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Contributions to Type 1 Diabetes in Children and Adolescents:

Understanding the factors contributing to metabolic control and the short- and long-term complications of the disorder

VOLUME 1

Denis Daneman

University of the Witwatersrand

2012

Contributions to Type 1 Diabetes in Children and Adolescents:

Understanding the factors contributing to metabolic control and the short- and long-term complications of the disorder

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Denis Daneman

Published work submitted to the Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa, in fulfillment of the requirements for the Degree of Doctor of Science in Medicine

2012.

Declaration

I hereby declare that the work being submitted for the DSc Med has not been submitted by me to any higher degrees institution/university for any other degree.

Denis Daneman, BSc MBBCh FRCPC
Signed July 2012.

Life can only be understood backwards; but it must be lived forwards.
Soren Kierkegaard

Dedication:

To my maternal grandfather, Bendit Segal, who had not a single day's formal education in his life, but believed with a fiery passion that a good education is the essential foundation stone in life's journey; my parents, Sheila and Isy Daneman, who passed the same passion on to their children; my wife, Meredyth, who shares this value; and our sons, Nick and Rich who perpetuate this family tradition.

Contribution to publications submitted in support of the application:

My contribution to the submitted publications is as follows:

1. **Primary author** refers to publications in which the work was largely carried out by me from inception of the study, data collection and analysis and manuscript writing:

   Papers 1, 2, 3, 8, 9, 21, 45, 56, 57, 62

2. **Senior Responsible Author** refers to papers carried out in my laboratory by a student or postdoctoral fellow during their training with me and my collaborators. In these papers I have had a major role in supervising the trainee and ensuring integrity of the studies throughout all its phases:

   Papers 6, 7, 10, 15, 16, 18-20, 39-44, 52, 53, 58-60, 63, 64, 67-70

3. **Co-Senior Responsible Author** refers to sharing of the responsibilities in 2 above:

   Papers 17, 25-27, 29-31, 33, 46, 47, 61, 66

4. **Collaborator** refers to substantial contribution to the work together with a colleague who was Senior Responsible Author:

   Papers 4, 5, 11, 12, 14, 22-24, 28, 32, 34-37, 48-51, 54, 55, 65, 71

5. **Review articles and consensus statements:**

   Papers 13 (member of international executive committee overseeing consensus statement), 37 (review as co-senior author), 53 (Co-investigator in University of Toronto site of DCCT), 71 (sole author of review)

6. The work represented in this thesis was carried out in various institutions, including the Department of Paediatrics at the University of Pittsburgh and Children's Hospital of Pittsburgh, Pittsburgh, USA (1978-1981), and the Department of Paediatrics at the University of Toronto and The Hospital for Sick Children, Toronto, Canada (since 1981). Of note, a number of studies represent multi-institutional collaborations.

7. None of the work submitted here has been submitted by me for a higher degree. A number of trainees (under my direct or collaborative supervision) submitted the following papers as part of the requirements for an MSc degree (17, McGill University, senior supervisor of field work; 28, University of Toronto, co-supervisor; 60, 61 and 64, University of Toronto, senior supervisor of graduate degree) or PhD (24, University of Toronto, co-supervisor; 29-32, York University, co-supervisor of field work). All of the MSc students performed their work under my direct supervision and with research funding obtained by me as Principal Investigator. The two PhD students were co-supervised by Dr. G. Rodin (Department of Psychiatry) and me.

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1. ACKNOWLEDGEMENTS

My motivation for applying for admission to the Senior Doctorate program at the University of the Witwatersrand (Wits) has a number of roots; first and perhaps foremost is my intense desire to reflect on the past 45 years since entering Wits Medical School as a naïve 17 year old in an attempt to make 'sense' of my career as an academic paediatrician; second, is the vain notion that, in doing this, I will be repaying in some small way my alma mater for the seven glorious years of my education and somehow retiring the debt of having left South Africa soon after completing this education; third, it is an opportunity to thank those who have played the major role in shaping my career; fourth, to test my hypothesis that the story is worth telling; and, finally, if successful, I will have come nearly full circle in my educational relationship with Wits.

The major contributors to my choice of career path are: first, my parents: my father always wanted to be a paediatrician, but economic reality demanded he work and study at the same time and law was just a more practical path to do this, and my mother, also a lawyer, had aspirations that both her sons become professors, a wish fulfilled; second, Professor Phillip Tobias, who during my 'science year' in 1969 ignited a curiosity for attacking interesting questions that remains intense over 40 years later; third, Professor Harry Seftel for focusing that curiosity in diabetes; fourth, to all those who made it clear that I belonged in paediatrics; fifth, to Professor Robert Ehrlich at the University of Toronto and The Hospital for Sick Children, who befriended, mentored and nurtured, but never molly-coddled, me in the direction of paediatric endocrinology; fifth, Professor Allan Drash at the University of Pittsburgh and Children's Hospital of Pittsburgh who gave me my real investigative start: most trainees are lucky to have one academic 'parent': in Bob and Allan I have had two spectacular mentors, colleagues, collaborators, supporters, and

friends; finally, The Hospital for Sick Children and University of Toronto have been my homes since 1981, and have afforded me opportunities for career and personal development I would not have even begun to dream of when the journey started with the first tentative step into Wits in 1967.

I need also to mention a number of individuals whose careers have intertwined with mine for shorter or longer periods of time and who have contributed substantively to the story I hope is well told: first my collaborators, then those trainees whose contributions are enormous. On returning to Toronto in 1981, Bernie Zinman, Professor of Medicine, welcomed me into the University of Toronto centre of the Diabetes Control and Complications Trial (DCCT). Gary Rodin, Professor of Psychiatry asked me in 1982 if I had any clinical experience with teenage girls with diabetes and eating disorders. In answering yes, we set off on a research partnership that has lasted 30 years. It was Gary who mentioned to me the Kierkegard quotation at the head of these acknowledgements. It is an apt description as one looks back on a long and fulfilling career. Bill Balfe, Professor of Paediatrics, collaborated on many of the early nephropathy studies. Amira Klip, Professor of Paediatrics and Biochemistry, helped me bring the bench to the bedside. Teresa To and Astrid Guttmann have made asking health services research questions very much worthwhile.

The opportunity to work with trainees is an enormous joy, as is the ability to step back and watch their own career growth. Those whose direct work contributes to my story are, in sequence; Cheril Clarson, now an Associate Professor of Paediatrics at the University of Western Ontario, was my first research fellow and was involved a variety of studies in both children with type 1

diabetes as well as starting our rat studies of diabetes etiology (not included in this submission); Etienne Sochett, an Associate Professor of Paediatrics at the University of Toronto, who performed the remission phase studies and initiated the work in early diabetic nephropathy, and continues to make considerable contributions in this field; Jenny Couper (Cook), Professor and Head of Paediatrics at the University of Adelaide, who continued the nephropathy work completing the first study of ACE inhibition in the adolescent population; Margaret Lawson (Associate Professor, University of Ottawa) and Beth Cummings (Associate Professor, Dalhousie University), who sequentially worked on studies of metabolic control and pathophysiology of nephropathy; Jill Hamilton, who completed her MSc with me, opened up the area of insulin resistance/metabolic syndrome/obesity in our group and is an Associate Professor at the University of Toronto, now as an incredibly productive independent investigator; Elizabeth Estrada (University of Connecticut), Vera Zdravkovic (University of Belgrade), Jacqueline Curtis (University of Toronto), Helen Bui and Meranda Nakhla (both McGill University), Fergus Cameron (Professor, University of Melbourne) and Louise Conwell (University of Brisbane) all of whom have added pieces of the puzzle.

Of great note is my eternal gratitude to my patients and their families who willingly consented to participation in one or more of the studies reported here, but even more importantly for allowing me a window into their lives through care of their diabetes. My story is really theirs. Also, I have had the inordinately wonderful pleasure of always working in an interdisciplinary team with other physicians, nurses, dietitians, behavioral specialists and more, all of whom influenced my thinking, none more so than Marcia Frank, a diabetes nurse specialist of unparalleled ability.

A word of thanks is also due to four Wits DSc recipients. Three are on the Wits faculty: Professor Peter Cleaton-Jones who led me through the process of applying for admission; Professor Barry Joffe who has kindly mentored/supervised me through this process; and Professor Charles Feldman who shared his personal road to the DSc. The fourth, Jeffrey Maisels, Professor and Chair of the Department of Paediatrics, Oakland University William Beaumont School of Medicine in Detroit, was the first to ignite my interest in taking this journey: I am indebted to Jeff for his encouragement and support, as well as for providing comments on the final write-up.

Finally, I have a family that keeps me rooted in reality. Hopefully, we all take what we do very seriously, but we take ourselves a little less so. My wife, Meredyth, and I have been on an academic journey together for over 39 years, hopefully mostly supportive, even if occasionally competitive. We must have done something right since both of our sons, Nick and Rich are making academic careers for themselves in their own distinct fields. Our children and grandchildren make everything worthwhile. Zachary, Julian and Chloe bear the burden for carrying the torch into further generations.

Denis Daneman.

Toronto 2012

There can be no keener revelation of a society's soul than the way in which it treats its children.

Nelson Mandela

2. Introduction

Today type 1 diabetes is considered an autoimmune disease in which the target of the immune attack is the pancreatic beta cell which secretes insulin. Previously called insulin-dependent diabetes mellitus or IDDM, individuals developing this condition become dependent on insulin given by subcutaneous injection (and more recently by continuous infusion via an insulin pump). Prior to the discovery of insulin at the University of Toronto in 1921-22 by Banting and Best, individuals developing this disorder inevitably died in diabetic ketoacidosis. Since the availability of insulin there has been a significant 'transmutation' of type 1 diabetes (T1D) with the recognition of the impact of short- and long-term diabetes-related complications, the steady evolution of insulin preparations, the demonstration of a close relationship between glycemic control and the onset and progression of long-term complications, and the immense efforts to reverse this condition with either beta cell therapy (pancreatic or islet transplants, stem cell therapy) or technical improvements that allow physiological or near physiological insulin delivery.

My personal fascination with type 1 diabetes is based on three factors: first, my interest in biochemical pathways developed in part during my BSc Medicine degree at Wits (1969); second, the role models to whom I was exposed, particularly, as a medical student, Dr. Harry Seftel, and as a postgraduate trainee, Dr. Robert Ehrlich in Toronto and Dr. Allan Drash in Pittsburgh; and, finally, my personal exposure to T1D in my wife's grandfather and brother.

The studies that inform this submission are based on the confluence of certain technologies, such as the development of methods for the measurement of hemoglobin A1c (HbA1c or glycated hemoglobin) as the first objective measure of long-term metabolic control, and C-peptide as a

measure of residual insulin secretion, the development of strips and meters for self-monitoring of blood glucose, methods to evaluate early diabetes-related complications (retinopathy, and, more particularly nephropathy) with specific observations that I or others have made. These technological advances have made possible a more in-depth study of the natural history of T1D, its treatment and complications.

The sentinel observations that form the foundation of this submission include the following:

1. The Early Remission or "Honeymoon" period: For a considerable time it had been observed that most, but not all individuals developing T1D experienced a partial remission, or "honeymoon" period, shortly after diagnosis, as evidenced by excellent metabolic control in the face of low exogenous insulin requirements. While previous studies had shown a reciprocal rise in C-peptide concentrations, none had evaluated this phenomenon extensively.

2. The variability in frequency of short-term diabetes-related complications (diabetic ketoacidosis, DKA, and hypoglycemia) within individual patients, between patients, and even reported between different centres: DKA represents the end result of insulinopenia, with hyperglycemia and glycosuria leading to eventual dehydration, and ketogenesis unrestrained by physiological levels of hepatic insulin, leading to ketoacidosis. This occurs both at diabetes onset as well as during the course of the disorder. The epidemiology of DKA and its major complication, cerebral edema, had been little studied when my journey began.

3. The uncertainty of what causes longer-term complications and the variability in outcome: The demonstration of microalbuminuria as an early sign of and predictor of progression of diabetic nephropathy allowed me to explore the epidemiology of early diabetes-related complications, as well as interventions to modulate risk.

4. The factors affecting metabolic control in youth with T1D, particularly those that are behavioral, psychosocial or psychological in origin: the experience with a single patient ignited my suspicion that T1D may be an instigator of abnormal eating attitudes and behavior in teenage and young adult females with T1D, a forerunner to full-blown eating and weight psychopathology.

5. Finally, as in most research careers, one is challenged by interesting findings, clinical experiences, or curious trainees to stray from the main focus of one's research into new and challenging areas.

As a result of these experiences, my research has attempted to answer clinically relevant questions in a number of areas linked to the evolution of T1D in childhood and adolescence. I have gathered my contributions into the following themes:

i. Setting the stage: The measurement of HbA1(c) and its application to clinical medicine (references 1-5)

ii. Understanding the early course of T1D (references 6-12)

iii. The epidemiology of DKA and its complications, and diabetes-associated hypoglycemia (13-21)

iv. Eating disorders in teenage and young adult women with T1D: causes, course and complications (22-37)

v. The epidemiology of diabetic nephropathy and other diabetes-related complications (38-52)

vi. Interventions aimed at changing the course of T1D (53-60), and

vii. Miscellaneous (61-70).

3. Setting the stage:

i. The measurement of glycated hemoglobin and its application to clinical medicine:

The initial series of studies performed in the late 1970's evaluated the clinical utility of glycated hemoglobin (HbA1) measurement in children and teens with T1D. Just a few years previously a chance observation had been made that the hemoglobin electrophoretic pattern of individuals with diabetes differed from nondiabetics by the presence of a higher proportion of the HbA1 or HbA1c fraction, and that the proportion of this fraction related to average blood glucose over the life span of the red cell (about 100-120 days). This relationship of glycated hemoglobin to average blood glucose required that the glycation of hemoglobin (via an Amadori rearrangement) was irreversible.

In the first study (1), HbA1 was measured serially by minicolumn chromatography in 38 children with newly diagnosed T1D. Unexpectedly, HbA1 levels fell significantly from day 0 (prior to the initiation of insulin therapy) both to day 1 (mean 1.6% decrease) and to day 3-5 (2.6% decrease). This decrease correlated closely with changes in blood glucose, but not with prior duration of symptoms or changes in serum cholesterol and triglyceride concentrations. HbA1 levels reached a trough 3 weeks to 6 months after diagnosis, correlating with decreasing insulin dosage, and then rose again in 21 patients followed for more than 3-6 months. These results indicated that (1) HbA1 levels change rapidly during initial stabilization of T1D suggesting that glycation may not

be entirely irreversible, and (2) HbA1 levels are consistent with clinical assessment of control during the remission and early post-remission plases. This was the first demonstration that HbA1 measurement, at least by column chromatography, may be subject, in part, to ambient glycaemia and not totally reflective of average blood glucose concentrations over the prior 90-120 days as originally claimed. We postulated the presence of a rapidly reversible component of HbA1, the so-called labile fraction.

In the next study (2), we further evaluated the relationship between short-term glycemic control and what we termed the stable (irreversible) and labile (rapidly reversible) fractions of HbA1. HbA1 was measured 6 times over 24 hours in 13 children with T1D undergoing hourly blood glucose samplings for 24 hours. HbA1 was measured both in hemolysates of whole blood (standard technique) and after 48 hr incubation at 4 degrees C in normal saline in an attempt to remove the labile fraction. Saline incubated-HbA1 levels were always lower than whole blood-HbA1. Mean 24 hour blood glucose correlated closely with whole blood-HbA1c and much less so with saline incubated–HbA1. The daily fluctuations in HbA1 were always significantly less after saline incubation. The saline incubation had thus removed the rapidly reversible or labile fraction of HbA1, leaving the irreversible or stable fraction. The daily mean labile fraction correlated closely with the mean amplitude of glycemic excursions, MAGE, a measure of glycemic variability. The results of this study confirmed the presence of stable and labile forms of HbA1. When communicated with the companies providing laboratory measures of HbA1, then HbA1c, our findings led to changes in the recommendations for measurement not only by

minicolumn, but also by High Performance Liquid Chromatography, by application of a step to remove the labile fraction.

Having dealt with the vagaries of HbA1 measurement, the next studies were designed to evaluate the direct clinical utility of this measurement (3, 4). The first of these was in a large clinic cohort of children and teens with T1D attending the Diabetes Clinic at Children's Hospital of Pittsburgh (3). We measured HbA1 and a simultaneous random blood sugar in 477 children and teens with T1D over an 18-month period as indicators of metabolic control (once in 61 children, twice in 99, three or more times in 317). The conventional treatment of T1D at this time included: one to two insulin injections daily, either urine or blood glucose monitoring and a nutritional plan. We assessed the effects on HbA1 levels of patient's age, sex, disease duration, and the number of daily insulin injections and insulin dose (U/kg). The mean$\pm$SEM HbA1 was 11.8$\pm$0.2%, with only 1.4% in the normal range (<7.5% on this assay). HbA1 correlated closely with both age and blood glucose concentration but not with disease duration greater than one year. These data indicate a closer relationship between metabolic control in children with T1D and age of the child, particularly in females, than with disease duration. Using conventional therapeutic methods, these data also demonstrated that the ability to improve control over the short term as measured by changes in HbA1 has been quite limited. This study helped to target children and youth with T1D, particularly teenage girls, in need of more aggressive therapeutic interventions to improve control. The observation in teenage girls set the stage for later studies in Toronto aimed at understanding the relationship between T1D and eating disorders in this population.

The second study of clinical utility evaluated HbA1 as a potential screening tool for diagnosing diabetes in a large cohort of first degree relatives of children and youth with recent onset T1D as part of the Allegheny County Diabetes Epidemiology Study (4). The principal author of this study, Dr. Trevor Orchard, sought my collaboration, given my knowledge of the assay through the previous studies. In brief, the data showed lesser sensitivity of HbA1 as a screening tool for diabetes than results of an oral glucose tolerance test. With the introduction of increasingly more sophisticated HPLC and other methods for HbA1c measurement, the issue of these measures in screening for diabetes has been studied in greater depth: the current literature supports the use of HbA1c as a screening tool for diabetes in at risk populations.

Reference 5 represents a collaboration with Dr. Graham Ellis, then director of the Endocrine Service Laboratory at The Hospital for Sick Children. This was an evaluation of HPLC methodology, demonstrating the constant need to have a step to remove the labile fraction, but a very low intra- and interassay coefficient of variation, underlining the excellence of these assays. This and further studies have ensured the delivery of a state-of-the-art HPLC measure of HbA1c in our service laboratory.

The major contributions to the literature from these studies were: (i) the observed rapid fall in HbA1c levels immediately following diabetes diagnosis and institution of insulin to reduce hyperglycemia, suggesting a rapidly reversible or labile component of HbA1c, well demonstrated in the study employing saline incubation to remove the labile fraction; and (ii) the observations

made concerning the relationship between HbA1c and diabetes-related demographics, that remain as relevant today as more than 30 years ago.

ii. Understanding the early course of T1D (references 6-12)

Having contributed to the understanding of HbA1c measurement and its clinical utility, I then set off on a path aimed at elucidating the course of residual insulin secretion after the diagnosis of T1D. These studies utilize the measurement of C-peptide, cleaved off in equimolar amounts as insulin from the proinsulin molecule on first pass through the liver. The first study performed during my transition from Children's Hospital of Pittsburgh/University of Pittsburgh to The Hospital for Sick Children and University of Toronto was to define a sensitive and specific test for measuring C-peptide in these children (6). Two groups of studies were performed: (i) reproducibility of C-peptide secretion was assessed in 20 children with T1D by their responses to two Sustacal (a mixed liquid meal) stimulation tests performed 7-14 days apart; and (ii) the effect of exogenous insulin on C-peptide secretion was assessed in a further 20 children with T1D by their responses to two Sustacal tests, one test without and one with soluble insulin injected subcutaneously before testing. In both groups, those children who were C-peptide positive had no differences in C-peptide response between tests 1 and 2. These results were combined with those from 44 others undergoing a single Sustacal test. There was a very close correlation between basal and peak C-peptide concentrations in the 44 C-peptide-positive children. Peak C-peptide concentrations correlated inversely with HbA1, insulin dose (units/kg), and duration of diabetes, and positively with age at onset of diabetes. The C-peptide-positive children had reduced glucose response to Sustacal, lower HbA1 concentration, lower insulin requirement, later age of onset,

and shorter duration of diabetes than children who were C-peptide negative. These data allowed us and many other researchers to apply the Sustacal test in further studies.

Next, we studied the remission period of T1D in children and teens (7-12). First, serum C-peptide, glucose, pH, islet antibodies and insulin antibody binding were measured at diagnosis in 84 children with T1D, then, in a subgroup of 33 children, residual insulin secretion (basal and peak C-peptide response to Sustacal), insulin antibody binding and HbA1c were measured at 10 days, 1, 3, 6 and 12 months (7). At presentation C-peptide correlated positively with age at onset and negatively with the blood glucose concentration. Median C-peptide concentration at diagnosis was low, rose significantly at 10 days, reached a maximum at 1-3 months and declined gradually to 1 year. C-peptide concentration both at diagnosis and at 10 days correlated with that at 3 and 6 months. Of the factors investigated, only age and sex (higher in females) were found to have a significant influence on basal/peak C-peptide levels throughout the first year. In particular there was no relationship between C-peptide, HbA1c and insulin dose during this period. A peak C-peptide response at 3-6 months greater than/less than 0.32 nmol/l was used to divide the group into two: 16 had a peak response less than 0.32 nmol/l (low secretors) while in 17, the peak C-peptide was greater than 0.32 nmol/l (high secretors). While the low secretors had significantly lower C-peptide levels during the first year, there were no differences between low and high secretors in HbA1c or insulin dose. We proposed at the time that factors other than simply residual insulin secretion were also contributing to the manifestation of the remission period. Subsequently, changes in insulin sensitivity have been shown to mirror the expression of the remission period.

Then, in collaboration with Dr. Mikael Knip, a visiting fellow from Oulu, Finland, we undertook a study to evaluate whether differences in T1D incidence in two separate geographical locations (Oulu: very high incidence; Toronto, Canada: medium incidence) may be associated with differences in biochemical and demographic features at diabetes onset (8). The cohorts consisted of all children under 16 years of age who presented at the time of T1D onset to the children's hospitals in Oulu (n = 43) and Toronto (n = 87) during 1984-1985: children from Northern Finland had lower blood glucose and HbAlc levels, and higher C-peptide concentrations than those from Southern Ontario. The Finnish group also had a higher incidence of multiplex families (18.6 vs. 4.6%): in this group; those from multiplex families had a higher C-peptide concentration and lower frequency of ketoacidosis than those from simplex families. This was the first demonstration that differences do exist at the onset of diabetes in these groups from geographical locations with greatly different incidences of T1D. The question was raised whether these differences result from a greater awareness of T1D in an area of very high incidence or from real differences in etiopathology.

Using the specimens from our longitudinal study of the honeymoon period, we were then able to perform a series of studies evaluating the natural history of immune markers of T1D, specifically the insulin autoantibodies (IAA) and 64k-antibody (9-12). First, in collaboration with Dr. J-W Yoon in Calgary, we measured islet cell (ICA) and islet cell surface (ICSA) antibodies in 30 children (aged 6-17.7 years) with newly diagnosed T1D to describe the relationship of antibody status (positive/negative) to factors both at presentation (e.g., age, severity of onset, residual

insulin secretion, insulin autoantibodies) and during the first year thereafter (HbA1c, insulin antibody binding, residual insulin secretion) (9). At diagnosis, 10 of 30 were ICA (+) and 13 ICSA (+): no differences were found between ICA (+) and (-) subjects at onset; however ICSA (+) children had a lower bicarbonate concentration than those (-) for ICSA. During the first year after diagnosis the only significant finding was that in ICA (+) patients, insulin dose (units/kg) was lower at both 6 and 12 months than ICA (-)'s. Those children positive for both ICA and ICSA did not differ in any way at onset or during the subsequent 12 months from those negative for both antibodies. Our results suggest that, except for minor variations, the presentation and course during the first year after diagnosis T1D do not differ in those children positive or negative for either or both ICA and ICSA.

Next we turned our attention to insulin antibodies, which had been documented before (insulin autoantibodies [IAAs]) and after (insulin antibodies) insulin administration in children with new-onset T1D (10). The relationship of IAA to various factors at presentation had been studied in some detail; however, nothing was known about their relationship to events during the first year after diagnosis. Furthermore, the course and factors affecting insulin-antibody response to human insulin administration in children with newly diagnosed T1D had not been well defined. To study these questions, we used the cohort of subjects described in reference 7. At presentation, IAAs were absent (binding below the mean$\pm$3SD of the binding of control serums) in 51 patients (61%) and present (binding above the mean$\pm$3SD) in 33 patients (39%). Multiple regression analysis showed a significant nonlinear relationship between IAAs and age and less so with blood glucose at onset. There was a stepwise increase in insulin-antibody binding throughout the

first year, most marked during the first month of insulin therapy and showed a statistically significant difference between successive measurements only during this period. This study confirmed and extended the data regarding the relationship of IAA to earlier age of onset of T1D, suggesting perhaps differences in etiopathology or triggering of T1D in the very young.

The final two studies in this section (11, 12) were performed in collaboration with the laboratory of Dr. Terry Delovitch, then at the University of Toronto. His laboratory was studying the 64K antibody, later defined as the GAD antibody. These studies demonstrated two findings: first that T1D is associated with the presence of at least two antibody reactivities to distinct determinants of the 64-kD antigen, and that some patients may possess antibodies to a cryptic epitope on the detergent-solubilized molecule. This suggested that the detection of antibodies to epitopes on tryptic polypeptides of the 64-kD antigen may be of even greater diagnostic value for the onset of T1D diabetes than analyses of antibodies reactive with the intact 64-kD antigen. Second, in studying 15 children with T1D followed to 3 years after diagnosis, we demonstrated that levels of 64K antibodies persisted, despite declining beta-cell function and decreased immune responses to other islet antigens, but decrease during the next 3-4 years as remaining beta-cell function disappears. These were novel observations at the time, but were superseded by the demonstration that GAD was the antigen involved, allowing more sensitive and specific assays to be developed.

The studies presented in section 2 contributed to a more complete description of the early remission period of T1D in children and youth. They also represent a series of collaborations with other scientists who have made major contributions to the field (Knip, Yoon, Delovitch).

4. The epidemiology of Diabetic Ketoacidosis and its complications, and diabetes-associated hypoglycemia (13-21)

i. Diabetic Ketoacidosis (DKA)

Diabetic ketoacidosis (DKA) is a life-threatening complication associated with severe insulin deficiency leading to hyperglycemia, glycosuria and eventual dehydration, together with unrestrained hepatic ketogenesis leading to acidosis. DKA occurs in a number of circumstances: (i) at disease onset: in different reported series from developed countries, 15 to approximately 70% are in DKA; and (ii) in those with established T1D, DKA results from insulin unavailability or omission (deliberate or inadvertent, e.g. insulin pump failure), inadequate insulin replacement during the stress of intercurrent illness. DKA is associated with morbidity and mortality resulting from the development of cerebral edema which occurs in up to 1% of those experiencing DKA, more so in the youngest children (13).

DKA is an exciting condition for trainees to treat: children present with severe dehydration and acidosis, often with altered level of consciousness and at times on death's door. With careful management and monitoring, this condition reverses usually within 24-48 hours and the children return to normal functioning. Nonetheless, my experiences suggested to me that most cases of DKA were preventable and that the morbidity and even tiny mortality associated with it were only preventable by eliminating DKA itself.

The first study of children with DKA with which I was a collaborator with a co-fellow in Pittsburgh (Eva Tsalikian) involved the assessment of EEG changes in children newly diagnosed

with T1D or in those during episodes of DKA (14). Serial EEGs were performed after initiation of treatment on 39 patients aged 1-16 years with new onset or previously diagnosed T1D: 27 were in ketoacidosis and 12 ketotic only. Abnormal EEGs were found in 30 patients on admission. We demonstrated that EEG changes are common in children with DKA or ketosis, the severity of the abnormalities being most closely associated with the degree of hyperosmolality rather than acidosis. These changes may persist in some cases, possibly accounting for the increased frequency of EEG abnormalities in children with T1D. These data also suggested the potential for long-term brain dysfunction in these children, a topic of ongoing controversy more than 30 years later.

In Toronto, I have initiated and executed a series of studies aimed at understanding the epidemiology of DKA and its complications as a way of developing improved approaches to prevent the complications of this condition. The next three studies are classified as health services research performed in collaboration with scientists (Drs Teresa To and Astrid Guttmann) at the Institute of Clinical Evaluative Sciences (ICES), a not-for-profit independent institute funded by the Government of the Province of Ontario, which houses all of the major administrative databases relating to health care in Canada (15, 16, 17). The first of these aimed to investigate trends and geographic variation in DKA hospitalization rates among children in the Province of Ontario (15). Canadian Institute for Health Information (CIHI) data were used to identify 15,872 diabetes-related hospital admissions in children younger than 19 years in Ontario from 1991 to 1999. Of these, 5,008 admissions were because of DKA and 10,864 were due to conditions other than DKA (non-DKA). Small area variation analysis was used to compare areas with high versus low DKA admission rates. In brief we found the following: (i) a 19% relative

decrease in the overall diabetes admission rate over the study period: non-DKA admissions decreased by almost 30%, while those for DKA remained stable; (ii) the fatality rate was 0.19% for non-DKA admissions and 0.18% for DKA admissions; and (iii) variation across geographic areas remained stable for DKA over the study period with an average 3.7-fold difference between the lowest and highest regions. This small area variation is clinically important for a preventable complication with a significant potential for long-term morbidity and mortality. These data supported the notion that prevention strategies are needed, particularly in areas identified with the highest rates.

We then performed a second health services research study aimed at determining whether DKA at the onset of T1D might represent the result of a missed diagnosis and, therefore, a lost opportunity to prevent the episode of DKA (16). We identified all medical encounters within the 4 weeks prior to the date of diagnosis for all new cases of diabetes in children <18 years of age identified from April 1994 to March 2000 by use of the ICES administrative databases. A total of 3947 new cases of diabetes was identified, 735 (18.6%) with DKA. DKA rates were very much age-dependent: 39.7% for children $\leq$ 3 years and 16.3% for children >3 years. During the week before diagnosis, 285 children with DKA (38.8%) and 1104 (34%) children with diabetes without DKA had at least 1 medical visit. Children with diabetes overall had more medical encounters before diagnosis than control subjects or subjects presenting with asthma. We concluded that children with diabetes presenting with DKA frequently had a medical encounter before diagnosis. These data have important implications for enhancing public and physician awareness of diabetes in children and for the opportunity to diagnose T1D before it progresses to DKA.

The goals of the final health services research study in this section were (1) to describe rates of diabetes-related hospitalizations (overwhelmingly due to DKA) and retinopathy screening in the two years prior to and after transition to adult care; and (2) to assess whether different methods of transfer of care were associated with improved outcomes (17). We performed a retrospective cohort study which included 1507 young adults with diabetes of ≥5-year duration and tracked these patients until 20 years of age. Diabetes-related hospitalization rates increased from 7.6 to 9.5 cases per 100 patient-years in the 2 years after transition to adult care. Risk factors for post-transition hospital admissions included previous diabetes-related hospitalizations, lower income, female gender, and living in areas with low physician supply. Controlling for all other factors, those teens who were transferred to a new allied health care team with no change in physician were 23% less likely (relative risk: 0.23 [95% confidence interval: 0.05-0.79]) to be hospitalized after the transition than were those transferred to a new physician with either a new or no allied health care team. The rates of eye examinations were stable across the transition to adult care (72% vs. 70%; P = .06). Female patients, patients with higher income, and patients with previous eye care were more likely to have an eye care visit after transfer. This study demonstrated that during the transition to adult health care, there is increased risk of diabetes-related hospitalizations, although this may be less in youths for whom there is physician continuity. Specific risk factors for these admissions were also demonstrated. Eye care visits were not related to transition; however, rates were below evidence-based guideline recommendations.

My contributions to DKA in children led to the invitation to join the Organizing team for a Consensus Statement on DKA that was developed as a joint effort between the (Lawson Wilkins) Pediatric Endocrine Society and the European Society for Pediatric Endocrinology (13). Among the recommendations in this consensus statement was one that 3% saline be considered in the treatment of cerebral edema in DKA. This is derived at least in part from a case report we published in which mannitol was unsuccessful in reversing cerebral edema; however, 3% saline produced a dramatic effect (18).

In order to determine incidence, outcomes, and risk factors for pediatric cerebral edema related to DKA (CEDKA) in Canada, we then performed a case-control study nested within a population-based active surveillance study of CEDKA in Canada from July 1999 to June 2001 (19). The study was incorporated in the Canadian Pediatric Surveillance Program: cases were those patients with DKA <16 years of age with cerebral edema; two unmatched subjects per case with DKA but without cerebral edema served as controls. We identified 13 cases of CEDKA over the surveillance period for an incidence rate of 0.51%; 23% died and 15% survived with neurologic sequelae. CEDKA was present at initial presentation of DKA in 19% of cases. CEDKA was associated with lower initial bicarbonate, higher initial urea, and higher glucose at presentation. Although there was a trend to association with higher fluid rates and treatment with bicarbonate, these were not independent predictors. We concluded that CEDKA remains a significant problem with a high mortality rate, but could find no association between the occurrence of CEDKA and treatment factors. The presence of cerebral edema before treatment and the lack of relationship to treatment factors underline the fact that prevention of DKA is the key to avoiding this and other potentially devastating complications.

The most recent contribution to the field of epidemiology of DKA was our observation of a close correlation between the frequency of DKA at disease onset and income inequality in the countries represented within the Organization of Economic Cooperation and Development (OECD) (20). These data suggest that the frequency of DKA at diabetes onset in children below 14 years of age may be a useful addition to the list of child health indicators in the representative countries. Our interpretation is that, where income inequality is high, the discrepancy between haves and have nots is exaggerated and the 'social safety net' more porous. This is a finding that warrants further evaluation.

The data derived from the DKA studies are all supportive of an hypothesis that I formulated some years ago, namely the "Failure Hypothesis" which postulates that most, if not all, episodes of DKA are preventable because they arise due to a failure at some point in the evolution of the DKA:

1. At disease onset, DKA represents a **failure** to recognize the signs and symptoms of diabetes before progression to DKA;
2. During intercurrent illness, DKA development represents **failure** to manage the illness appropriately;
3. DKA resulting from insulin omission (see section on Eating Disorders and Diabetes) is a simple and expected outcome of **failure** to inject any or enough insulin; and
4. DKA resulting from insulin unavailability in the developing world is the direct consequence of our **failure** to provide the necessities of daily living.

Awareness of these "failures" has the potential to significantly decrease the frequency of DKA and its consequences.

ii. Hypoglycemia related to T1D

In order to study the epidemiology of hypoglycemia in children and teens with T1D, we conducted a survey of 311 children with T1D with the goal of evaluating the frequency and characteristics of those children experiencing severe hypoglycemia (defined by an episode of coma, convulsion, or both) (21). The children and/or their parents completed a questionnaire, and hospital records were reviewed for confirmation. 31% reported severe hypoglycemia, and a further 16% moderate hypoglycemia requiring the assistance of another person but not resulting in coma or convulsion. In just over half (53%) there was no history of either moderate or severe hypoglycemia; 22% reported more than one severe hypoglycemic episode (range 2 to 20), while 16% reported multiple events in a single year. Of 285 episodes reported, 39% occurred during sleep and 61% while awake. Children reporting such events tended to have diabetes of longer duration and be younger at the time of the first episode. HbA1c concentration at the time closest to the severe episode was significantly lower than in children reporting no hypoglycemia. Glucagon to reverse severe hypoglycemia at home was available in the vast majority but used in only 30%. Thus, we confirmed that severe hypoglycemia is common in children with T1D, and that strategies are required both to prevent and to treat severe hypoglycemia in these children.

These studies on DKA and hypoglycemia in children and teens with T1D have contributed significantly to our understanding of the epidemiology of these acute complications of TID and

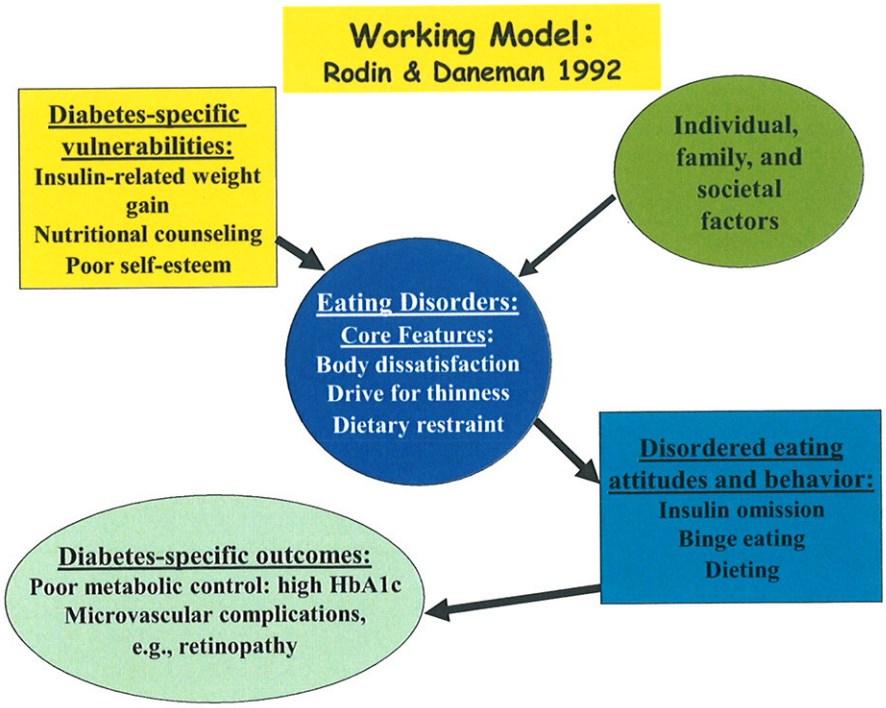
are leading to attempts worldwide to introduce both public health and individual treatment measures to prevent these acute diabetes-related complications.

5. Eating Disorders (references 22-37):

During my training in Pediatric Endocrinology, I became aware that (i) adolescence is a time of deteriorating metabolic control in those with T1D; (ii) girls tend to have a greater rise in HbA1c levels during this period than boys (see reference 3); and (iii) that more of the deterioration in control was related to psychosocial or psychological variables than to biologic phenomena. An experience with one patient in particular suggested that, at least in some of the girls, deterioration in metabolic control may be related to eating and weight psychopathology, not specifically to an association with anorexia nervosa the most obvious eating disorder described at the time. Shortly after returning to Toronto in 1981, a conversation with Dr. Gary Rodin, a staff psychiatrist at The Toronto General Hospital, led to a collaboration which has lasted over 30 years and has produced a major part of the extant literature in this field (22-37).

Gary Rodin and I postulated an interaction between T1D and eating and weight psychopathology that we have been able to test and which, we believe, remains relevant today about 20 years after we first published this model (Figure 1).

Figure 1: Model of interaction between Type 1 diabetes and eating and weight psychopathology:



Studies performed by our research group have aimed at providing the evidence to support the model above. The first question to be answered was whether eating disorders are, in fact, more common in adolescent and young adult females with T1D than in their nondiabetic peers. A series of early studies by our group and others produced confusing results for a number of reasons: (a) all were inadequately powered and/or did not include a control group; (b) different criteria were used to define eating disorders; and (c) many studies included younger or older females not in the age of greatest risk of an eating disorder (22, 23). The definitive study by our group (24) followed by a meta-analysis, has concluded that these females with T1D have a significantly greater (2-2.5-fold) risk of a full blown or subthreshold eating disorder when compared to their nondiabetic peers. This study aimed to determine the prevalence of eating disorders in adolescent females with T1D compared with that in their non-diabetic peers, using a cross sectional case-controlled study in

diabetes clinics and schools in three Canadian cities. The study consisted of 356 females aged 12-19 with T1D and 1098 age matched non-diabetic controls. Eating disorders meeting Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria were more prevalent in diabetic subjects (n=36, 10%) than in non-diabetic controls (n=49, 4%) (odds ratio 2.4, 95% confidence interval 1.5 to 3.7; P<0.001). Subthreshold eating disorders were also more common in those with diabetes (n=49, 14%) than in controls (n=84, 8%) (odds ratio 1.9, 95% confidence interval 1.3 to 2.8; P<0.001). Mean HbA1c was higher in diabetes subjects with an eating disorder (9.4±1.8%) than in those without (8.6±1.6%, P=0.04). Thus (i) DSM-IV and subthreshold eating disorders are almost twice as common in adolescent females with T1D as in their non-diabetic peers; (ii) the presence of an eating disorder is associated with poor glycemic control; and (iii) of note, the eating disorder specifically overrepresented in the girls with T1D is ED-NOS or eating disorder not otherwise specified, rather than bulimia nervosa or anorexia nervosa.

Certain behaviours are indicative of eating disorders in girls with T1D, most specifically insulin dose omission or adjustment with the intent of inducing glycosuria as a means of losing calories and controlling weight. Our studies show that, while it is uncommon in the preteen girls with T1D, insulin omission increases exponentially during the period of greatest risk (12-14% in the 12-18 year olds, increasing to 34% when the same group is studied 4 years later) (25-29).

These behaviours are not without risk since our studies demonstrate higher HbA1c levels in the girls with full blown eating disorders compared to those without, with those with subthreshold

eating disorders being intermediate (27). Furthermore, this is associated with a significantly increased risk of retinopathy, and perhaps also nephropathy and neuropathy, as consequences of the poor control (27). To this end, we studied 91 young women with T1D at baseline and four to five years later to determine the prevalence and persistence of disordered eating behavior (on the basis of self-reported eating and weight-loss practices, including the intentional omission or underdosing of insulin to control weight) and the association of such eating disorders with metabolic control, diabetic retinopathy, and urinary albumin excretion. At baseline, the mean age of the young women was 15±2 years and the duration of diabetes was 7±4 years: 26 of the 91 (29%) had highly or moderately disordered eating behavior, which persisted in 16 (18%) and improved in 10 (11%). Of the 65 (71%) with normal eating behavior at base line, 14 (15%) had disordered eating at follow-up. Omission or underdosing of insulin lose weight was reported by 12 of 88 young women (14%) at baseline and 30 (34%) at follow-up (P=0.003). At baseline, the mean ±SD HbA1c was higher in the group with highly disordered eating behavior (11.1±1.2%) than in the groups whose eating behavior was moderately disordered (8.9±1.7%) or nondisordered (8.7±1.6%, P<0.001). Disordered eating at baseline was associated with retinopathy four years later (P=0.004), when 86% of the young women with highly disordered eating behavior, 43% of those with moderately disordered eating behavior, and 24% of those with nondisordered eating behavior had retinopathy. Disordered eating behavior is common and persistent in young women with T1D and is associated with impaired metabolic control and a higher risk of diabetic retinopathy. This paper, published in 1997 in the New England Journal of Medicine, has had a very important impact in defining the relationship between T1D and eating disorders, and in highlighting the serious consequences of this relationship (27).

We then proceeded to study the interactions between eating disorders in teens with T1D and various aspects of family functioning. In a series of innovative analyses as a doctoral and then postdoctoral student working with us, Sherry Maharaj demonstrated significant intra- and interpersonal factors in the girls with full blown and subthreshold eating disorders and in their mothers as well (29, 30, 31, 32). The first report of the study of 113 adolescent females with T1D and their mothers investigated whether: (1) interaction patterns are more dysfunctional in families of girls with eating disturbances than in those without; and (2) the relationship between family functioning and metabolic control is mediated by an eating disturbance (29). Based on self-reported eating attitudes and behaviors, we categorized the subjects as Nondisturbed (N = 56), Mildly Disturbed (N = 37), or Highly Disturbed (N = 20). Mothers and daughters rated overall family functioning, and daughters rated parental relationships. This study (i) illustrated that eating disturbances are associated with the perception of poor communication with mothers and fathers, a lack of trust in their accessibility and responsiveness, and overall family environments perceived to be conflictual and inadequate in support and structure; and (ii) revealed that the presence and severity of an eating disturbance mediates the influence of family functioning on metabolic control.

We then examined whether eating problems are linked to autonomy and intimacy in the observed interactions of 88 diabetic girls (M = 14.9 years) and their mothers (30). On the basis of self-reported symptoms in the first part of the study, these teens were classified as having no eating problems (n = 40), mild eating problems (n = 30), and frequent eating problems (n = 18). Mothers and daughters participated in 2 videotaped problem-solving tasks (a diabetes-related and

a general parent-teen issue) that were rated with a macroanalytic coding system (Autonomy and Intimacy Rating System). Compared with interactions among mothers and daughters with no eating problems, interactions among mothers and daughters with eating problems simultaneously constrained the expression of autonomy and intimacy. Findings support clinical theory that links eating problems to emotional misattunement in the mother-daughter relationship, which is postulated to interfere with the teen's capacity for individuation.

The third phase of the study examined the relative contribution of adolescent self-concept, maternal weight and shape concerns (WSC), and mother-daughter relationships to eating disturbances among these 88 girls and their mothers (31). Self-concept was assessed by adolescent self-report. Mother-daughter relationships were assessed by adolescent self-report and by the observed mother-daughter interactions. Hierarchical regressions illustrated that adolescent self-concept deficits, maternal WSC, and impaired mother-daughter relationships significantly predicted eating disturbances in these girls with T1D, accounting for 57% of the variance. Mothers who engaged in dieting and binge-eating were more impaired in their ability to support their daughters' emerging autonomy. The quality of mother-daughter relationships partly mediated the influence of maternal WSC on adolescent eating disturbances. Moreover, the impact of maternal WSC and mother-daughter relationships on eating disturbances was mediated by adolescent self-concept.

Finally, we used this cohort to investigate whether intimacy and autonomy in mother-daughter interactions and relational aspects of the self are associated with metabolic control in adolescent girls with T1D (32). Self-concept in domains of perceived behavioral conduct (P=0.003), social acceptance (P=0.03), romantic appeal (P=0.03), and close friendships (P=0.04) independently predicted HbA1c levels, together accounting for 30% of the variance. Also, the experience of emotional closeness (i.e., intimacy) rather than separateness (i.e., autonomy) in mother-daughter relationships was associated with lower HbA1c (P=0.03). We concluded that relational aspects of the self and the experience of emotional closeness in relationships are associated with metabolic control in adolescent girls.

Minimal attempts had been undertaken to mitigate the impact of an eating disorders on metabolic control and future complications in teenage girls with T1D. Our next study, therefore, aimed to evaluate whether a six-session psychoeducation (PE) program in young women with T1D and disordered eating attitudes and behavior could improve both their HbA1c and their attitudes and behavior (33). We screened 212 teenage girls attending our pediatric diabetes clinic for signs of eating disturbance. Of these, 130 were eligible for the study and were invited to participate in the intervention phase. Eighty-five subjects were randomized to the PE or treatment-as-usual group. Assessments were conducted before and after treatment and at 6-month follow-up. Intention-to-treat group by time multivariate analyses of variance (MANOVAs) indicated significant reductions following PE treatment on the Restraint and Eating Concern subscales of the Eating Disorder Examination (EDE) and on the Drive for Thinness and Body Dissatisfaction subscales of the Eating Disorder Inventory (EDI), but no improvement in frequency of purging by insulin

omission or HbA1c levels. Thus this psychoeducation intervention was associated with reductions in eating disturbance, but not with improved metabolic control.

The most recent set of studies aim to define the natural history (or pathophysiology) of eating and weight psychopathology in girls with T1D. Thus, this series of investigations started by recruitment of an inception cohort of girls in the peripubertal period and has followed the evolution of these eating disorders for now more than 8 years. The lead investigator has been Dr. Pat Colton, initially as our trainee, but more recently as a full collaborator. These studies suggest ongoing significant psychosocial stresses in many of these teens (28, 34, 35, 36).

First, we conducted a cross-sectional, case-controlled study of 101 girls with T1D, 9-14 years of age, and 303 age-matched, female nondiabetic control subjects in order to compare the prevalence of eating disturbances in preteen and early teenage girls with and without diabetes (28). Using self-report and demographic data we found that binge eating; the use of intense, excessive exercise for weight control; the combination of two disturbed eating-related behaviors; and subthreshold eating disorders were all more common in girls with T1D. However, unlike older teens and young adults, metabolic control was not related to eating behavior in this study population. Thus even at this young age and stage of vulnerability to eating and weight psychopathology, girls with T1D were already showing significantly more abnormalities than their non-diabetic peers.

Next, these girls with T1D completed a battery of tests one year later in order to determine early progression/regression of the initial findings (34). Potential predictors of disturbed eating behavior at one year follow-up were body mass index (BMI), self-esteem, depressive symptoms, attachment to parents, and parental eating attitudes. Disturbed eating behavior was reported by 14% of girls at study inception, and 17% one year later, and persisted in 8/15 girls over 1 year. Lower self-esteem, higher BMI and more disturbed maternal eating attitudes at inception accounted for 35% of the variance in eating disorders scores at one year, while higher BMI and more disturbed attachment to one's mother predicted new-onset disturbed eating behavior. Again, glycemic control was not associated with or predicted by disturbed eating behavior. There was only moderate stability (persistence) of findings.

At five year follow up, one-half of 98 girls with T1D remaining in the study reported disturbed eating behavior (DEB) at some point during this longitudinal study, and early DEB almost universally persisted (35). The expected relationship between DEB and poorer metabolic control was not evident at 5 years, although there was a trend for higher HbA1c in individuals with an eating disorder. Low rates of binge eating and deliberate insulin omission may account for this weaker-than-expected association. Higher BMI and DEB were strongly associated.

The purpose of the most recent report published to date was to identify predictors of the onset of disturbed eating behavior (DEB) in adolescent girls with T1D after five years of follow-up (36). Logistic regression indicated that a model including BMI percentile, weight and shape concern,

global and physical appearance-based self-worth, and depression was significantly associated with DEB onset (chi(2) = 46.0, 5 d.f., $P < 0.0001$) and accounted for 48.2% of the variance. Even though scores on the measures were within the published normal range, the onset of DEB was predicted by higher depression and weight and shape concerns and lower global and physical appearance-based self-worth as well as higher BMI percentile 1-2 years earlier compared with those not developing DEB.

Ongoing follow up of this study is being conducted both to continue to describe the natural history of eating and weight disturbances in this high risk group, as well as to tease out the emergence of depression as an important contributor.

Of note is the support provided by the studies performed to our model presented in Figure 1 (37).

6. Diabetes-related complications:

i. Nephropathy (38-50):

Starting in the early to mid 1980's my laboratory embarked on a series of studies aimed at defining the prevalence of early diabetic nephropathy, its natural history and the first intervention trial in youth with microalbuminuria using angiotensin converting enzyme inhibition (38, 39, 40, 41). This was followed by studies of potential contributors to or effects of early nephropathy, namely early changes in blood pressure regulation, sodium-lithium countertransport and prorenin (42, 43, 44). Then, in collaboration with Etienne Sochett, starting in a junior faculty position and increasingly taking the lead on the nephropathy studies, we evaluated potential mechanisms involved in early nephropathy, specifically glomerular hyperfiltration/hypertension and the growth hormone-IGF-I axis during puberty and the role of dietary protein intake (45, 46, 47). Finally, we have embarked on a multicentre, multinational trial of early nephropathy in teens with T1D: the Adolescent Diabetes Cardiorenal Intervention Trial (AdDIT) aims to evaluate the potential protective effect of statins and angiotensin converting enzyme (ACE) inhibition either alone or in combination on the evolution of nephropathy and cardiac outcomes during puberty (48, 49, 50). I am the Principal Investigator for the Canadian arm of AdDIT (UK PI Dr. David Dunger, Cambridge University; Australian PI Dr. Tim Jones, University of Western Australia, Perth).

The first of the studies in early diabetic nephropathy (DN) aimed to define the sensitivity and specificity of different approaches to the measurement of microalbuminuria (MA) (38). It was at

this time that the detection of MA in adults with T1D was reported to be highly predictive of progression to advanced DN over the following 5-10 years. Using the timed 24 hour urine collection as the gold standard, we demonstrated a hierarchy of tests: albumin excretion rate (AER) in timed overnight specimens being the most sensitive and specific, followed by first morning albumin to creatinine ratios (ACRs), followed by ACRs in random (spot) urine collections. Of interest, it is this least sensitive test that most recently has been adopted in screening programs.

Next we studied the prevalence of MA in adolescents with T1D (39): 210 adolescents aged 12 to 18 years were screened for MA (AER of 15 to 300 micrograms/min). Sixteen (7.6%) showed persistent microalbuminuria (mean$\pm$SD AER of 70.9$\pm$56.2 micrograms/min). We did not find any significant differences between those with and without MA with respect to age, sex, disease duration, and blood pressure over the previous 9 months and HbA1c level measured over the preceding 3 years. Within the group with MA, there was no correlation between AER and blood pressure. However, there was a significant positive correlation between log AER and mean HbA1c measured over the preceding 3 years. Our findings suggest that when MA has developed, poorer metabolic control is associated with a higher albumin excretion rate. Elevated systemic blood pressure did not seem to precede the development of MA in this population.

We then performed a study in order to describe the natural history of urinary albumin excretion measured initially during the first decade of T1D in adolescents and to identify predictors of the

onset and progression of MA in this population (40). This was designed as a retrospective cohort follow-up study on 76 adolescents whose AER had been determined in the first decade of their diabetes and who were monitored for a mean of 6 years after initial AER testing. Those with MA were compared with a group with similar age, sex, and diabetes duration who initially had normoalbuminuria (NA). Of the 28 with initial MA, 9 (32%) regressed (8 to within the NA range), whereas MA was persistent in 10 (36%) and progressed in 9 (32%), 5 to overt proteinuria. Of the 47 who had initial NA, MA developed in 14 (30%) and overt proteinuria in 3 (6%). With MA status at follow-up as the dependent variable, multiple regression analysis showed that initial AER (P =.0002) and HbA1c (P =.02) measured at the same time were significant independent variables. Our data in adolescents with T1D demonstrated that: (1) MA detected in the first decade of disease will persist or progress in the second decade in approximately two thirds of patients, and new MA will develop in a third of those initially normoalbuminuric; and (2) the appearance, persistence, or progression of MA is influenced in large part by metabolic control assessed by HbA1c both at initial MA screening and throughout the course of diabetes. This underlines the need for MA screening starting early in the course of T1D in adolescents and for maintenance of good metabolic control. These data were markedly different from those in adults which suggested progression in over 75%; however, more recently adult outcomes have been shown to be more like those described in our and other studies, i.e. regression of MA in about one third of individuals.

It had been proposed that lowering glomerular pressure in individuals with T1D by means of an angiotensin converting enzyme inhibitor (ACEi) would reduce MA and that this reduction may

preserve renal function. This hypothesis had been tested in adults with T1D, but not in children and youth. We therefore conducted a double-blind, placebo-controlled, crossover trial to compare 3 months of treatment with the ACE inhibitor, captopril (0.9 mg/kg/day), and 3 months of placebo administration to 12 normotensive adolescents with TID, 11 with MA (AER of 15 to 200 micrograms/min) and one with early overt nephropathy (41). Mean age±SD was 14.4±1.7 years, and disease duration 5.1±2.5 years. AER decreased significantly during captopril therapy (baseline 78±114 micrograms/min; mean of monthly measurements 38±55 micrograms/min vs. placebo 78±140 micrograms/min; $P < 0.001$). During captopril therapy, albumin excretion was reduced by 41±44% and decreased in 10 of 12 subjects, but was unchanged in two, one with a borderline AER (16.3 micrograms/min) and one with diabetes of short duration (2.9 years). Plasma renin activity rose significantly during captopril therapy, and mean arterial pressure decreased slightly ($P = 0.004$). After 3 months of captopril treatment, glomerular filtration rate and renal plasma flow did not change significantly. We concluded that, in the short term, captopril is effective in decreasing AER in normotensive adolescents with T1D and microalbuminuria, without significant side effects. Longer trials are indicated in an attempt to delay or prevent overt nephropathy in the at risk adolescent population. This is one of the trials that have given impetus to AdDIT (see below).

The next series of studies was more mechanistic in nature, trying to understand either the pathophysiology of MA or its effects (42, 43, 44, 45, 46, 47). The first aimed to compare ambulatory blood pressure monitoring (ABPM) measures (mean systolic/diastolic blood pressure, diurnal rhythm, and pressure burden) in matched normo- and microalbuminuric T1D

adolescents and healthy controls (42). Twenty-four hour monitoring was undertaken in 39 normotensive (i.e. normal clinic blood pressure measurements) adolescents with T1D (22 normo- and 17 microalbuminuric subjects) and 23 controls. Subjects were matched for age, body mass index, gender, and T1D duration. Microalbuminuria was diagnosed on the basis of a urinary AER >15 <200 micrograms/min in two of three 24-h urine collections. The microalbuminuric patients differed from the normoalbuminuric subjects and controls in having higher mean 24-h and overnight systolic pressure, loss of systolic diurnal rhythm and increased systolic and diastolic pressure burden. There were no differences between the three groups in diastolic blood pressure. The normoalbuminuric group differed from the controls only with respect to an increased systolic pressure burden. Microalbuminuric adolescents with T1D show similar, albeit milder changes in ABPM, to those reported in adults with microalbuminuria. We postulated that these milder changes represent an earlier phase to that observed in the adult population and that taken together, the adolescent and adult data suggests a specific order in the development of ABPM changes in diabetic subjects.

The aims of the next two studies (43, 44) were to examine genetic and environmental influences in the development of early diabetic nephropathy and to assess the value of measuring membrane sodium transport and plasma prorenin as markers for early nephropathy. We initiated this as a family study into which we recruited an adolescent with T1D, and, wherever possible his/her nearest in age nondiabetic sibling plus mother and father. Two separate and interesting manuscripts resulted from this study, the first reporting the data on sodium-lithium countertransport (43), the second, the data on prorenin (44). These two factors were chosen for the

following reasons: first, the rate of sodium-lithium transport has been implicated as a potential risk factor for the development of essential hypertension, and abnormalities in this transport system had been demonstrated in some studies of individuals with T1D and nephropathy; and, second, early observations suggested that plasma prorenin may be an early marker of progressive diabetic nephropathy. The emergence of one or both of these factors as an indicator of risk for later development of advanced diabetic nephropathy would have obvious importance in identifying those with T1D who might benefit from more aggressive medical interventions aimed at renoprotection.

We measured erythrocyte sodium-lithium (Na-Li) countertransport, blood pressure (BP), HbA1c, and microalbuminuria (MA) in 84 adolescents with T1D, 29 of whom had MA. Twenty-nine non-MA patients were selected and matched for age, sex, and diabetes duration with the 29 diabetic subjects with MA. The 84 diabetic adolescents were also compared with 85 nondiabetic siblings. The erythrocyte Na-Li countertransport was significantly greater in the T1D group than in the sibling group ($P < 0.0001$), but a significant correlation was noted between the results in T1D subjects and their siblings ($r = 0.42$, $P < 0.0008$). Na-Li countertransport was not different in the diabetic subjects with or without MA. There was a significant correlation in the T1D group between recent diabetic control (HbA1c) and Na-Li countertransport ($r = 0.37$, $P < 0.003$). These results suggest that erythrocyte Na-Li countertransport is influenced by the diabetic milieu. However, there was also evidence in our subjects of a genetic contribution to Na-Li countertransport as seen by the correlation between levels in the T1D subjects and their siblings. Using Na-Li countertransport, we were not able to segregate those T1D adolescents with and without early nephropathy.

Next we reported on a subgroup of the cohort in the previous study: 50 adolescents, average age 16 years, with diagnosed T1D present for about seven years. Twenty-five had microalbuminuria (MA) averaging 111.0±34.0 (SEM) micrograms/min albumin excretion rate versus 6.7±7.4 micrograms/min in the 25 without MA. These subgroups were closely matched for gender, age, body mass index, duration of diabetes, HbA1c, and normotensive systolic, diastolic and mean BP. We compared them with a control group of 39 normotensive adolescents, of whom 18 were carefully matched siblings of the T1D subjects with MA and 21 were similarly matched siblings of the T1D non-MA subjects. Plasma renin concentration was determined by a direct radioimmunoassay method and found to be virtually the same in the control and T1D adolescents as a whole. There was also no real difference between the MA and non-MA subgroups. In contrast, plasma prorenin was significantly higher in the combined T1D group (197.5±9.3 vs. control, 134.0±7.9 pg/ml, $P < 0.0001$). It was also higher in the MA subgroup than in the non-MA subgroup (226.4±13.6 vs. 168.5±10.1 pg/ml, $P < 0.001$). Interestingly, the 18 control siblings matching the MA subgroup had higher plasma prorenin than the 21 control siblings matching the non-MA subgroup ($P < 0.001$), suggesting a familial predisposition that precedes detectable diabetes and nephropathy. Our findings confirm and extend reports by others that elevated plasma prorenin is associated with incipient nephropathy, manifested by MA. The exclusive renal origin of this prorenin, its role in plasma, and the mechanism responsible for its elevation in T1D with MA, are yet to be demonstrated, as is the general applicability of these findings to different populations of individuals with diabetes, with a higher incidence and severity of complications.

Epidemiological data had been published that implicated puberty as an important factor in the initiation and/or acceleration of diabetic nephropathy. However, the mechanisms had not been studied. We hypothesized (i) that puberty would result in an increase in glomerular hypertrophy and hypertension; and (ii) that these changes might be mediated by the known changes in the growth hormone (GH)-IGF-1 axis which mediates the pubertal growth spurt (55, 56). These two early concomitant events are seen as pivotal to the pathophysiology of diabetic nephropathy. First, we studied the effect of pubertal duration on three surrogate markers of glomerular hypertrophy/hypertension: kidney volume (KV), microalbuminuria (MA), and Na-Li countertransport (CT) (45): 177 subjects (87 female and 90 male; aged 6.2-22.1 years) with T1D for 5 to 10 years (6.8±1.6 years) were recruited into three groups with different pubertal duration: prepubertal since T1D diagnosis; prepubertal at diagnosis, now pubertal; or early puberty at diagnosis, now postpubertal. KV was measured by ultrasound and corrected for body surface area; MA was defined as urinary albumin excretion of 15-200 micrograms/min in two of three 24-h samples, and Na-Li CT was measured in erythrocytes. As pubertal duration increased, there was a disproportionate increase in mean KV (prepubertal, 247± 6 [SE] ml/1.73 m2; pubertal, 282±7/1.73 m2; postpubertal, 295±7/1.73 m2, P = 0.001), prevalence of nephromegaly (KV > 300 ml/1.73 m2) (14, 31, and 45%, respectively, P = 0.001), and prevalence of MA (0, 9.7, and 20.5%, respectively, P = 0.003). Subjects with KV > 300 ml/1.73 m2 were eight times more likely to have MA than those with KV < 300 (odds ratio 8.1, 95% confidence interval 2.4-27.4, P = 0.0001). There was no effect of pubertal duration on Na-Li CT. Multiple regression with KV as the dependent variable found an association with pubertal duration, MA, Na-Li CT, and current HbA1c (P < 0.0001). We interpreted these findings to indicate that pubertal duration is an

important determinant of both KV and MA and suggest that nephromegaly precedes microalbuminuria.

We then postulated that GH, IGF-I, testosterone, and prorenin may be potential mediators of the impact of puberty on glomerular hypertrophy/hypertension. The next study was designed to examine the relationship of these hormonal factors to kidney volume (KV) and MA in 155 subjects from the cohort in the previous report (46): 78 males, age 13.2±3.5 years) with similar diabetes duration (6.83±1.6 years) but varying pubertal experience (0-10 years). KV, plasma IGF-I, testosterone, prorenin, and NaLi countertransport, and urinary albumin, urinary GH, and urinary IGF-I were measured. Multiple regression analysis showed that body surface area ($P < 0.0001$) and urinary IGF-I ($P = 0.001$) were significantly associated with KV. MA subjects (albumin excretion rate 15-200 microg/min) had higher urinary IGF-I ($P = 0.005$) and urinary GH ($P = 0.05$) compared with normoalbuminuric subjects. The strong association of urinary IGF-I with KV, a marker for glomerular hypertrophy, and of both urinary IGF-I and urinary GH with MA suggests a role for these growth factors in the development of human diabetic nephropathy. Together, these data support animal studies that have shown that renal GH and IGF-I may contribute significantly to the pathogenesis of early diabetic nephropathy.

Data in adults with T1D suggested that dietary protein intake may have a negative impact on the evolution of diabetic nephropathy. Since dietary protein intake increases markedly, we utilized the cohort described in the previous two studies to examine the relationship between dietary

protein intake and possible early markers of diabetic nephropathy (creatinine clearance (CrCl), kidney volume and albumin excretion rate (AER)) (47). This analysis included 145 of the subjects with T1D for 5-10 years, who were divided into three pubertal groups. Kidney volume was measured, and serum creatinine and HbA1c assayed. Two or three 24-h urine collections were obtained for albumin, creatinine and urea excretion rates. Dietary protein intake was estimated from urinary urea nitrogen excretion rate. Glomerular filtration rate was estimated by creatinine clearance (CrCl). Mean protein intake was 1.22 ± 0.48 g x kg(-1) x day(-1), significantly higher in males than females ($P < 0.0001$) and highest in prepubertal compared to mid-pubertal and post-pubertal subjects ($P < 0.001$). In multiple regression analysis, protein intake was positively associated with CrCl ($P < 0.0001$), and male sex ($P < 0.0001$) and negatively associated with body surface area ($P = 0.0013$) and age ($P = 0.01$). Kidney volume and AER were not related to dietary protein intake. Thus, in this study we failed to show a significant relationship between dietary protein intake and markers of early nephropathy, other than CrCl. However, a longitudinal, prospective study would be required to definitively assess the role of protein intake in the evolution of diabetic nephropathy.

Based on the data presented in the studies of early diabetic nephropathy in youth with T1D published particularly by our group and that of Dr. David Dunger in the Oxford Regional Prospective Study (ORPS), an international collaborative study group was developed (Dr. David Dunger in the UK, Dr. Tim Jones in Australia, and me in Canada). We postulated that identification of adolescents at risk of diabetic nephropathy using an albumin excretion phenotype is feasible (48). When combined with elevated HbA1c, it may identify subjects for a

trial of early intervention with angiotensin-converting enzyme inhibitors/angiotensin-II receptor antagonists and statins to improve long-term prognosis in these subjects where sustained improvement in glycaemic control may be difficult to achieve.

The Adolescent type 1 Diabetes cardio-renal Intervention Trial (AdDIT) has been developed as a multi-center, randomized, double-blind, placebo-controlled trial of ACE inhibition and Statin therapy, alone or in combination in adolescents with T1D (49): to date (July 2012) almost 400 of a target of 500 high-risk adolescents, defined on the basis of their albumin excretion, have been randomized to receive either ACEI (Quinapril) or Statins (Atorvastatin) or combination therapy or placebo for 3-4 years. There is also a parallel open observational study, based on the follow-up of 400 low-risk non-randomized adolescents. The major endpoint of the study is the change in albumin excretion; secondary endpoints include markers of cardiovascular disease (CVD), renal function, retinopathy, quality of life combined with assessment of compliance and potential health economic benefits. AdDIT will provide important data on the potential renal and cardiovascular protective effects of ACEI and Statins in high-risk adolescents. Long-term follow-up of the randomized subjects will provide direct evidence of disease outcomes, in addition to the data on early surrogate measures of DN and CVD. Follow-up of non-randomized low-risk subjects will determine the potential impact of intervention on DN and CVD. AdDIT will help to determine whether, in addition to encouraging young people to achieve good glycaemic control, pharmacological cardio-renal protection should also be implemented.

To date, we have published one ancillary study from subjects who have been screened for inclusion in the in the AdDIT cohort (50). The aim of this preliminary analysis was to characterize the urinary excretion of cytokines/chemokines in normoalbuminuric adolescents with T1D to determine whether higher range normoalbuminuria is associated with evidence of renal inflammation: 42 urinary cytokines/chemokines were compared across low (n=50), middle (n=50) or high (n=50) albumin:creatinine ratio tertile groups in the AdDIT subjects in Canada. Results: At baseline, participants in the upper tertile were younger and had shorter diabetes duration compared with the other groups. Other clinical characteristics were similar. Urinary levels of interleukin 6, interleukin 8, platelet-derived growth factor-AA and RANTES differed across albumin:creatinine ratio tertiles, with higher values in patients in the middle and high tertiles compared with the lower tertile (ANCOVA $P \leq 0.01$). Thus, in this preliminary study, we have demonstrated that even within the normal albumin:creatinine ratio range, higher urinary albumin excretion is associated with elevated urinary levels of inflammatory markers. Ultimately, this may provide mechanistic insights into disease pathophysiology and stratify the risk of nephropathy in T1D.

The studies above (38-50) represent a significant contribution to our understanding of the prevalence, natural history and potential pathophysiological mechanisms responsible for the development and evolution of early diabetic nephropathy in youth with T1D.

ii. Macrovascular complications (51, 52)

Most of the studies of diabetes-related complications in youth with T1D have focused on microvascular, and not macrovascular, disease. We performed two studies, the first cross-sectional, the second a three year follow up of the same cohort, in order to determine the presence and correlates of early heart and blood vessel dysfunction in adolescents with T1D of relatively short duration (51, 52). We recruited 33 adolescents with T1D (20 male, mean age 15.8±1.3 years, mean DM duration 9.3±3.9 years) and 16 healthy subjects in a nondiabetic control group (7 male, mean age 17.4±1.7 years), who underwent (1) ultrasonography of the right carotid artery to assess distensibility, compliance, and intimal-medial thickness (IMT), (2) echocardiographic assessment of systolic and diastolic ventricular function, (3) lipid profile and HbA1c, and (4) overnight timed urine collections for albumin excretion rate (51). Ultrasonography showed significantly lower carotid artery distensibility in the DM group (38.5±8.2 x 10(-3) vs. 46.5±11.7 x 10(-3)/kPa, P =.01) but no difference in compliance. Left ventricular (LV) end-diastolic diameter, LV posterior wall thickness, end-systolic wall stress, shortening fraction, ejection fraction, LV mass, and diastolic function were similar in both groups. Total cholesterol, low density lipoprotein, high density lipoprotein, triglycerides, and blood pressure were also similar. HbA1c correlated inversely with both distensibility (r = -.43, P =.02) and compliance (r = -.39, P =.032). We concluded from this study that early changes in macrovascular function, namely lower carotid artery distensibility, may precede abnormalities in cardiac function or in arterial IMT in adolescents with short duration T1D. It also supported a relationship between hyperglycemia and carotid artery dysfunction.

We repeated the same studies in this cohort of adolescents and young adults with TID 3 years later (52). Of 33 T1D subjects in the initial study, 28 returned for follow-up. There were 28 controls without diabetes. The T1D group showed no significant change over the 3-year follow-up in lipid profile, HbA1c level, or albumin excretion rate, but a significant increase in body mass index. The diabetes and control groups were similar in age, lipid profile, and albumin excretion rate. Carotid artery distensibility and compliance in the diabetes group increased significantly from baseline to follow-up but did not differ significantly from controls. The intimal-medial thickness of the diabetes group remained unchanged over time but tended to be higher than controls. Echocardiographic studies showed no difference between the diabetes and control groups, but there was a small change in left ventricular posterior diastolic wall diameter in the subjects with diabetes over the 3-year period. There was an overall improvement in carotid function and no change in cardiac measures in subjects with diabetes over the 3 years, such that cardiac and vascular function was similar to those of controls. The reason for the improvement is uncertain, but may relate to the improvement of insulin sensitivity at the end of the pubertal growth period, rather than to changes in metabolic control or lipid profiles.

These two studies highlight the fact although it is feasible to perform accurate measures of both carotid and cardiac function in teens with T1D, these studies are likely insufficiently sensitive to detect the very earliest features of macrovascular disease. These and other measures of cardiac and carotid function are an integral part of the AdDIT collaborative (49).

7. Interventions (references 53-60)

At different stages throughout my career, I have been involved in intervention studies, most frequently randomized controlled trials, aimed at evaluating the impact of new approaches to therapy in children and teens with T1D. The studies reported in this section exclude my participation as a site investigator in the landmark Diabetes Control and Complications Trial (DCCT), a multicentre study which demonstrated unequivocally the close relationship between the level of metabolic control achieved (based on mean HbA1c levels) and the onset and progression of diabetes-related microvascular complications (53). This study, performed between 1982 and 1993, continues to inform the intensive management philosophy for all individuals with T1D. In addition, where more appropriate, intervention studies are embedded within the appropriate thematic section (e.g. 33, Eating Disorders; 41, Diabetic Nephropathy).

a. Self-adherence/Behaviour Modification Study:

First, in collaboration with the research team of Dr. Leonard Epstein, then a behavioral psychologist at the University of Pittsburgh, we performed a three-phase, 32-wk program to improve both self-regulation of adherence behaviors and insulin delivery in children with diabetes: 20 children, aged 8-12 yr with T1D were enrolled (54, 55). Phase 1 (wk 1-12) used behavior modification to improve diet, exercise, urine testing, and insulin adjustment, targeting an increased percentage negative urines. Feedback training and parent checks were used to improve reliability; Phase 2 (wk 13-20) was a stabilization period; and Phase 3 (wk 21-32) studied the effect of insulin dose adjustment, comparing once-versus twice-daily shots in 10 pairs of children matched for HbA1. We found a significant and sustained increase in negative urine tests, but no change in HbA1. Reliability of and adherence to urine tests were 83% and 76%, respectively. During phase 3, no significant differences were noted between groups receiving

once- or twice-daily insulin injections. Thus, behavior modification resulted in increased reliability and adherence to routines, associated with a reliable increase in negative urines, but did not, however, produce changes in other measures of glycaemic control.

b. **Self-monitoring of blood glucose:**

In the late 1970's monitoring of glycemic control transitioned very rapidly from traditional urine glucose testing to finger-prick self monitoring of blood glucose concentrations. The next intervention study (56) was designed as a double-crossover study to assess the impact of self-monitoring of blood glucose (SMBG) on the glycemic control of children with T1D on a conventional therapeutic regimen: 16 children with T1D were assigned to Group A, period 1 (wk 1-13): urine testing plus SMBG; period 2 (wk 14-26): urine testing only; or Group B, period 1: urine only; period 2: urine testing plus SMBG. Frequent telephone contact was maintained throughout to help optimize insulin dose adjustment. At the outset, the two groups were similar in age, diabetes duration, and HbA1. We were unable to demonstrate significant differences between the two groups at any stage of the study. There was, however, a trend toward lower mean blood glucose (MBG) concentrations in both groups toward the end of the SMBG period. SMBG confirmed symptoms of hypoglycemia in all children, and detected asymptomatic hypoglycemia in 11 children. Sixty-nine percent preferred SMBG to urine testing. In this study, one of the first to assess SMBG in children with T1D, we concluded that SMBG is an acceptable part of routine diabetes care in children. It was associated with very few complications and helps to confirm symptomatic hypoglycemia and detect asymptomatic hypoglycemia. However, the addition of SMBG to routine diabetes care does not necessarily lead to improved metabolic control.

c. Intensive diabetes management:

Following completion of the Diabetes Control and Complications Trial (DCCT) in 1993, intensive diabetes management (IDM) has become the standard of care in the treatment of individuals with T1D. However, at the time minimal information existed on the education and follow-up required to successfully initiate this treatment approach in adolescents with T1D. We performed a retrospective analysis of HbA1c 3 and 15 months after initiation of IDM in two cohorts: (1) 17 patients who received individualized education in IDM and intensive early follow-up, and (2) 11 patients who participated in group education for initiation of IDM with standard follow-up (57). Of note, is that this is a retrospective outcome audit of two separate, non-randomized clinical approaches to the introduction of IDM. Entry HbA1c was higher in the individualized education patients (9.5 versus 8.2%, $P = 0.02$). After 3 months of IDM, HbA1c improved in both cohorts reaching similar levels (individualized: $7.0\pm0.1\%$, $P < 0.0001$ vs. entry; group: $7.3\pm0.2\%$, $P = 0.05$). During the following year, with routine follow-up for both cohorts, HbA1c levels rose approximately 1% suggesting that, irrespective of the educational approach, maintenance of IDM and optimal HbA1c requires long-term intensive follow-up. This finding has been borne out in many studies of IDM whether by multiple daily insulin injections or continuous insulin infusion pumps.

We then performed a randomized control trial using a crossover design to study the separate effects of enalapril and intensive diabetes management (IDM) on sodium-lithium countertransport (Na-Li CT), kidney volume (KV) and AER in 17 children and adolescents with

type 1 diabetes (5-10 years duration) with large kidneys (>275 ml/1. 73 m(2)) and predominantly normoalbuminuria (58). Subjects were randomized to receive 3 months of either enalapril (0.25 mg/kg/day) or IDM, a 3-month washout, followed by the alternate treatment for 3 months. During IDM, HbA1c decreased 2.5% (pre 9.5±0.3% (mean±SE), post 7.0±0.1%, P<0.0001), but was unchanged while on enalapril (pre 8.8±0.3%, post 8.5±0.3%). A significant decrease in Na-Li CT was seen with IDM (P=0.006) but not angiotensin converting enzyme inhibition (ACE-i). Neither ACE-i nor IDM affected KV or AER. It is concerning that kidney enlargement does not appear reversible at this early stage in the pathogenesis of diabetic nephropathy, although our conclusions are limited by the short duration of intervention and small sample size. The reduction in Na-Li CT with IDM suggests this may be a potentially modifiable risk factor for diabetic nephropathy.

d. Interventions aimed at improving insulin resistance of adolescence

The recognition that insulin resistance increased during the pubertal years, likely due to changes in the Growth Hormone-IGF-1 axis, and that this might be contributing to the deterioration in metabolic control during this period, led me to hypothesize that the use of an insulin sensitizer as an adjunct to standard insulin therapy might mitigate the deterioration in control in some teens. The first study was developed to evaluate whether, in adolescents with T1D, the addition of metformin to insulin and standard diabetes management may improve insulin sensitivity and, thereby, lower HbA1c, fasting glucose, insulin dosage (units per kilogram per day) and BMI (59). The major impact of metformin is through its effect on suppressing hepatic glucose production

rather than by a peripheral insulin sensitizing effect. We performed a randomized, placebo-controlled 3-month trial of metformin therapy in 27 adolescents with T1D, high insulin dosage (>1 unit. kg(-1). day(-1)), and HbA1c >8%, with measurements of insulin sensitivity (by frequently sampled intravenous glucose tolerance test [FSIGT]), HbA1c, insulin dosage, and BMI at the onset and end of treatment. The metformin and placebo groups had no differences in HbA1c, insulin dosage, fasting glucose, or BMI at baseline. At the end of the study, HbA1c was 0.6% lower in the metformin group than in the placebo group. This was achieved at lower daily insulin dosages, and with no significant change in BMI. Change in insulin sensitivity, measured by FSIGT, was not significantly different between the two groups at study end although the degree of variability in each group was very large. Thus, metformin treatment lowered HbA1c and decreased insulin dosage with no weight gain in teens with T1D in relatively poor metabolic control. Changes in insulin sensitivity were not documented in this study using the FSIGT.

We then hypothesized that, if metformin were successful in this population, the use of a peripheral insulin sensitizer, namely a thiazolidinedione preparation, ought to be more so. This led to the next study (60), a randomized, placebo-controlled 6-month 2-site trial of pioglitazone therapy in 35 adolescents with T1D, high insulin requirement, and suboptimal metabolic control, with the primary outcome of change in HbA1c, and secondary outcomes including change in insulin dose, body mass index (BMI), lipids, and waist and hip circumference. Unlike the metformin study, we found no significant difference between the pioglitazone and placebo treatment groups at 6 months in any of the outcome parameters except BMI which increased in the pioglitazone group and remained unchanged in the placebo group. There was no significant difference in change in any lipid parameters between the pioglitazone and placebo groups at 6

month. Thus, adjunctive pioglitazone therapy was ineffective in improving glycemic control in adolescents with T1D, but was associated with increased BMI, a highly undesirable side-effect for teens.

It was very clear from these studies that thiazolodinediones have no place in the adjunctive management of T1D in teens, while metformin has been studied by others with similar findings. It has not yet, however, been approved for use under these indications, although off-label metformin use is applied by a number of centres worldwide.

8. Miscellaneous (61-70)

a. Measuring insulin sensitivity in circulating mononuclear cells

I became interested in finding an alternative to measuring insulin sensitivity by the available techniques such as insulin/glucose "clamp" techniques and measures derived from the frequent sampled intravenous glucose tolerance test, both difficult to perform in either younger children or in large cohorts. The attempt was made, therefore, to evaluate whether insulin-mediated glucose transport in circulating cells may provide this alternative. Two studies were performed in collaboration with Dr. Amira Klip, who remains a leader in the field of the cell biology of glucose transport (61, 62).

The objectives of the first study were to evaluate (i) glucose transport and its regulation by insulin in easily accessible human cells, (ii) the glucose transporter isoforms involved, and (iii) whether a defect in glucose transport is associated with peripheral insulin resistance, common in subjects with TID and controls (61). We measured 2-deoxyglucose (2-DG) uptake in circulating mononuclear cells from 23 nondiabetic adults, 16 adults and 10 children with T1D. Circulating mononuclear cells were separated from whole blood by Ficoll gradients and incubated with and without 1 nM insulin. 2-DG uptake was measured after incubation with [3H]2-DG and cell separation through corn oil-phthalate. Cytochalasin B-inhibitable 2-DG uptake (basal and insulin stimulated) was higher in control than in T1D subjects ($P < 0.001$). Insulin significantly increased 2-DG uptake or 3-O-methylglucose uptake in both groups. Basal and insulin-stimulated 2-DG uptake was similar for adults and children with T1D and did not correlate with age or body mass index in any group or disease duration, insulin dosage, or HbA1c. In separated monocytes and

lymphocytes, 2-DG uptake increased in response to insulin only in the monocyte population. Immunoblotting with specific antibodies revealed that circulating mononuclear cells and separated monocytes express the GLUT1 but not the GLUT4 isoform of the glucose transporter. Although we demonstrated insulin resistance in T1D relative to controls, the nature of the methodology and the absence of an insulin-mediated difference, suggested that this would not be an in vitro alternative to in vivo measures of insulin sensitivity.

In the second study, we attempted to further elucidate the mechanisms responsible for stimulation of glucose transport in these circulating mononuclear cells (CMCs), by investigating (i) the response to insulin-like growth factor-I (IGF-I) and insulin-mimetic agents, and (ii) the expression of other glucose transporter isoforms in CMCs of nondiabetic and T1D individuals (62). The time course of insulin-stimulated glucose uptake in CMCs was rapid, reaching a plateau within 30 minutes. CMCs showed a dose-dependent and highly sensitive increase in glucose uptake to IGF-I. The IGF-I dose-response curve was similar for CMCs of control and T1D individuals, but both the basal and maximal response to IGF-I were lower in the diabetic group ($P < .01$). CMCs did not respond to vanadate, lithium, hydrogen peroxide, or short incubation (1 hour) with metformin, but glucose uptake increased in response to peroxides of vanadate and longer-duration (14 hours) metformin incubations. The glucose transporter isoforms of separated monocytes and lymphocytes were further investigated by Northern blotting of total RNA with a GLUT3-specific cDNA probe and by Western blotting of total membranes using GLUT3-specific antiserum.

These studies were not pursued by my research group in view of their lack of clinical applicability. Nonetheless, they provide valuable insights into the dynamics of glucose transport in circulating mononuclear cells in both T1D and control subjects.

b. Psychosocial studies or observations (63-65)

Although the major thrust of my research in the psychological or psychosocial arena has been the relationship between T1D and eating and weight psychopathology in teenage girls, a number of other studies have also contributed to the field. First we performed a pilot study (not shown), then a more definitive analysis (63) of school attendance and performance in 6-12 year old children with T1D to determine whether these children miss more school than their non-diabetic siblings and peers and to identify factors associated with school absenteeism. Data for the 2000-01 school year were obtained for 78 children with T1D, 38 non-diabetic siblings and 118,269 age-matched peers in Toronto, Ontario using questionnaires and hospital records to evaluate child-, family- and diabetes-related factors. We found that children with T1D missed only slightly, albeit significantly more school than both their non-diabetic siblings (10.9 ± 8.9 vs. 8.1 ± 8.1 days, $P < 0.001$) and peers (median: 8.8 vs. 5.5 days, $P = 0.0005$). Multiple regression analysis indicated that school absenteeism in children with T1D was associated with their parents' attitudes towards school attendance, poorer metabolic control, shorter disease duration and a lack of aggressive behaviour. We concluded that with current management strategies, near normal school attendance is a reasonable goal for all children with T1D and should be strongly encouraged by parents, educators and health care professionals.

In an earlier study (64) we sought to test the hypothesis that poorer adherence to diabetes care is related to four variables associated with self-concept in adolescents with diabetes: self-esteem, self-efficacy, depression, and binging behavior: 193 patients (aged 13-18 yr) with T1D were recruited. All completed the Rosenberg Self-Esteem Scale, the Children's Depression Inventory,

an assessment of the frequency of binging in the past 3 mo, and parallel forms of an adherence scale and a self-efficacy scale developed for use in this study. Adolescents who reported lower adherence tended to report lower self-esteem and self-efficacy, more depressive symptoms, more binging, and had higher HbA1c than those with higher adherence scores. Together, the psychological variables accounted for 50% of the variance in adherence. There was no sex difference in reported binging, but, as expected, adolescent females reported less adherence overall ($F[7,184] = 2.5$, $P = 0.018$). These findings suggest that specific behavioral and cognitive interventions could be used to improve adherence in those individuals who lack confidence in their ability to perform diabetes-related tasks.

Finally here, together with Fergus Cameron a prior postdoctoral fellow, now on faculty at Royal Children's Hospital in Melbourne, we published what could be termed an hypothesis paper (65) in which a strong case is made for the inclusion of psychological and psychosocial disturbances in the routine screening of children with T1D and their families. The reasons for this are twofold: first, these disturbance (e.g. poor adherence, eating and weight psychopathology) are common in this population, and, second, when present are invariably associated with poor glycaemic control and therefore the risk for earlier micro- and macrovascular complications.

c. Treatment and technology assessments: Outcomes and systematic reviews (66-70) :

This section will very briefly summarize a series of studies which fit into the categories of treatment outcomes, patient safety and/or quality improvement. At the time they were performed to assess the impact of treatment (impact on growth and puberty) and/or the use of new technology (self-monitoring of blood glucose, continuous insulin infusion pumps, for example).

Growth and pubertal development were studied in 122 children aged 13.4±2.9 yr with T1D of 6.1±3.8 yr duration (66). Height and weight, pubertal status, insulin dose (u/kg), frequency of insulin administration and HbA1 (non-diabetic range for this minicolumn method <7.5%) were measured every 3 months for a minimum period of 1 yr. The mean and distribution of height and height velocity percentiles were normal for boys and girls. The mean weight percentile for boys was increased (62±27), but was normal for girls. The mean and distribution of weight velocity percentiles were normal for both sexes. The mean and distribution of age of onset of Tanner 2 in both boys and girls was normal, as was the age of menarche (13.2±1.2 yr). The mean HbA1 level was 11.1±2.0%, and there was no correlation of mean HbA1 levels with any of the growth parameters. We concluded that diabetes control, reflected by HbA1 levels, was not a major determinant of growth in this group of children with T1D. Normal growth of children with T1D should be an expected outcome.

We then studied the accuracy of self-monitoring of blood glucose (SMBG) using Chemstrip bG (Bio-Dynamics, Indianapolis, Indiana) in 90 children with T1D (67). For 28 younger children

(mean age 8.3±3.6 yr) a parent routinely read the Chemstrip at home, while the remaining 62 (mean age 13.7±2.8 yr) read the Chemstrip themselves. Each child or parent analyzed 20 capillary blood samples using Chemstrips and answered a questionnaire on SMBG. The accuracy of SMBG of the group was high (mean correlation coefficient = 0.89±0.05), but consistency of measurement was variable (mean standard deviation = 1.90±0.57) and there was a general tendency to under read Chemstrips. For each subject, 0-65% (mean of 34%) of readings were within 10% of the laboratory measurement, and 17-100% (mean 68%) within 20%. These results indicate that most subjects were fairly accurate in reading Chemstrips; however, analysis of accuracy is useful in identifying individuals who are inaccurate or inconsistent in SMBG.

We have also evaluated aspects of insulin pump therapy in youth with T1D (68, 69). First, we reviewed the data from 73 consecutive children and adolescents with T1D using insulin pumps for more than 6 months in our clinic (68). Statistically significant differences in HbA1c (-0.8%), body mass index (+1.45 kg/m2) and total daily dose of insulin (-0.23 U/kg/day) were found between the start of pump use and evaluation 6-30 months later. There was a close correlation between the HbA1c before and after 6-30 months of pump therapy. These data were certainly supportive of pump use in children and adolescents.

We then performed a cross-sectional study of 50 consecutive youth with T1D to describe the dermatological changes associated with insulin pump therapy in youth with T1D and to assess their association with duration of CSII, age, adiposity, HbA1c, insulin dose, insulin brand,

infusion set or site (69). A grading scale was devised. Ultrasound scanning was performed in 8 subjects. The mean severity score was 6.3 (range, 0-14; maximum possible, 69). Most common were scars <3 mm diameter (94%), erythema not associated with nodules (66%), subcutaneous nodules (62%), and lipohypertrophy (42%). There was a significant negative correlation between severity score and body mass index z-score ($r = -0.3$, $P = .039$), but no correlation with HbA1(c), insulin brand or site. Infusion sets inserted at 90 degrees were associated with lower scores ($P = .03$). Less than 5% of patients and parents considered stopping CSII because of skin concerns. Ultrasound scanning results of infusion sites revealed mild increased echogenicity of the dermis and hypodermis. Dermatological changes were frequent, with increased severity associated with lower adiposity. These complications were not associated with glycemic control, nor did they prompt most to consider stopping CSII.

Finally, in this section, a study lead by Astrid Guttmann was performed to validate a case definition of pediatric diabetes using administrative health data and describe trends in incidence and prevalence over time in Ontario, Canada (70). Hospital records of 700 children from 1994 to 2003 with a prior history of at least one outpatient or hospital record for diabetes mellitus and 300 randomly selected children with no diabetes records were reviewed. We defined patients as having diabetes based on diagnoses and drug utilization from chart abstraction and compared sensitivity and specificity of a number of combinations of overall health care use using administrative data to develop a highly specific definition. Use of four physician claims and no hospital records over a 2-yr period yielded the most specific definition (83% sensitivity, 99% specificity). Using this definition overall age/sex standardized incidence per 100,000 was 32.3 [95% confidence intervals (CI) 30.4, 34.4] and prevalence 241.5 per 100 000 (95% CI 236.2-249.9) in 2003/2004. Overall incidence differs by age, (peaking in 10-14 yr olds) but not

significantly by sex. The overall incidence has increased on average by 3.1% per year since 1994 (95% CI 1.02-1.04), with no difference in the rate of increase by age. We concluded that population-based surveillance of diabetes in children is possible using administrative data. This will facilitate further study of trends in incidence but also in use of health services and outcomes.

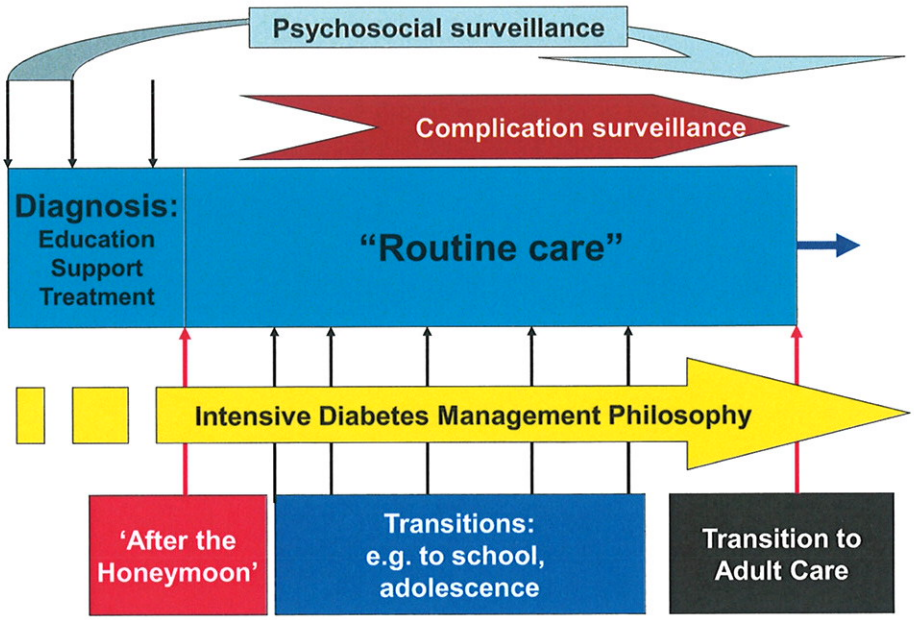
9. Summary and Conclusions:

Type 1 diabetes is an increasingly common and always complex condition which is triggered in those with genetic predisposition by events still unknown but likely very early in life. It is one of a number of chronic diseases which has undergone 'transmutation' over the course of the last 50-100 years; that is from being uniformly acutely lethal in the pre-insulin era to its intensive management with the considerable risk of both acute and long-term complications. Other conditions undergoing their own 'transmutation' include, for example, cystic fibrosis with median survivals increasing from 15 to 55 years of age since I began my career in paediatrics, and acute lymphoblastic leukemia with a survival to 5 years of less than 10% in the 1960s and well over 80% now, but with considerable late effects.

As a paediatric endocrinologist it is to the investigation of the natural and changing history of T1D that I have committed my research career. The express purpose of this commitment has been the need to better understand the disorder in order to provide the best possible care throughout its course. Figure 2 summarizes the components of the natural history of T1D and its complications that form the basis of my senior doctoral submission. The major contributions of my research can be summarized under the sections represented in this figure: the early course of T1D and its complications in children and youth, and interventions to enhance the outcomes.

The impact of my research has been such that I have been invited to write review articles and editorials (e.g. Diabetes Care (37), The Lancet (71); other references can be found in my curriculum vitae) for prestigious journals, participate in the development of national and international clinical practice guidelines (e.g. references 13, 72, 73, 74) or technological reviews

(e.g. 75, 76), and to be a site Prinicpal Investigator, Co-Investigator or Collaborator in multi-centre and/or multinational clinical trials (e.g. site PI in the Hvidore International Study Group, TRIGR and AdDIT; Co-Investigator/Collaborator in the DCCT).



It is with a sense of both achievement and humility that I submit this for the senior doctorate.

PUBLICATIONS submitted in support of the application:

Annotations:

i Trainees working under my supervision are underlined.

ii. IF = impact factor of journal as of 2009 wherever possible

Themes:

The measurement of GLYCATED HEMOGLOBIN (A1c) and its relationship to clinical medicine:

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International ranking (2011) of journals in their fields of Medicine: (The number in brackets after each journal represents the number of my publications in that journal)

General Medical Journals:
Highest ranked:
1. The New England Journal of Medicine (2)
3. The Lancet (1)
7. British Medical Journal (1)

Pediatrics and Pediatric Subspecialties (of 186 journals):
1. Pediatrics (2)
2. Journal of Pediatrics (13)
6. Archives of Disease in Childhood
12. Hormone Research
15. Pediatric Clinics of North America
27. Journal of Ped Endo Metab (3)
30. Pediatric Diabetes (5)
59. BMC Pediatrics (1)

Endocrinology and Diabetes (of 117 journals):
1. Journal of Clinical Endocrinology and Metabolism
2. Diabetes (4)
3. Diabetes Care (21)
5. Diabetologia (2)
14. Endocrinology and Metabolism Clinics of North America
16. Hormone Research
20. Diabetes Technology and Therapeutics (2)
26. Pediatric Diabetes (5)
52. Diabetes Spectrum (1)
Metabolism (2)
53. Diabetic Medicine (6)

Contributions to Type 1 Diabetes in Children and Adolescents:

Understanding the factors contributing to metabolic control and the short- and long-term complications of the disorder

VOLUME 2

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