. *Diabetes Manage.* 2, 119–138 (2012).

3 Cameron FJ, Northam EA, Ambler GR, Daneman D. Routine psychological screening in youth with Type 1 diabetes and their parents: a notion whose time has come? *Diabetes Care* 30, 2716–2724 (2007).

4 Wherrett D, Daneman D. Prevention of Type 1 diabetes. *Pediatr. Clin. North Am.* 58, 1257–1270 (2011).

5 DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Engl. J. Med*. 329, 977–986 (1993).

6 White NH, Sun W, Cleary PA *et al.*; DCCT-EDIC Research Group. Effect of prior intensive therapy in Type 1 diabetes on 10-year progression of retinopathy in the DCCT/EDIC: comparison of adults and adolescents. *Diabetes* 59, 1244–1253 (2010).

7 DCCT Research Group. Effect of intensive diabetes treatment on the development and progression of long-term complications in adolescents with insulin-dependent diabetes mellitus: Diabetes Control and Complications Trial. *J. Pediatr.* 125, 177–188 (1994).

8 Hamilton J, Daneman D. Deteriorating metabolic control in adolescents with Type 1 diabetes: physiologic or psychosocial? *J. Ped. Endocrinol. Metab*. 15, 115–126 (2002).

9 Swift P, Skinner T, de Beaufort C *et al.*; for the Hvidoere Study Group on Childhood Diabetes. Target setting in intensive insulin management is associated with metabolic control: the Hvidoere Childhood Diabetes Study Group Centre Differences Study 2005. *Pediatr. Diabetes* 11, 271–278 (2010).

10 Anderson BJ. Can we break down barriers to excellent diabetes healthcare for teenagers with diabetes? *Diabetes Manage.* 471–473 (2012).

11 Lawson ML. What is the role of sensor augmented pump therapy in young children with Type 1 diabetes? *Diabetes Manage.* 475–478 (2012).

12 Merino PM, Riquelme JE, Codner E. Addressing fertility and reproductive issues in female adolescents with diabetes. *Diabetes Manage.* 479–482 (2012).

13 Luca P, Hamilton J, Mahmud FH, Usher-Smith J. Pediatric Type 1 diabetes: adjunctive therapies, celiac disease and the role of the primary care physician. *Diabetes Manage.* 521–535 (2012).

14 Arslanian S. Pediatric diabetes management: past, present and future. *Diabetes Manage.* 537–547 (2012).

15 Ly TT, Jones TW. Managing hypoglycemia in children: what the clinician needs to know before advising parents. *Diabetes Manage.* 503–512 (2012).

16 Cameron FJ, Northam EA. Screening for psychological disorders in youth with Type 1 diabetes: who, when, what and how? *Diabetes Manage.* 513–520 (2012).

17 Amed S, Hamilton J. The emerging landscape of childhood diabetes: unraveling the diagnosis. *Diabetes Manage.* 521–535 (2012).

18 Nakhla MM, Daneman D. Transitions in the care of children and youth with Type 1 diabetes *Diabetes Manage.* 537–547 (2012).

19 Marcovecchio ML, Dunger DB. Comorbidities and complications: when, how and who to screen and when to treat? Microalbuminuria in adolescents with Type 1 diabetes. *Diabetes Manage.* 549–557 (2012).

20 Cass HG, Benitez-Aguirre PZ, Donaghue KC. Prevention and management of diabetic retinopathy in young persons with Type 1 diabetes. *Diabetes Manage.* 559–569 (2012).

21 Daneman D, Nakhla MM. Diabetic ketoacidosis in children and youth. *Diabetes Manage.* 571–578 (2012).

■ Website

101 The James Lind Alliance. Type 1 Diabetes: A JLA Priority Setting Partnership. www.lindalliance.org/Type1DiabetesAJamesLindAlliancePrioritySettingPartnership.asp (Accessed May 2011)