

Intervening in the Pathway of Beta Cell Destruction in Type 1 Diabetes

BY NATASHA RAZACK, MPH, AND DIANE WHERRETT, MD, FRCP

Significant advances in understanding the pathogenesis of type 1 diabetes mellitus (T1DM) have led to a multitude of opportunities for intervention. Specifically, a more thorough understanding has evolved of the potential for primary prevention efforts and beta-cell preservation strategies at the time of diagnosis. The TrialNet study group is an international, multicentre, collaboration of researchers dedicated to studying the prevention of T1DM and preservation of beta cells at diagnosis. Several studies sponsored by TrialNet are currently enrolling both newly-diagnosed individuals, as well as relatives of people with T1DM, to participate in clinical trials and natural history studies to learn more about disease pathogenesis and the efficacy of interventions. While knowledge of the disease pathogenesis and risk prediction have advanced substantially, the complexity of T1DM still poses a challenge for researchers and clinicians.

There is a significant window of opportunity during the asymptomatic phase of T1DM when intervention is plausible.¹ T1DM pathogenesis involves the autoimmune destruction of beta cells via a T lymphocyte-mediated process and the production of beta cell specific-antibodies.² The presence of these antibodies is predictive, but not causative of T1DM.³ Risk for T1DM can be predicted based on antibodies, other immunologic markers, and tests of beta cell function.³⁻⁵ Relatives of individuals with T1DM with these antibodies are at a higher risk of developing T1DM.⁶ This group has been targeted by T1DM research efforts to prevent or stop the disease. Strategies to prevent T1DM span 3 levels of prevention:

- primary (preventing the initiation of the autoimmune destruction of beta cells)
- secondary (stopping the autoimmunity against beta cells), and
- tertiary (arresting beta cell autoimmune reaction in newly-diagnosed individuals).

The pathogenesis of type 1 diabetes

T1DM results from an autoimmune process that destroys insulin-secreting pancreatic islet beta cells.⁷ The presentation of clinically-overt T1DM marks the end of a lengthy progressive destruction of beta cells, referred to as "prediabetes."^{8,9} The proposed model of the natural history of T1DM suggests that an interplay between genetic susceptibility and environmental factors, triggers prediabetes, usually identifiable by antibodies directed against beta cell components.^{1,9} Clinical onset of the disease occurs once beta cell destruction has reached the point when insulin production is inadequate; however, some beta cells remain and recover function during a "honeymoon" period.⁹ Figure 1 illustrates the current model of the natural history of the development of T1DM.

Environmental triggers

The etiology of T1DM is unknown, but environmental factors may play a role.¹⁰ Environmental factors that are being investigated as potential triggers for T1DM include viral infections, early infant diet, and toxins.¹¹⁻¹³ Finnish studies have demonstrated that exposure to cow's milk formula before the age of 4 months is an independent risk factor for T1DM.^{2,14} Other studies however, have not demonstrated the association between early cow's milk exposure and T1DM onset.¹⁵⁻¹⁷ Possible correlations to other environmental triggers such as



Leading with Innovation
Serving with Compassion

ST. MICHAEL'S HOSPITAL

A teaching hospital affiliated with the University of Toronto



Members of the Division of Endocrinology and Metabolism at St. Michael's Hospital

LAWRENCE LEITER, MD (HEAD)
EDITOR, *ENDOCRINOLOGY ROUNDS*

GILLIAN BOOTH, MD

ALICE CHENG, MD

PHILIP CONNELLY, PHD

CHRISTINE DERZKO, MD

RICHARD GILBERT, PHD, MD

JEANNETTE GOGUEN, MD

LOREN GROSSMAN, MD

AMIR HANNA, MD

SOPHIE JAMAL, MD, PHD

DAVID JENKINS, MD, PHD

ROBERT JOSSE, MD

MARIA KRAW, MD

TIM MURRAY, MD

DOMINIC NG, PHD, MD

JOEL RAY, MD

WILLIAM SINGER, MD

VLAD VUKSAN, PHD

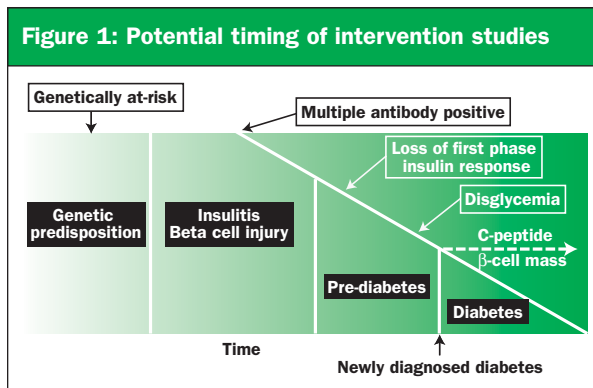
QINGHUA WANG, MD, PHD

TOM WOLEVER, MD, PHD

MINNA WOO, MD, PHD

St. Michael's Hospital
6121-61 Queen St. E.
Toronto, Ont. M5C 2T2
Fax: (416) 867-3696

The opinions expressed in this publication do not necessarily represent those of the Division of Endocrinology and Metabolism, St. Michael's Hospital, the University of Toronto, the educational sponsor, or the publisher, but rather are those of the author based on the available scientific literature. The author has been required to disclose any potential conflicts of interest relative to the content of this publication. *Endocrinology Rounds* is made possible by an unrestricted educational grant.



enteroviral infection or timing of vaccination have not been proven to date.¹⁵⁻¹⁷ In response to conflicting evidence surrounding environmental triggers for T1DM, The Environmental Determinants of Diabetes in the Young (TEDDY) Study Group initiated the first prospective study aimed at identifying environmental agents, including psychosocial factors that may trigger T1DM in newborns with a human leukocyte antigen (HLA) genotype that is associated with a high risk of T1DM from the general public and from families with a history of T1DM.¹⁸

The genetics of T1DM

T1DM is 15 times more likely in siblings of people with the condition; ie, the risk of developing T1DM in the general population is approximately 0.4%, while for siblings of affected individuals, the risk is approximately 6%.⁶ Genes located within the HLA class II region on chromosome 6p²¹ (IDDM1) account for approximately 50% of genetic risk for T1DM.^{1,5} High-risk haplotypes associated with T1DM include: DQA1*0301-DQB1*0302 with HLA DRB1*0401, *0402 or *0405 alleles with HLA DRB1*0301-DQA1*0501-DQB1*0201.⁶ The insulin gene (INS) locus has also been shown to provide approximately 10% of the genetic susceptibility for T1DM.¹⁹ Other HLA alleles – DQA1*0102 and DQB1*0602 – are protective for T1DM.²⁰ Since the HLA locus and the INS locus combined account for approximately 60% of the genetic risk for T1DM, additional susceptibility genes are currently being investigated.

Polymorphisms of the MHC I-related gene A (MIC-A), specifically in the 5 allele and the 5.1 allele, have been found to be associated with T1DM.²⁰ Another polymorphism in the PTPN22 gene is hypothesized to downregulate T-cell receptor signaling and contribute to the development of T1DM.^{21,22} The PTPN22 gene is also known to play a role in susceptibility for other autoimmune diseases as well, including rheumatoid arthritis, and lupus.²⁰ Polymorphisms observed in the cytotoxic T lymphocyte-associated gene (CTLA-4) have also been linked to the devel-

opment of T1DM and in synergy with the HLA alleles to Addison's Disease.^{23,24} T1DM is a heterogeneous and polygenic disease that likely involves genes from the HLA region and non-HLA loci.²⁵ T1DM genetics studies have been limited in power by small sample sizes. The Type 1 Diabetes Genetics Consortium is an international study group formed to collect large numbers of families with 2 siblings with T1DM to learn more about the genes associated with diabetes and their involvement in the T1DM pathogenesis.

Prediction

Autoantibodies in prediction: Autoantibodies are detected years before the onset of diabetes and continue to be produced after diagnosis. Antibodies produced during the autoimmune process include islet cell antibodies (ICAs), insulin autoantibodies (IAAs), glutamic acid decarboxylase (GAD), and tyrosine phosphatase (IA-2).²⁶ Studies have indicated that it is feasible to stage preclinical T1DM based on the number of detectable autoantibodies.²⁷

Autoantibodies have been observed to appear sequentially.²⁰ One large, prospective, observational study revealed that IAAs were the first, or among the first, autoantibodies to appear in 96% of children who develop multiple autoantibodies and half the subjects with multiple antibodies by the age of 2 developed diabetes by the age of 5 years.²⁷ Higher levels of each of the biochemical autoantibodies are also associated with the persistence of autoantibodies and progression to T1DM.³ One study showed that relatives with ≥ 1 antibodies had a 25% risk of developing T1DM over a 5-year period, those with ≥ 2 antibodies had a 39% risk of developing T1DM within 3 years, and those with ≥ 3 antibodies had a 75% risk of developing T1DM over a 5-year period.²⁸

Metabolic prediction: Evidence from the Diabetes Prevention Trial (DPT-1) indicates that there are predictive patterns of metabolic progression to T1DM.^{4,29} Specifically, over a 2-year period prior to developing T1DM, glucose tolerance gradually deteriorates as stimulated C-peptide levels slowly decline.⁴ Among ICA-positive relatives of people with T1DM in DPT-1, the oral glucose tolerance test (OGTT) results revealed the presence of subtle metabolic abnormalities several years before the diagnosis of T1DM.²⁹ In over 50% of children expressing multiple autoantibodies, a decreased first-phase insulin response (FPIR) was apparent at first evaluation.³¹ Follow-up in the DPT-1 with OGTTs in at-risk subjects every 6 months revealed that 60% were diagnosed with T1DM based on elevated 2-hour glucose readings alone.³²

Genetic prediction: Specifically, the HLA genotypes appear to make a significant contribution to predicting the

risk for T1DM.³³ Individuals who express the highest-risk HLA genotype (DR3-DQ2, DR4-DQ8) have a 5% risk of developing T1DM by age 15 years.³⁴ The presence of a low-risk genotype does not exclude the progression to T1DM, nor does a high-risk genotype result in the development of T1DM. A high/moderate risk genotype is associated with positivity for multiple autoantibodies in the siblings of affected relatives.

Status of research to prevent beta cell loss

Many strategies are being used to prevent the development of T1DM or prevent further beta cell loss after diagnosis. Each strategy targets a specific level in T1DM pathogenesis: before autoimmunity (primary prevention); after autoimmunity is detected (secondary prevention); and to maintain the honeymoon period (tertiary prevention).

TRIALNET

A variety of diabetes prevention trials and networks of collaboration are currently examining different strategies in this area of research. One such network is the TrialNet study group, a large international, multicentre collaboration supported by the National Institutes of Health (NIH) and the Juvenile Diabetes Research Foundation, and dedicated to studying the prevention of T1DM and the preservation of beta cell mass at diagnosis. The TrialNet network spans the globe with 13 clinical centres within the United States, one in Canada (located at the Hospital for Sick Children in Toronto), and 4 internationally (located in Italy, England, Germany, and Finland). Within Canada, there are affiliated TrialNet sites throughout the country. TrialNet is also carrying out a large natural history of diabetes development study to refine prediction models, better understand pathogenesis, and identify at-risk individuals. Table 1 lists the Canadian TrialNet sites and Principal Investigator contacts.

T1DM research prevention strategies

Primary prevention efforts

Primary prevention studies aim to prevent the initiation of autoimmune activity against beta cells and focus on environmental factors. The Trial to Reduce IDDM in the Genetically at Risk (TRIGR) is a primary prevention study investigating whether avoidance of cow's milk protein for at least the first 6 to 8 months after birth can prevent the development of T1DM among first-degree relative newborns with high-risk HLA genotypes.³⁵ This study recently finished recruitment and is continuing with a 10-year follow-up. The TrialNet study group has initiated another nutrition-focused primary prevention pilot study in the United States. Similar to TRIGR, the Nutritional Intervention

Table 1: TrialNet Study Group: Clinical Centres and Canadian Network

Site	Principal Investigator / Contact Information
Vancouver, British Columbia	Dr. Dina Pangiatopolous 604-875-2345 ext. 6658
Winnipeg, Manitoba	Dr. Shane Taback 204-480-1304
Edmonton, Alberta	Dr. Robert Couch 780-407-6888
Calgary, Alberta	Dr. Carol Huang 403-210-3977
Toronto, Ontario	Dr. Diane Wherrett 416-813-5858
London, Ontario	Dr. Jeffery Mahon 519-646-6000 ext. 65996
Hamilton, Ontario	Dr. Karen McAssey 905-521-2659 ext. 73967
Montreal, Quebec	Dr. Constantin Polychronakos 514-412-4400 ext. 22521
Saint John, New Brunswick	Dr. Susan Sanderson 506-648-7751
St. John's, Newfoundland	Dr. LeighAnne Newhook 709-777-4972
Halifax, Nova Scotia	Dr. Elizabeth Cummings 902-470-6489

to Prevent Type 1 Diabetes protocol (NIP) will investigate whether nutritional supplements with the omega-3 fatty acid, docosahexaenoic acid (DHA) – given in pregnancy and/or early childhood – prevent the development of islet autoimmunity in children with a first-degree relative with T1DM.

Secondary prevention efforts

Secondary prevention studies focus on stopping the autoimmune reactivity towards beta cells before T1DM symptoms appear, but after autoantibodies are found. The European Nicotinamide Diabetes Intervention Trial (ENDIT) used nicotinamide as a secondary preventative agent. Nicotinamide demonstrated efficacy in protecting beta cells in animal models; however, in humans, its administration in ICA-positive relatives did not delay the onset of T1DM.³⁶

The principal of immune tolerance was used in the DPT-1, using insulin as an autoantigen (administered either orally or parenterally), in an attempt to develop a suppressive or tolerant immune response to insulin.^{8,37} Participants deemed at high risk of developing T1DM received insulin parenterally, and those deemed at moderate risk were provided with insulin orally. Risk for

Table 2: Active/currently enrolling studies and their eligibility criteria

TrialNet Study Group – Natural history study of the development of T1DM	– Age 1 to 45 years and a 1st degree relative of a person with T1DM OR – Age 1 to 20 years and a 2nd degree relative of a person with T1DM
TrialNet Study Group – Anti-CD20/ Rituximab Study	– Age 12 to 45 years newly-diagnosed with T1DM (within 90 days of diagnosis)
TrialNet Study Group – Oral Insulin Prevention Study	– Age 3 to 45 years with confirmed positivity for insulin autoantibodies
TrialNet Study Group – Nutritional Intervention to Prevent Type 1 Diabetes Study (pilot study) US ONLY	– Pregnant women in their 3rd trimester (>24 weeks) may enroll if the baby they are expecting has a relative with T1DM – Babies up to 5 months old, if they have a relative with T1DM
Type 1 Diabetes Genetics Consortium	– Families with the following composition: 2 affected (non-identical twin) siblings, both biological parents, and up to 2 unaffected full siblings

diabetes was assessed based on autoantibody status and level of insulin secretion. The primary analysis of both arms of DPT-1 did not reveal any effect on the development of T1DM. Post hoc analysis of data from the DPT-1 oral insulin arm, however, did suggest a potential beneficial effect in a subgroup of individuals with a high titre of insulin autoantibodies.³⁷

In an effort to further investigate these findings, the TrialNet study group has initiated an international oral insulin prevention trial in relatives with insulin autoantibodies and one other autoantibody.³⁷ Study participants will take 1 capsule daily (either placebo or the study drug [oral insulin 7.5 mg]) for the study's duration. Recruitment has started in the United States and recruitment in Canada will begin in the spring, 2007.

Tertiary prevention efforts

Tertiary prevention strategies for T1DM focus on stopping the destruction of beta cells after disease onset, helping to preserve endogenous insulin production, and reducing the probability of disease-related complications.³⁸ Several agents have been investigated for their efficacy as tertiary preventive agents, including cyclosporine, azathioprine, and prednisone. Studies have revealed some positive outcomes; however, the observed toxicity associated with these agents has precluded their further use in clinical trials for the prevention of T1DM.³⁹⁻⁴² There is recent evi-

dence that a single course of a monoclonal antibody (anti-CD3) results in improvement in C-peptide responses, HbA1c, and insulin requirements for at least 2 years in individuals with newly diagnosed T1DM.^{43,44}

The TrialNet study group is actively involved in tertiary prevention trials in newly-diagnosed T1DM individuals. One TrialNet study is using mycophenolate mofetil (MMF) and dacluzimab (DZB) to arrest ongoing beta-cell destruction in recently diagnosed people. Both MMF and DZB have been shown to be effective in transplantation regimens and are well characterized and tolerated thus far. Enrollment into this study closed in October 2006; 126 subjects are enrolled worldwide and results are expected within 2 years. TrialNet is also investigating the use of the anti-B lymphocyte monoclonal antibody, rituximab, in preserving beta cell function in newly-diagnosed people with T1DM. Rituximab has been used in the management of other autoimmune diseases, including lupus and rheumatoid arthritis. This drug has been extensively used in children and adults and works to affect B-lymphocyte function, which is known to play a significant role in T cell-mediated conditions such as T1DM. International enrollment into this study is open at TrialNet Clinical Centres. Other agents under consideration by the TrialNet Study Group include anti-CD3 ± exenatide, thymoglobulin, and IL-2 plus sirolimus. Table 2 lists active studies and their eligibility criteria.

Challenges to T1DM research in the future

The pathogenesis and natural history of T1DM clearly reveals a “treatment dilemma.”¹ While early intervention could be an effective method of disease prevention for T1DM, individuals who demonstrate early autoimmunity may or may not develop the disease. As a result, interventions must not compromise the health of such individuals who may not develop the disease. The upcoming oral insulin study by TrialNet is one such intervention that poses few, if any, side effects to study participants. Individuals who are at, or near, disease-onset should also be assessed carefully for their degree of residual beta cell mass in conjunction with the proposed therapeutic intervention since the purpose of tertiary prevention is to preserve pancreatic beta cells and prolong endogenous insulin production.

Only 15% of newly-diagnosed patients have a family history of T1DM, making a general population approach to prevention research crucial. Unfortunately, based on our current knowledge of the pathogenesis of T1DM, a general population prevention effort is not yet feasible.

In spite of the treatment dilemma, knowledge of the pathogenesis of T1DM and risk prediction have advanced substantially. We are more aware of the pathogenic complexity of the condition and are using this knowledge to develop innovative strategies to stop the further destruction of beta cells in newly-diagnosed individuals or to prevent the disease altogether. Over 100 therapies have been shown to prevent diabetes in animal models;⁴⁵ however, translating animal model findings into human research is an intricate undertaking with many challenges. Regardless, several highly-supported and well thought out studies are in progress and geared towards further decoding the complexities of the pathogenesis of T1DM, the genes associated with the disease, how to prevent further destruction of beta cells, and how to prevent the disease altogether. T1DM research is in an exciting phase and many new study results are anticipated.

Natasha Razack, MPH, and Diane Wherrett, MD, FRCP, are affiliated with the Division of Endocrinology, Hospital for Sick Children, University of Toronto, Toronto, Ontario. **Natasha Razack** is Clinical Research Project Manager, TrialNet Study Group, Canada. **Dr. Diane Wherrett** is the Principal Investigator, TrialNet Study Group, Canada.

References

1. Atkinson MA, Eisenbarth GS. Type 1 diabetes: new perspectives on disease pathogenesis and treatment. *Lancet* 2001;358(9277): 221-229.
2. Kaufman FR. Type 1 diabetes mellitus. *Pediatr Rev* 2003; 24(9):291-300.
3. Barker JM, Barriga KJ, Yu L, et al. Prediction of autoantibody positivity and progression to type 1 diabetes: Diabetes Autoimmunity Study in the Young (DAISY). *J Clin Endocrinol Metab* 2004;89(8):3896-3902.
4. Sosenko JM, Palmer JP, Greenbaum CJ, et al. Patterns of metabolic progression to type 1 diabetes in the Diabetes Prevention Trial-Type 1. *Diabetes Care* 2006;29(3):643-649.
5. Achenbach P, Bonifacio E, Koczwara K, Ziegler AG. Natural history of type 1 diabetes. *Diabetes* 2005;54 Suppl 2:S25-31.
6. Redondo MJ, Eisenbarth GS. Genetic control of autoimmunity in Type I diabetes and associated disorders. *Diabetologia* 2002;45(5):605-622.
7. Vlahos WD, Seemayer TA, Yale JF. Diabetes prevention in BB rats by inhibition of endogenous insulin secretion. *Metabolism* 1991;40(8):825-829.
8. Effects of insulin in relatives of patients with type 1 diabetes mellitus. *N Engl J Med* 2002;346(22):1685-1691.
9. Eisenbarth GS. Type I diabetes mellitus. A chronic autoimmune disease. *N Engl J Med* 1986;314(21):1360-1368.
10. Rich SS. Mapping genes in diabetes. Genetic epidemiological perspective. *Diabetes* 1990;39(11):1315-1319.
11. Ellis TM, Atkinson MA. Early infant diets and insulin-dependent diabetes. *Lancet* 1996;347(9013):1464-1465.
12. Dahlquist GG. Viruses and other perinatal exposures as initiating events for beta-cell destruction. *Ann Med* 1997;29(5): 413-417.
13. Knip M, Akerblom HK. Environmental factors in the pathogenesis of type 1 diabetes mellitus. *Exp Clin Endocrinol Diabetes* 1999;107 Suppl 3:S93-100.
14. Hyponen E, Kenward MG, Virtanen SM, et al. Infant feeding, early weight gain, and risk of type 1 diabetes. Childhood Diabetes in Finland (DiMe) Study Group. *Diabetes Care* 1999;22(12): 1961-1965.
15. Norris JM, Scott FW. A meta-analysis of infant diet and insulin-dependent diabetes mellitus: do biases play a role? *Epidemiology* 1996;7(1):87-92.
16. Graves PM, Barriga KJ, Norris JM, et al. Lack of association between early childhood immunizations and beta-cell autoimmunity. *Diabetes Care* 1999;22(10):1694-1697.
17. Hummel M, Fuchtenbusch M, Schenker M, Ziegler AG. No major association of breast-feeding, vaccinations, and childhood viral diseases with early islet autoimmunity in the German BABYDIAB Study. *Diabetes Care* 2000;23(7):969-974.
18. Hagopian WA, Lernmark A, Rewers MJ, et al. TEDDY – The Environmental Determinants of Diabetes in the Young: an observational clinical trial. *Ann N Y Acad Sci* 2006;1079:320-326.
19. Bottino R, Trucco M. Multifaceted therapeutic approaches for a multigenic disease. *Diabetes* 2005;54 Suppl 2:S79-86.
20. Barker JM. Clinical review: Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. *J Clin Endocrinol Metab* 2006;91(4):1210-1217.
21. Smyth D, Cooper JD, Collins JE, et al. Replication of an association between the lymphoid tyrosine phosphatase locus (LYP/PTPN22) with type 1 diabetes, and evidence for its role as a general autoimmunity locus. *Diabetes* 2004;53(11):3020-3023.

22. Bottini N, Musumeci L, Alonso A, et al. A functional variant of lymphoid tyrosine phosphatase is associated with type I diabetes. *Nat Genet* 2004;36(4):337-338.
23. Ueda H, Howson JM, Esposito L, et al. Association of the T-cell regulatory gene CTLA4 with susceptibility to autoimmune disease. *Nature* 2003;423(6939):506-511.
24. Einarsdottir E, Soderstrom I, Lofgren-Burström A, et al. The CTLA4 region as a general autoimmunity factor: an extended pedigree provides evidence for synergy with the HLA locus in the etiology of type 1 diabetes mellitus, Hashimoto's thyroiditis and Graves' disease. *Eur J Hum Genet* 2003;11(1):81-84.
25. Faideau B, Larger E, Lepault F, Carel JC, Boitard C. Role of beta-cells in type 1 diabetes pathogenesis. *Diabetes* 2005;54 Suppl 2: S87-96.
26. Achenbach P, Warncke K, Reiter J, et al. Stratification of type 1 diabetes risk on the basis of islet autoantibody characteristics. *Diabetes* 2004;53(2):384-392.
27. Knip M. Natural course of preclinical type 1 diabetes. *Horm Res* 2002;57 Suppl 1:6-11.
28. Verge CF, Gianani R, Kawasaki E, et al. Prediction of type I diabetes in first-degree relatives using a combination of insulin, GAD, and ICA512bdc/IA-2 autoantibodies. *Diabetes* 1996;45(7): 926-933.
29. Sosenko JM, Palmer JP, Greenbaum CJ, et al. Increasing the accuracy of oral glucose tolerance testing and extending its application to individuals with normal glucose tolerance for the prediction of type 1 diabetes: the Diabetes Prevention Trial-Type 1. *Diabetes Care* 2007;30 (1):38-42.
30. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. *Ann Intern Med* 1998;128(7):517-523.
31. Keskinen P, Korhonen S, Kupila A, et al. First-phase insulin response in young healthy children at genetic and immunological risk for Type 1 diabetes. *Diabetologia* 2002;45(12):1639-1648.
32. Greenbaum CJ, Cuthbertson D, Krischer JP. Type I diabetes manifested solely by 2-h oral glucose tolerance test criteria. *Diabetes* 2001; 50(2):470-476.
33. Lambert AP, Gillespie KM, Bingley PJ, Gale EA, Pani MA, Van Autreve J, Van der Auwera BJ, Gorus FK, Badenhoop K (2002) Non-transmitted maternal HLA DQ2 or DQ8 alleles and risk of Type 1 diabetes in offspring: the importance of foetal or post partum exposure to diabetogenic molecules. *Diabetologia* 2003; 46(4):590-591; author reply 591-592.
34. Lambert AP, Gillespie KM, Thomson G, et al. Absolute risk of childhood-onset type 1 diabetes defined by human leukocyte antigen class II genotype: a population-based study in the United Kingdom. *J Clin Endocrinol Metab* 2004;89(8):4037-4043.
35. Akerblom HK, Vaarala O, Hyoty H, Ilonen J, Knip M. Environmental factors in the etiology of type 1 diabetes. *Am J Med Genet* 2002;115(1):18-29.
36. Gale EA, Bingley PJ, Emmett CL, Collier T. European Nicotinamide Diabetes Intervention Trial (ENDIT): a randomised controlled trial of intervention before the onset of type 1 diabetes. *Lancet* 2004;363 (9413):925-931.
37. Skyler JS, Krischer JP, Wolfsdorf J, et al. Effects of oral insulin in relatives of patients with type 1 diabetes: The Diabetes Prevention Trial – Type 1. *Diabetes Care* 2005;28(5):1068-1076.
38. Effect of intensive therapy on residual beta-cell function in patients with type 1 diabetes in the diabetes control and complications trial. A randomized, controlled trial. The Diabetes Control and Complications Trial Research Group. [see comment]. *Ann Intern Med* 1998;128(7): 517-523.
39. Feutren G, Papoz L, Assan R, et al. Cyclosporin increases the rate and length of remissions in insulin-dependent diabetes of recent onset. Results of a multicentre double-blind trial. *Lancet* 1986; 2(8499):119-124.
40. Cyclosporin-induced remission of IDDM after early intervention. Association of 1 yr of cyclosporin treatment with enhanced insulin secretion. The Canadian-European Randomized Control Trial Group. *Diabetes* 1988;37(11):1574-1582.
41. Silverstein J, Maclaren N, Riley W, Spillar R, Radjenovic D, Johnson S. Immunosuppression with azathioprine and prednisone in recent-onset insulin-dependent diabetes mellitus. *N Engl J Med* 1988; 319(10):599-604.
42. Harrison LC, Colman PG, Dean B, Baxter R, Martin FI. Increase in remission rate in newly diagnosed type I diabetic subjects treated with azathioprine. *Diabetes* 1985;34(12):1306-1308.
43. Herold KC, Gitelman SE, Masharani U, et al. A single course of anti-CD3 monoclonal antibody hOKT3gamma1 (Ala-Ala) results in improvement in C-peptide responses and clinical parameters for at least 2 years after onset of type 1 diabetes. *Diabetes* 2005;54(6): 1763-1769.
44. Keymeulen B, Vandemeulebroucke E, Ziegler AG, et al. Insulin needs after CD3-antibody therapy in new-onset type 1 diabetes. *N Engl J Med* 2005;352(25):2598-2608.
45. Atkinson MA, Leiter EH. The NOD mouse model of type 1 diabetes: as good as it gets? *Nat Med* 1999;5(6):601-604.

Upcoming Scientific Meetings

2-5 June, 2007

The Endocrine Society 89th Annual Meeting ENDO 07

The Metro Centre
Toronto, Ontario

CONTACT: Website: www.endo-society.org

22-26 June 2007

American Diabetes Association 67th Scientific Sessions

Chicago, Illinois

CONTACT: Website: scientificsessions.diabetes.org

10-13 June 2007

76th Annual Meeting of the European Atherosclerosis Society

Helsinki, Finland

CONTACT: Congress Secretariat

Tel. 41-229-080-488

Website: eas-society.org

Disclosure Statement: Dr. D. Wherrett and N. Razack, MPH, have no disclosures to announce in association with the contents of this issue.

Change of address notices and requests for subscriptions to *Endocrinology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Endocrinology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an educational grant from

sanofi-aventis