INVITED SPEAKERS

INV01

Family involvement in the management of the child's diabetes

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Parent involvement with, and patient adherence to, diabetes management tasks are greatest shortly after diagnosis. Within 1 to 2 years of diagnosis, however, patient and parent behaviors consistent with optimal diabetes management often deteriorate, as does glycemic control. In recent family studies, it has been documented that there is an erosion of parental involvement and support for diabetes management tasks over the early- and middle-adolescent years. In addition, research has documented a steady decrease in adherence to diabetes treatment over this same developmental period. However, empirical studies have also shown that young adolescents who have more parental involvement in diabetes management, which are developmentally appropriate tend to achieve and maintain better diabetes outcomes. Moreover, studies have also shown the importance of developmentally-appropriate family involvement around diabetes management, for preventing acute and chronic complications in youth with diabetes. Interventions in this area have focused on increasing family involvement in diabetes tasks to encourage adherence as well as successful adaptation of the child, and adolescent. Interventions have also addressed family communication, and conflict management. Results of research on the efficacy of family-based interventions with children and adolescents, with T1DM are encouraging, and suggest the integration of specific intervention strategies into the clinical care of children with diabetes and their families.

INV02

Insulin resistance during puberty: is it good or bad?

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Even though insulin resistance plays an important role in disorders of glucose metabolism and other pathological conditions, there are developmental changes in both insulin sensitivity and secretion in childhood, particularly at puberty, which may serve important physiological function(s). During puberty, insulin action is diminished and is manifested in lower rates of insulin-stimulated glucose metabolism in pubertal compared with pre-pubertal or adult subjects. Moreover, during puberty there is a marked acceleration of growth with increasing body size, muscle mass, and body composition changes. This lecture will summarize that: i) Normal puberty is associated with an approximately 25–30% decline in insulin sensitivity of glucose metabolism, which is transient in nature, with recovery to pre-pubertal levels upon completion of puberty; ii) Insulin resistance in puberty, involves both lipid and protein metabolism, and may serve a teleological function to allow for accelerated growth; iii) The hormonal mediator of pubertal insulin resistance in males is not testosterone or dihydrotestosterone, but is increased growth hormone secretion during puberty; and iv) Competition between free fatty acids and glucose oxidation, i.e. the Randle cycle, underlie pubertal insulin resistance. Pathophysiological conditions such as type 1 diabetes and type 2 diabetes are adversely impacted by this important developmental stage in childhood. In the case of type 1 diabetes, deteriorating glycemic control in adolescents should not be attributed to only behavioral causes, but also the physiological deterioration in insulin action, and the consequent need to increase insulin delivery in this age group. In the case of type 2 diabetes, the disease heralds its clinical manifestation at the time of puberty. Awareness of the physiological changes in insulin action during puberty is essential for a comprehensive evaluation of pathophysiological conditions.

INV03

Vitamin D status: genes and environmental interplay in type 1 diabetes risk and protection

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Type 1 diabetes results from the immune mediated selective destruction of pancreatic ß-cells and occurs mostly in children, adolescents, and young adults, but also in older age groups. The immune pathogenesis remains to be clarified but a genetic susceptibility is the background on which the environmental pathogenic agent can act, and trigger off an immune cascade leading first to insulitis without clinical signs and later to the final ß-cell destruction. Vitamin D deficiency is a common finding not only in type 1 diabetes but also in other autoimmune diseases. Epidemiological data from Sweden and the EURODIAB suggest an inverse correlation of vitamin D levels with the risk to develop type 1 diabetes. Furthermore, supplementation of vitamin D can reduce the rate of manifestation in some studies. This can also be observed in NOD mice, where active 1.25-OH vitamin D3 and also new non-calcemic analogs reduce diabetes incidence. The vitamin D action is mediated through its receptor (VDR) and serum levels are regulated by enzymes like 1-alpha-hydroxylase (CYP27B1). Both genes have been shown to confer susceptibility to type 1 diabetes, though with conflicting results from diverse populations. Pilot studies are underway to supplement higher doses of vitamin D (cholecalciferol) in high risk individuals, monitor immune, and ß-cell function. Genetic variants of the VDR (in particular the shorter F-VDR allele), appear to display a more active immune system as detected by cytokine, and transcription factor production in monocytes thus contributing to the lymphocyte regulation. Thereby the vitamin D status may need to be tailored to the genetic background in order to prevent type 1 diabetes.

INV04

New kids on the block: adipocytokines for pediatric endocrinologists. What does the future hold? Clinical applications of adipocyte secreted hormones

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Objective: The adipose tissue has been recognized lately as an active endocrine organ producing several bioactive molecules on top of its classical physiological functions. Tremendous research activities focus on its metabolic importance in regulating crucial pathways already in childhood and adolescence by secreting a variety of adipocytokines. Adiponectin, an adipokine exclusively expressed in adipose tissue, has beneficial anti-atherogenic, anti-diabetogenic, and anti-inflammatory/-proliferative effects. It is markedly decreased in obesity, and low circulating adiponectin levels correlate strongly with metabolic and cardiovascular risk factors already in obese children. Adiponectin may thus serve as an early predictor for the occurrence of the metabolic syndrome even in childhood and adolescence. The euphoria on leptin has changed its focus lately. Leptińs main functions are included to promote an anorexigenic turnover, to exert direct effects in metabolically active tissues and/or indirect effects by activation of hypothalamic centers via leptin receptors. It significantly influences and regulates vital neuroendocrine and reproductive functions by inhibition of glucocorticoids and enhancement of thyroxin, sex and growth

hormone concentrations. Leptin triggers the onset of pubertal development and maintains normal function of the HPG-axis in post-pubertal life. The role of additional adipocytokines such as resistin, visfatin, TNFα, and IL-6 in the paediatric population is still controversial.

Conclusions: Obesity-related insulin resistance seems to be triggered by dysregulation and dysfunction of adipose tissue. Abnormal secretion patterns of adipocytokines might promote this low grade inflammatory process, leading to the typical clinical features of the metabolic syndrome. The molecular mechanisms and physiological/clinical implications of most adipocytokines in childhood and adolescence are still poorly understood and need to be fully elucidated.

INV05
Estrogens and diabetes
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Girls with type 1 diabetes mellitus (T1DM) face an array of difficulties during puberty; some of them are typically observed in this gender. Excessive weight and fat mass gain, deterioration in metabolic control, loss in height gain and a delay in pubertal development may complicate this period for girls. Puberty in girls is characterized by increasing estrogen levels. Some of the problems observed during this period may be in part due to the relationship between estrogen and insulin action, since these two hormones influence each other. Patients with aromatase deficiency or estrogen receptor mutations develop insulin resistance and diabetes mellitus. In addition, animal models have shown that β cells have estrogen receptors, and that this hormone is involved in preventing apoptosis of these cells in mice, and even stimulating insulin secretion from islet cells. In spite of the beneficial effects of estrogen regarding insulin action and secretion in women without T1DM, it is striking that several problems are observed in women with T1DM once estrogen secretion begins. On the other hand, ovarian function may be affected in women with T1DM and appearances of menstrual irregularities, polycystic ovaries and early menopause have been reported. It is possible that the interaction between sex steroids and insulin sensitivity may lead to some of the problems observed during puberty in girls with T1DM.

INV06
Diabetic nephropathy and childhood onset diabetes – is there epidemiological evidence for optimism?
G. Dahlquist

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The rapid increase and shift to younger age at onset of T1DM implies that the incidence of late complications and early death may show similar trends. Clinical studies have shown that improved metabolic control, and early antihypertensive treatment will decrease, or delay progress of markers of diabetic nephropathy (DN) and studies in patients treated in dedicated diabetes centres have shown the cumulative incidence of DN to decrease by calendar time. This provides hope but will this ultimately lead to decrease in end stage renal disease (ESRD) at the population level? The incidence of DN has been shown to vary between 25–40% in different populations and ethnic groups. A peak incidence is described in the second decade of diabetes, but after 25 years the risk of DN will decrease sharply in contrast to other diabetic complications indicating that genetic factors are necessary, though not sufficient for DN occurrence. The incidence of DN varies in different populations and besides genetic set up access to preventive

care may vary. Population based comparisons of mortality rates point to a strong geographic variation also within Europe, where the more affluent countries have lower T1DM mortality. Population based studies on ESRD are few. A study based on ESRD registers comparing eight ethnically and economically similar countries showed a tendency to decrease in ESRD incidence due to T1DM over time. A Finnish study including cases 1965–1999, showed that ESRD prevalence at 20 years after diagnosis was 2.2%, and at 30 years 7.8%, and patients diagnosed after 1975 had lower DN and mortality rates. A recent population based Swedish study involving childhood cases 1977–2003 showed ESRD prevalence at 15–29 years duration of 1.1% with a tendency to delay in time to event by year of diagnosis. In conclusion, a few population based studies indicate a decreasing trend of ESRD in T1DM but mainly in countries with good access to expensive care and medication.

INV07
Predictors of diabetic nephropathy: how to diagnose and when to treat?
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Despite a copious literature on the subject of diabetic nephropathy (DN) in youth with type 1 diabetes (T1D), major questions remain as to the early pathogenetic steps in its development, the role of genetic modifiers, predictive models, and the best approach to screening and management. Finally, while adults with early nephropathy are invariably treated with ACE inhibitors or ARBs, their use in the younger population has not been systematically studied. This presentation will focus on: i) Pathogenesis of early DN and the potential to identify those at risk by genetic screening; ii) The pivotal role of glycemic control and other risk factors in the evolution of DN; iii) A rational approach to screening youth with T1D starting in early puberty; and, finally; andiv) An analysis of interventions that are being tested or should be tested in this population. This presentation is also given against the backdrop of both a decreasing prevalence of microalbuminuria (MA) in youth with T1D, and the high degree of variability in measurement of MA in this group.

INV08
Do we need age-dependent glycaemic targets: the European perspective
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In selecting glycemic goals, the difficulty in achieving an optimal A1C must be balanced against the disadvantages of targeting a higher (although more achievable) goal that may not promote optimal long-term health outcomes. Recent evidence for a glycemic memory, whereas early poor control has potential long-term consequences despite later improvement of glycaemia, adds to the importance of good control from early on. The wrong assumption of a lesser contribution of the pre-pubertal years to the development of complications and the consideration of the small child's unique vulnerability to hypoglycemia have led to age-specific glycemic goals. Despite, relatively high rates of recurrent severe hypoglycemia, the DCCT found no evidence of substantial long-term declines in cognitive function in a large group of mostly adult patients with type 1 diabetes. In addition, hyper- rather than hypoglycemia has been implemented for poor cognitive develop-

ment in some pediatric studies. Nevertheless, current international guidelines show a variation of recommended pediatric target HbA1c's from < 7.0% to < 9.0%: higher for children < 6 years of age, moderately higher for those 6–12 years of age and slightly above adult target levels from 13 years of age. In recent multicenter surveys such differences in the glycemic targets have been shown to be strong predictors of average HbA1c at those centers. Medical professionals providing recommendations for persons with diabetes should recognize that a target HbA1c of close to 7.5% is achievable for more than half of the pediatric patients in all age groups with current means of therapy.

Conclusions: Although the benefits of improved glycemic control in children must be balanced with careful consideration to address the unique needs of the developing child, an HbA1c below 7.5% is proposed as an acceptable target for pediatric patients regardless of age, while the potential long-term risk of severe hypoglycemia should be deemphasized.

INV09

Glucose variability: how to treat

D. Deiss

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It becomes more and more evident that glycaemic variability increases the risk of diabetes complications independently of HbA1c. Beyond avoiding short-term complications such as hypoglycemia and ketoacidosis, minimizing glucose variability should be a therapeutic goal as well. The basis-bolus-concept of multiple daily injections includes the use of insulin management algorithms to maintain glucose levels in a specified range. Algorithms to simplify bolus estimation have been incorporated into 'smart' pumps, at this point designed for single point glucose measurements. With the availability of real-time continuous glucose monitoring (CGM), patients get to see in which direction and how fast glucose is changing. New algorithms are needed considering the increased amount of information in a real-time setting. For the first time, an effect of real-time CGM on metabolic control with significant reduction of HbA1c was achieved under continuous use of Guardian RT (Medtronic Minimed) over 3 months. Short-term clinical trials using the STS Sensor (Dexcom), and Freestyle Navigator (Abbott) showed an improvement of hyper- and hypoglycemia in patients with diabetes. Since it was demonstrated, that tight glycaemic control reduces morbidity and mortality in critically ill patients, numerous, mostly paper based algorithms, have been used in the intensive care units. The computerization of these algorithms enables with automated insulin delivery. In a fully external closed loop system, subcutaneous CGM, algorithm and insulin pump are linked. One approach for an automated algorithm can be the PID controller. Additionally, computer simulations based on modeling glucose kinetics can be used to optimize new insulin delivery algorithms. In conclusion, real-time CGM is the tool to fine tune insulin decision algorithms and to decrease glucose variability. Complex algorithms enable automated insulin delivery with considerable promises towards creating the complete artificial pancreas.

INV10

Autonomic and peripheral neuropathy: do we have to deal with it in paediatrics?

K. C. Donaghue

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Clinical neuropathy is uncommonly diagnosed during adolescence, but many recent studies confirm the subclinical neuro-

pathy. Peripheral and autonomic neuropathy can cause significant disability in young adults with childhood onset disease, especially gastrointestinal symptoms and painful neuropathy. Adult studies show the quantitative sensory tests predict the development of ulcers, and correlate with pain. Autonomic neuropathy causes specific cardiac abnormalities and predisposes to arrhthymias. Meta-analysis of 15 studies shows an increase in mortality with one cardiovascular test abnormality (1). Pupillary abnormalities in adolescents may also have prognostic significance for subsequent development of complications (2,3). Risk factors for neuropathy, shared with other complications, are high blood pressure, abnormal lipids, hyperglycemia but body mass index is emerging as an independent risk factor (4). Whilst there has been a reduction in retinopathy and microalbuminuria in T1DM over recent years in many centers, there are no reports of reduction in neuropathy. This may be in part due to diagnostic difficulties, but our review of 15 year olds clinic attendees actually found an increase in peripheral nerve abnormalities and no change in cardiovascular autonomic abnormalities (5). Abnormalities associated with higher BMI. When adolescents with T2DM were compared, we found similar rates of nerve abnormalities with shorter duration and lower HbA1c than age matched T1DM adolescents (6). The increase in body mass index in T1DM and the increase in T2DM are certainly calls for concern that we may not be able to ignore neuropathy in paediatrics. Additionally, neuropathy can be present in pre-diabetes and obesity.

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INV11

Perinatal programming and risk of later disease

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The etiology of diseases was traditionally attributed to a combination of environmental and genetic circumstances. More recently, however, the concept of perinatal programming was introduced as a third major etiologic pathway. Perinatal programming describes the permanent fixation of temporary metabolic changes in fetus, and neonate, leading to pathological consequences later in life. One example of perinatal programming in man is the permanent reduction of energy expenditure, after intrauterine fetal malnourishment (thrifty phenotype hypothesis). This predisposes to obesity, type II diabetes and the metabolic syndrome later in life. A second field of fetal programming is gestational diabetes mellitus, reflecting an increased maternal supply of glucose with the consequence of fetal hyperinsulinism. The sequealae of fetal hyperinsulinism are carried far beyond infancy, and are clinically reflected in an increased risk for obesity and diabetes mellitus. Therefore, again a temporary environmental event "programs" disease later in life. It is of interest that various environmental changes may predispose to the same phenotype later in life. The other interesting observation is that the process of programming does not stop with birth. In fact, breast feeding and postnatal weight gain may modulate the effect of fetal programming to a large degree. As a consequence, two aspects are presently in the focus of research: The exact mechanisms of perinatal programming and preventive postnatal stategies.

Invited Speakers

INV12
Androgens and diabetes
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Insulin resistance and compensatory hyperinsulinaemia have been linked to risk for the development of ovarian hyperandrogenism and the occurrence of polycystic ovarian morphology during adolescence. In female subjects with Type I Diabetes (TID), elevations in serum testosterone levels are commonly observed and up to 50% of subjects may have polycystic ovarian morphology on ultrasound examination. These abnormalities have been associated with increased rates of menstrual irregularity, and oligomenorrhea but other clinical evidence of ovarian excess such as hirsutism, may not be evident. PCOS is often associated with reduced SHBG levels in subjects without diabetes, because of the role of portal insulin in regulating SHBG production by the liver. In TID variable effects on SHBG are observed because, despite peripheral hyperinsulinaemia, portal levels of insulin may be reduced. There is evidence that the ovarian hyperandrogenism may be greatest in those on intensive insulin therapy, and it has been associated with increased weight gain, and risk for diabetic complications. In longitudinal studies, the development of microalbuminuria has been associated with elevated testosterone levels, reduced SHBG and an increased free androgen index. Ovarian hyperandrogenism may contribute to the sexual dimorphism in clinical outcome during adolescence: girls having poorer glycaemic control, more problems with weight gain and an increased incidence of microalbuminuria. Combinations of insulin sensitizers with anti-androgens can have dramatic effects on insulin sensitivity, body composition and ovarian function in non-diabetic populations and such treatments may also be benefit in patients with TID. Recent pilot data indicate that combination therapy with Metformin and Flutamide may have positive effects on weight gain and HbA1c values.

INV13
DKA as health problem in the year of the child
J. A. Edge

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The IDF has declared 2007 to be the Year of the Child, and aims, among other objectives, to send the message that no child should die of diabetes. IDF figures suggest that over 70 000 children worldwide develop Type 1 diabetes each year. There is also a growing number with Type 2 diabetes. Published incidence rates for diabetic ketoacidosis (DKA) at diabetes diagnosis range from 20% (Finland) to 80% (United Arab Emirates); therefore, tens of thousands of children per year will present in DKA worldwide. Re-presentations with DKA in children already known to have diabetes also vary widely, depending on the culture and the availability of insulin. Furthermore, DKA occurs at onset of Type 2 diabetes in 5–50% children. DKA is the commonest cause of death in children with diabetes, even in developed countries, accounting for around 80% diabetes-related deaths in young people under the age of 20 in the UK. Cerebral oedema is the most serious complication of DKA occurring in around 1% of DKA episodes at diagnosis and accounting for 80% deaths in children under the age of 12. Since studies have failed to identify a 'cause' for cerebral oedema, prevention of DKA is itself a goal, which needs to be pursued, if deaths from diabetes are to be reduced. In the young person with known diabetes, most cases of DKA are potentially preventable with education, and psychological interventions together with measures to ensure that insulin is given by a responsible adult. However, it is at diagnosis, when the children are often younger and the cerebral oedema is more likely to occur, that greater efforts need to be made in prevention of DKA.

INV14
Glucose variability: How to measure?
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The DCCT demonstrated the role of glycaemia per se as a causative factor in diabetes complications. *In vitro*, data on vascular endothelial function have invoked glucose variability, in addition to the absolute glucose value, as a factor in damaging vascular function. Variability is a common feature in endocrinology. Insulin secretion is pulsatile, whereas blood glucose (BG) concentrations vary little, such that a measurement at one point in time is highly predictive of a subsequent measure. A number of techniques are available to determine regularity and irregularity in a time series. Central to all techniques is the requirement for regularly timed samples to avoid false peak and trough identification (aliaising). For an individual data can be easily depicted as mean and standard deviation of which HbA1c is a reflection of the former but is susceptible to minor and major fluctuations. For group data more sophisticated methods of time series analysis are required. Regularity in BG profiles from patients with diabetes is not easy to discern other than food related events and the data are better described in terms of irregularity or chaos (Approximate entropy). Values increase with increasing dysregulation and unpredictability from close to 0 in non-diabetics through to greater than one in poorly controlled patients with type 1 diabetes. GRADE is a method of identifying glycaemic variability, which weights BG values in terms of severity - hyper or hypo glycaemia. The method allows the clinician to use large BG datasets to complement HbA1c measurement and to identify hyper and hypo glycaemic events not immediately apparent from data scanning by eye. Data can be presented in terms of control charts which can be tailored to the individual in terms of action points. These techniques generate new concepts in what constitutes optimal diabetes control which can be extended from not just managing absolute BG values but to normalizing glucose variability.

INV15
Use of intensified diabetes management to achieve glycemic targets
G. J. Klingensmith & M. Rewers

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This session will discuss safely achieving glycemic targets using intensified diabetes management, focusing on a basal-bolus approach to treatment. With recent recommendation for lower glycemic targets (ISPAD, American, Australian, and Canadian Diabetes Association Guidelines), more children are on multiple daily injection regimens or using continuous subcutaneous insulin infusion(CSII), to achieve better metabolic control. However, it is estimated that only about 30% of children with diabetes meet these new goals. Hypoglycemia is a major limiting factor to the implementation of intensive glycemic control, especially in young children, who are at risk of development of cognitive impairment with repetitive episodes of hypoglycemia. The achievement of optimal glycemic control in children is further complicated by their variability, and lack of predictability in eating habits, and activity

level. Intensive diabetes management includes insulin delivery designed to meet both basal and meal insulin requirements, and requires frequent blood glucose monitoring to guide insulin dosing, adjustment of the insulin to accommodate the carbohydrate consumed during meals and snacks, as well as flexibility to accommodate insulin reduction or increase in carbohydrate consumed for exercise. New technologies including insulin analogs, improved insulin pens and pumps, continuous subcutaneous glucose monitoring and perhaps a closed loop system in the near future will help us to achieve more optimal glycemic targets in children without increased side effects. In addition, continuous glucose monitoring may teach us better ways to use insulin in children, who do not have this newest technology available to them.

INV16

Individualized diabetes education in paediatrics

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The diagnosis of type 1 diabetes represents a critical life event to children and their parents, and requires numerous adjustments in every day life. Treatment targets include good metabolic control, good quality of life and emotional well-being of the child and its family. Successful self-management of the disease requires profound knowledge, a diversity of practical and social skills, sustainable motivation and a stable sense of self-efficacy. Thus, structured diabetes education is the keystone to integrate, all aspects of diabetes therapy into the family's normal course of life. Effective education programs in paediatrics provide more than knowledge and practical skills. They integrate empowerment principles, problem solving, goal setting, and promote self-efficacy in the continuing educational process from diabetes onset, until transition to adult services. In addition to an interdisciplinary paediatric diabetes team provide support in rearing a child with diabetes, and in psychosocial adjustment to the disease. Each diabetes education session needs to be adapted to the individual family's situation, e.g. age and maturity of the child, diabetes duration, educational level of the parents, psychological well-being of all members, especially of the mother, the child's current status of independence and responsibility in diabetes-management as well as family coherence. Furthermore, the structure of the family (single parent), the socioeconomic situation, lifestyle, cultural specifics as well as individual wishes, and needs should be considered in learner centred diabetes education. According to the child's developmental level and age specific needs, different curricula for parents of infants and toddlers, of school-age children and of adolescents are necessary. Likewise, specific principle of teaching and age appropriate individualized topics for children of different developmental levels, are important determinants of successful diabetes therapy and psychosocial development.

INV17

Carbohydrate counting: How to educate?

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A major therapeutic goal in children and young patients with diabetes is to achieve, and keep blood glucose (BG) levels as normal as possible by balancing insulin substitution and food intake. During the last year, the focus in dietary advice moved from previously used sophisticated instructions to more common basic rules. Main aspects regarding the effect of food intake on blood glucose levels are the total amount of carbohydrates (CHO) as well as associated parameters like the 'glycemic index'. In general, an average percentage of calories from CHO of about 45% to 55% of the total daily food intake are recommended. Moreover, the basal-bolus-concept of multiple daily injection or pump therapy enables the patients and their families to adapt insulin delivery to CHO intake in a flexible manner. However, parents and children have to learn how to use and implement programs based on CHO calculation. The workshop will deal with educational aspects in training patients and their families concerning dietary recommendations. Traditionally, CHO intake has been estimated by 'bread exchange' (BE) with 1 BE corresponding to 10–12 g digestible CHO. We train parents and children to learn how to count CHO and what might be the effect on blood glucose (glycemic index) using following tools: i) Printed tables of simple classes of food (fast, slow, and very slow rising BG); ii) Exchange lists; iii) Reading food labels; iv) Analyzing family recipes; v) Analyzing restaurant menus; and vi) Go to the supermarket.We recommend these tools to be introduced in individualized teaching units. The educator has to realize that balancing diet and insulin is not solely a cognitive task, but also a psychological one. Patients have to be encouraged to change their basic behavioral pattern and to accept that food intake should be accompanied by cognitive actions instead of simply meeting spontaneous needs. From our experience, this part of education is more difficult than teaching the CHO content of different food.

INV18

The fetal origins of the metabolic syndrome: the case of the Haguenau cohort

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Over the past 15 years, a large body of studies has evidenced the relation between SGA (being born small for gestational age) and the increased risk of insulin-resistance, type 2 diabetes and cardiovascular diseases later in life. The first reports focused on elderly and in populations where the prevalence of diabetes is already high. The association with insulin resistance and the metabolic syndrome was later extended to young adults and to pre-pubertal children. We made use of a specially developed cohort, which characteristics are given below. The Haguenau cohort is unique for many reasons. Two groups of subjects have been carefully selected on their birth data from a Maternity registry. It is a community-based and not hospital-based population. Children were grown at a time when nutrition conditions were optimal and quite uniform in the small area of Haguenau. Subjects have been identified from a population-based registry of the metropolitan area of the city of Haguenau in France. This registry included information about all pregnancies and deliveries occurring in the maternity unit of the same community hospital between 1971 and 1985 (n = 27 366). The SGA group included all singleton subjects born between 32 and 42 weeks of gestation with birth weight < 10th percentile for gender and gestational age according to the local growth standard curves. Selection of the AGA group was made of singleton subjects, born between 32 and 42 weeks of gestation with birth size between the 25th and the 75th percentiles, who were the first babies in the registry born immediately after a subject born SGA.

Results on fetal programming of the metabolic syndrome: After fetal growth restriction, SGA newborns have a reduced fat-mass related to poor in utero conditions and subsequently experience a period of catch-up growth in height and weight during the first 2 years of life. Catch-up in weight necessarily implies catch-up in adiposity and individuals born SGA have a tendency to show higher (mostly abdominal) adiposity. This catch-up-induced excess of adiposity is

a strong determining factor of insulin-resistance in SGA born individuals. The adipose tissue is a dynamic endocrine organ as well as a highly active metabolic tissue and plays a critical role in energy homeostasis, insulin sensitivity and lipids/carbohydrates metabolism, which actions are mediated by hormones such as leptin and adiponectin, the latter exerting a potent insulin-sensitizing effect. Beside the abnormal perinatal growth pattern, the functions of the adipose tissue at the time of catch-up have not been studied in humans. In adults born SGA, we have reported a number of malfunctions of the adipose tissue persisting after puberty (22 year old) suggesting an abnormal adipose tissue which could participate to insulin-resistance and the metabolic syndrome: i) They show an excess of fat mass, preferentially abdominal, without obesity; ii) Insulin action on lipolysis is reduced and FFA release is not suppressed under physiological insulin concentrations; iii) An excessive lipolysis in response to catecholamines was observed by microdialysis of the abdominal adipose tissue; iv) Leptin levels show an impaired regulation during catch-up and are low in adults; and v) Adiponectin levels are low and the insulin-sensitizing action is impaired. At the same time the different features of the metabolic syndrome (hypertension, dyslipidemia, impaired glucose tolerance) were manifested in these SGA subjects and were clustering around IR However, the phenotype was mild meaning that the differences between the subjects born SGA and their pairs born adapted for gestational age (AGA) were indeed significant for all features but of low magnitude. As a matter of fact, the proportion of disorders of glucose tolerance was low but twice as high in SGA in comparison to AGA (3.8% vs. 1.6%) and that of MS six fold higher (2.3% vs. 0.4%). We anticipate that these differences would even diverge more between the two groups when subjects get older due to further increased fat mass and amplification of the process by the abnormal adipose tissue.

INV19

Stem cell transplantation in children with type 1 diabetes: how far are we?

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Like in other degenerative and loss of cell mass diseases it is believed that the cure of diabetes resides in cell-based therapy. Pancreatic islet transplantation can lead to insulin independence but this approach is limited by shortage of human islets and long-lasting immunosupression. Thus, alternative sources of insulin producing cells have been intensively investigated in the last year. Development of pancreatic beta-cell lines from rodent or human origin has progressed slowly in recent years. Experiments for ex vivo expansion of beta-cells and *in vitro* differentiation of embryonic and adult stem cells into insulin producing beta-cell phenotypes led to promising results. Nevertheless, the cells generated to date lack important characteristics of mature beta-cells. Transplantation of embryonic stem cells in diabetic mice, successfully reverted hyperglycemia but tumors aroused. In contrast, recent experiments *in vivo* have shown the great potential of adult stem cells to induce regeneration of recipient beta-cells and to normalize glycaemia in diabetic animal models. To harness the power of regenerative medicine for diabetes therapy, more information is required to identify potential candidates and their niches. This presentation summarizes new advances in the fascinating field of stem cells and their application to the treatment of type 1 diabetes, providing an overview to what is already achieved and what has to be accomplished to finally translate research from bench to bedside.

INV20

Is carbohydrate counting essential for successful treatment?

J. Ludvigsson

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We know that intense treatment may reduce late complications, but not the importance of the different components of such treatment. With physiological insulin substitution, no special dietary rules would be needed, but such good insulin substitution does not exist. Multiple Insulin Therapy or CSII with multiple meal boluses may come rather close to physiology but is no guarantee for good metabolic control. As the carbohydrate content plays an important role for what bolus doses are needed before meals, carbohydrate counting has returned into the therapeutic arsenal, especially when using CSII. Although, there are enthusiastic advocates for the benefit of carbohydrate counting, some studies show that several patients often fail in their estimations of carbohydrates of a meal. In addition, the bolus dose of insulin will be dependent on several other things such as previous insulin dose, basal insulin, glycaemic index of the carbohydrates and of the total meal (fibers, fat content, fluid intake etc), physical activity, infections, pubertal stage etc. Carbohydrate counting in some patients may make treatment load too heavy, which in worst case may lead to omission of insulin doses, and problems with blood glucose self-control. Our unselected patient population (> 200), have a mean HbA1c of 6.5–6.7% (= 7.5–7.7 DCCT) beyond partial remission, and we have reduced both acute and late complications. This has been possible with active insulin treatment, regular meals, dietary rules (but without or with adjusted forms of carbohydrate counting), self-control of blood glucose, and with all treatment based on psychological support, education and collaboration with the patients and parents.

Conclusions: Carbohydrate counting may be helpful during certain periods of life but the rules have to be adjusted to the intellectual and psycho-social capacity of the individual patient and his/her family to avoid either overload of rules or a false freedom the patients cannot handle.

INV21

New kids on the block: Adipokines for pediatric endocrinologists

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Adipokines, adipocyte secreted hormones with a tertiary structure, resembling that of cytokines have recently been identified and found to play an important role in human physiology and pathophysiology. In this symposium, the biology of adipokines will be presented, their pathophysiological significance will be discussed and their potential future applications in pediatric endocrinolgy and diabetes will be explored.

INV22

Reducing DKA at onset – how to monitor success

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With a frequency of 20–25% diabetic ketoacidosis (DKA) is the most important complication in childhood diabetes at onset. Already at the beginning of the 20th century, Elliot P. Joslin demanded to prevent children from the fatal consequences of DKA. To shorten the period of hyperglycemia-associated symptoms was the aim of different prevention strategies. Limited data

however, exist with respect to the success of these prevention programs. Monitoring a success means first monitoring the disease. Collaborative networks and a long observation period are appropriate prerequisites for the documentation of the effectiveness of a programmer. Italian experiences with a prevention campaign exist and demonstrated a reduction in a considerable number of patients. The DPV-initiative or the Baden-Wuerttemberg (BW) Diabetes Registry DIARY offers a suitable framework for monitoring the disease and its complications in childhood. With a case observation of more than 5000 patients registered at onset the BW registry exists since 1987 and is part of the EURODIAB collaborative network. Patients are registered, if insulin treatment has been started before the 15th birthday. The registry covers 97.2% of all newly diagnosed cases in BW. Epidemiological and clinical data were analyzed. Over an observation period of more than 10 years the frequency of DKA (26.3%) has been nearly unchanged. Especially children under the age of 5 years and girls were at risk. In these patients, the duration of symptoms was shorter than in those without DKA. Thus we conclude that we may reduce DKA at onset to a certain amount, however, a certain proportion of DKA does not primarily result from unrecognized symptoms, but rather from a particularly aggressive course of the disease.

INV23

15 year trends in the incidence of type 1 diabetes in Europe

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Objectives: To monitor childhood type 1 diabetes incidence rates in Europe.
Methods: In 1989, the EURODIAB group established prospective, geographically-defined registers of new cases of type 1 diabetes in children aged below 15 years in a number of European centers. Multiple sources were used to validate completeness of ascertainment in each center by capture-recapture methodology. Nineteen centers continue to submit anonymous data on individual cases and annual population estimates.
Results: Most centers achieved > 90% completeness in the three 5-year sub-periods of the 1989–2003 periods. Standardized incidence rates during the 15-year period ranged from 6.8 cases per 100 000 per annum in Bucharest, Romania to 28.9 cases per 100 000 per annum in Stockholm County, Sweden. Poisson regression analysis revealed that there was a significantly increasing trend (p < 0.05) in all but two of the centers, most conforming well to a pattern of linear increase on a logarithmic scale of incidence. To analyze further, the pattern of trends in incidence, results from centers were pooled into five centre groupings: north Europe (Scandinavia), north west Europe (United Kingdom), west Europe (Spain, Belgium, Luxembourg, Germany) central Europe (Austria, Slovenia, Czech Republic) and east Europe (Lithuania, Romania, Poland, Slovakia, Hungary). Rates of increase pooled over centers and sexes were 5.3% (95%CI 4.7% to 6.0%) for 0–4 year olds, 4.1% (95%CI 3.6% to 4.6%) for 5–9 year olds and 2.8% (95%CI 2.4 to 3.3%) for 10–14 year olds. However, when centre groupings were examined it was apparent that rates of increase were greatest in the lowest incidence groupings of central and east Europe. Furthermore, disparities in the rates of increase between age-groups were most marked in the central and east Europe centers.
Conclusion: The most rapid rates of increase of childhood type 1 diabetes in Europe during 1989-2003 were in the 0–4 year age-group in central and east Europe.

INV24

The loop club: Introduction to the topic of glucose variability

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Are intraday blood glucose excursions important, or is it just the mean blood glucose levels that patients and clinicians should be concerned with? In long-term analysis of the DCCT database of the relationship between glucose variability, and relative risk of developing microangiopatic complications in type 1 patients, Kilpatric et al found that glucose variability does not have an important role as a risk factor. They claimed that only elevation of the mean blood glucose levels over time - as expressed by HbA1c - is associated with the risk of micro-vascular complications. In our session of the Loop Club, we will try to answer the questions: i) Was the glucose variability measured appropriately? ii) What new means of blood glucose excursions measurements do we have today? iii) Is the risk of long-term micro-vascular complications the only reason why one should prevent glucose excretions? iv) What are the ways to cope with sever blood glucose excursions and prevent them?

INV25

Genes and type 2 diabetes: how far is genetic screening for children?

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The recent increase in identified type 2 diabetes mellitus (T2D), in children and adolescents, points out the primary role of environmental factors. However, of all children exposed to the same environment, only a small proportion will develop T2D because genetic susceptibility is also required. T2D risk is a polygenic trait, likely composed of loci determining both insulin resistance and beta-cell reserve. Of the large number of reports of T2D-associated loci, only a handful had been validated by consistent replication, including polymorphisms in the transcription factor TCF7L2, the b-cell potassium channel Kir6.2 and the lipid sensor PPARg. These failures resulted in a pessimistic outlook, which is now changing, with the availability of high-density micro-arrays, capable of genotyping hundreds of thousands of single-nucleotide polymorphisms (SNPs), to capture most of the human genetic variation. Five major genome-wide studies recently used this technology to provide cross-replicated evidence for several additional T2D loci. These include a non-synonymous SNP at SLC30A8, a beta-cell specific zinc transporter, a block containing HHEX, a gene involved in pancreas development, two cycline-dependent kinases, and the translational regulator IMP2. Although, much more work is needed for genetic knowledge to translate into understanding of biology, these early successes finally allow hope that all important genetic components of T2D risk will be known in the next few years. This will permit a reasonable estimate of T2D risk at birth, on a DNA sample obtained from a drop of blood, knowledge that can be used to focus early lifestyle intervention on a small proportion of at-risk individuals. More importantly, T2D-focused genetic profiling may allow aetiologic classification, within this inhomogeneous phenotype, that will, with better understanding of physiology, result in intervention optimally suited to the individual (personalized medicine). The ethics of early testing will be discussed.

INV26

Macroangiopathy kills in type 1 and type 2 diabetes: lessons for pediatrics?

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Macroangiopathy caused by dyslipidemia, hypertension and disturbed glucose metabolism are well known in adults. However, the onset the cardiovascular changes are not well established. Measuring the intima- media thickness (IMT) of the common carotid artery, as a non-invasive marker for early atherosclerotic changes, has been reported to be reliable and predictive for later cardiovascular disease. IMT has to be evaluated, near the bifurcation of the carotid media at the far wall in subjects in the supine position with the head turned slightly to the side. Increased IMT has been reported in children with type 1 diabetes mellitus. The IMT was related to both hyperglycemia and dyslipidemia in these children. Furthermore, young men and children with borderline hypertension demonstrated increased IMT. Moreover, children with familial hypercholesterolemia have higher IMT values as compared to healthy children. Obese children with the feature of the metabolic syndrome (hypertension, dyslipidemia and impaired glucose tolerance) also demonstrated increased IMT. Reduction of overweight and normalization of blood pressure, glucose metabolism and dyslipidemia were associated with a reduction of IMT in children and adolescents. In conclusion, early vascular changes already occur in children with dyslipidemia, disturbed glucose metabolism and hypertension. However, these early changes are reversible if sufficient therapy of cardiovascular risk factors could be achieved. Since, both type 1 and type 2 diabetes are associated with hypertension and dyslipidemia, early treatment of cardiovascular risk factors is necessary to prevent later macroangiopathy. However, only the minority of the German children with type 1 or type 2 diabetes and dyslipidemia or hypertension is treated concerning their cardiovascular risk factors.

INV27

Global epidemiology of non-type 1 diabetes

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It has been recognized over the last few decades that all diabetes in childhood is not type 1. The ISPAD Consensus Guidelines 2006–2007 (Pediatric Diabetes, December 2006) on the classification of non-type 1 diabetes include the following subtypes: type 2 diabetes, maturity onset diabetes in the young (MODY), neonatal diabetes, mitochondrial diabetes, cystic fibrosis-related diabetes, and drug-induced diabetes. Compared to type 1 diabetes, there is little information available on the epidemiology of non-type 1 diabetes. This is at least in part, is due to the fact that the symptoms and diagnosis of non-type 1 diabetes are less straightforward than those of type 1 diabetes, and to monitor incidence changes repeated screening must be performed. Only a few population-based studies have examined the epidemiology of type 2 diabetes in children (e.g. Japan and United States). Information comes mainly from clinic-based studies or case reports in obese children and from screening of groups of obese children and adolescents. Type 2 diabetes affects mainly obese children who belong to certain ethnic populations; most children with type 2 diabetes are above the age of 10 years. The rise in obesity in children may lead to an increase in type 2 diabetes incidence in younger age group. Less than a few percent of European children in diabetes clinics have type 2 diabetes, but up to 80% of diabetic children of African, Hispanic, Asian, and Native American origin can have type 2 diabetes.

Screening of obese children with OGTT has demonstrated a 1–4% prevalence of silent type 2 diabetes and a 5–25% prevalence of IGT. Information on the epidemiology of other forms of non-type 1 diabetes is scarce, and there is a need for systematic and population based studies.

INV28

Facilitating regeneration of beta-cells: a valid option for clinical treatment in young people with diabetes

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Type 1 diabetes (T1D) is an autoimmune disease, characterized by a T-cell mediated, specific, insulin-producing beta cell destruction. The clinical onset of T1D most frequently presents in children and adolescents who are genetically predisposed. Even while the autoimmune process takes place, the well-differentiated and specialized islet beta cells, seem to physiologically retain the ability to compensate for the cells lost by reproducing themselves, while undifferentiated cell sources may help in generating new ones. Diabetes clinical onset, i.e., establishment of a detectable, chronic hyperglycemia, occurs at a critical stage when autoimmunity, finally supersedes the regenerative effort and reduces the number of beta cells below the physiologic threshold at which the produced insulin is insufficient for the body's needs. However, new accumulating evidence suggests that once autoimmunity is abrogated using non-diabetogenic means, the endocrine pancreas properties may be sufficient to allow the physiological regenerative process to restore endogenous insulin production, even after the disease has become clinically manifest. Knowledge of these properties of the endocrine pancreas, suggests the testing of reliable and clinically-translatable protocols for obliterating autoimmunity, thus allowing the regeneration of the patient's own endocrine cells. Safe, gene therapy-based approaches can be used to permanently obliterate autoimmunity by restoring central and peripheral tolerance. The safe induction of an autoimmunity-free status might become a new promising therapy for T1D since, by correcting hyperglycemia using conventional insulin administrations, 'nature' will be left to eventually heal the endocrine damage.

INV29

Probiotics - from designer food to disease prevention

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The incidence of spontaneous autoimmune diabetes is highest in NOD mice in an environment with a low microbial load and decreases when the microbial load increases. The administration of heat-killed *Lactobacillus casei* has been shown to decrease the incidence of diabetes in NOD-mice. In another study, the decrease in the incidence of diabetes in NOD-mice was demonstrated to be associated with increased IL-10 expression in the islets and in the mesentrial lymph nodes when a combination of several probiotic bacteria was given. Thus, modulation of the gut immune system with probiotics, "bacteria with health-promoting effects", affects the phenotype of the islet infiltrating immune cells. The gut immune system plays a key role in the development of type 1 diabetes. The aberrancies in the gut immune system, such as intestinal immune activation and increased gut permeability, are seen in children with type 1 diabetes. Also enhanced immunity to

food antigens is seen in children with type 1 diabetes. Some evidence suggests that the origin of beta-cell autoimmunity is in the gut and results from the broken oral tolerance. Genetic factors and environmental factors, such as early introduction of dietary proteins and gastrointestinal infections, may cause dysfunction of the gut immune system and trigger autoimmunity. Non-invasive microbes such as probiotics seem to support the development of oral tolerance and recover the gut permeability defects. Several studies indicate that probiotics could decrease the severity of the intestinal infections, such as enterovirus infections, associated with type 1 diabetes. Based on these beneficial actions of probiotics, their effect on the risk of type 1 diabetes should be studied. Our pilot study on the prevention of beta-cell autoimmunity in children at genetic risk of type 1 diabetes, the PRODIA-study, demonstrated that probiotics is a safe intervention for diabetes prevention. Thus, the study proper using probiotics in type 1 diabetes prevention is suggested.

INV30
DKA prevention in the primary care setting
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Parma group tested first that, thanks to a school and physician campaign centered on the early symptom of diabetes (nocturnal enuresis in a dry child), it is possible to shorten the period of carbohydrate intolerance prior to diagnosis and thus prevent ketoacidosis (DKA). The campaign was carried out for 8 years during which, the cumulative frequency of severe DKA in the province of Parma dropped from 78% to 12.5%. In the two provinces in which the campaign was not carried out, the incidence of severe or moderate ketoacidosis was higher (83%), similar to that observed in the province of Parma before the beginning of the preventive campaign. It is highly likely that this decreased incidence of DKA in children with diabetes in the province of Parma resulted from the children experiencing a shorter period of metabolic disturbance prior to developing overt diabetes. Ten years have passed since the end of the campaign and longer-term benefits continue today. In fact a retrospective study of the newly diagnosed children with diabetes admitted between January 1999 and December 2006 highlighted that moderate (pH < 7.2, bicarbonate < 10 mmol/l) or severe (pH < 7.1, bicarbonate < 5) DKA was found in 34 (80.9%) and in five children (15.6%; p < 0.002) coming from the two neighboring provinces in which no campaign had been carried out and from Parma respectively. Duration of symptoms before diagnosis was 4.5 ± 3.5 and 16.0 ± 8.0 (p < 0.0001) days in Parma and in other two neighboring provinces respectively. All parents reported unusual bed-wetting in their child, but only those from Parma linked this symptom to the campaign messages and most of them promptly consulted a paediatrician. Three unexpected severe episodes of ketoacidosis in children from Parma between 2004 and 2006 appear to indicate that time has weakened the campaign and that it needs to be renewed in order to regain its effectiveness.

INV31
Carbohydrate counting: what is the evidence?
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Dietary education in childhood diabetes has been inadequately evaluated. Lack of evidence has not prevented major and continuing change. Historically, rigid carbohydrate prescriptions were replaced by exchanges/portions, less quantification and the glycaemic index. The advent of insulin analogues in MIT and the increase in CSII resurrected carbohydrate counting. Global debate remains lively between 'amount and type' of carbohydrate, consensus suggests that both are important. The ADA states, that the use of exchanges or carbohydrate counting remain key strategies in achieving glycaemic control, the evidence for this statement is weak and a key issue is how do we approach families who find counting carbohydrate difficult? Historically, evidence suggested that the children did not follow prescribed intakes of carbohydrate, and health professionals underestimated the skills required to estimate carbohydrate. Recent interventions may improve on these historic viewpoints. Diet is just one element of a myriad of factors contributing to good glycaemic control. The DCCT showed a variety of meal planning strategies/tools were used to improve HbA1c, concluding that behavior was more important than the tool. Recent research has also shown paediatric diabetes centers can achieve excellent control in their children without carbohydrate counting. However, several recent interventions using carbohydrate counting have shown improved HbA1c, others not. A recent study investigated the precision required in carbohydrate counting to achieve good postprandial blood glucose levels, concluded that it is not necessary to count grams precisely but quantifying to within 10 grams is adequate.

Conclusion: It is possible to achieve good glycaemic control in children with diabetes without counting carbohydrate. Evidence is lacking to prove its efficacy. RCTs are needed in children to examine the necessity, practical acceptability, precision and implementation as a teaching tool.

INV32
Lessons from DCCT and EDIC: the role of "metabolic memory"
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The DCCT demonstrated benefits of improved glycemic control on the development and progression of T1DM complications. In DCCT, 1441 subjects (13–39 years old with T1DM for 1–15 years at randomization) were randomized to intensive therapy (IT) or conventional therapy (CT) and followed for a mean 6.5 years (range: 3–9). For 'adults' in DCCT (n = 1246; 18–39 years old), hemoglobin A1c (A1c) was similar at baseline between IT and CT (9.0 ± 1.5% vs. 8.9 ± 1.6%, respectively; mean ± SD) and fell to 7.2 ± 0.8% in IT compared to 9.0 ± 1.2% in CT. This was associated with a 34–76% risk reduction for retinopathy, nephropathy and neuropathy. For 'adolescents' in DCCT (n = 195; 13–18 years old), A1c fell from 9.6 ± 1.7% to 8.1 ± 1.1% in IT and 9.5 ± 1.8% to 9.7 ± 1.2% in CT (p < 0.001) with a similar risk reduction in complications (35–70%). At DCCT end, all subjects were offered IT and care reverted back to the primary physician. 1045 'adults' and 153 'adolescents' continued follow-up for another 10 years as part of EDIC. In 'adults', despite similar A1c between the former IT and CT groups during EDIC, further progression of complications was slower at 4 and 10 years (3-step progression of retinopathy - 4 years: 6.3% in IT vs. 21.3% in CT; - 10 years: 21.8% in IT vs. 40.2% in CT; both p < .0001). This continued benefit of IT vs. CT despite similar A1c has been called 'metabolic memory'. Metabolic memory is also seen in 'adolescents' (n = 175) at 4 years (3-step progression 8.2% in IT vs. 25.4% in CT; p = .0056), but waned at 10 years (40.0% in IT vs. 38.2% in CT; p = .82). 98% of this difference in 'metabolic memory' between 'adults' and 'adolescents' is explained by the A1c achieved during DCCT IT in adolescents compared to adults (8.1 ± 1.2% vs. 7.1 ± 0.7%, respectively). These data strongly suggest that the maximum and most sustained benefits of therapy to improve glycemic control in T1DM are achieved by lowering A1c as much

and as early as possible, starting at least during the adolescent years.

INV33
Metformin – slowing the accelerator?

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The Accelerator Hypothesis proposes that type 1 and type 2 diabetes are the same disorder of insulin resistance, set against different genetic backgrounds. It predicts a rise in the incidence of type 1 diabetes parallel to that of waist circumference (a surrogate for insulin resistance), its ever earlier presentation, a fall in the contribution of immunosusceptibility (*HLA*) genes to its prevalence and a convergence in the phenotypes of type 1 and type 2 diabetes. All of these changes have been documented epidemiologically. Most importantly, the hypothesis predicts that the fattest children will develop type 1 diabetes the youngest - true acceleration. This correlation has now been confirmed by five different population studies world-wide, and cites the only exposure (fatnes/insulin resistance) of the many proposed to have a dose-dependent effect on diabetes outcome. The Accelerator Hypothesis is based on tempo. All diabetes ultimately results from a failure of the beta cells to meet insulin needs, and the faster the loss of beta cells, the younger the presentation. The hypothesis sees type 2 diabetes, not as adult diabetes, but as diabetes in adulthood (slow tempo), and type 1 diabetes not as childhood diabetes, but as diabetes in childhood (fast tempo). It distinguishes three accelerators, two genetic and one largely acquired, that may influence the tempo of beta cell loss. The first is constitutional, the genes that determine beta cell mass at birth and their intrinsic rate of apoptosis throughout life. The second - and most important - is insulin resistance, which both accelerates apoptosis and increases the antigenicity of beta cells by up-regulating them metabolically. The third is the *HLA* genotype, which encodes the intensity of the immune response to the up-regulated beta cell. The presentation will outline an RCT to establish whether metformin, by reducing insulin resistance, can reduce the incidence of type 1 diabetes in at-risk children.