doses 3 times from vials and/or cartridges containing saline mixed with small amounts of [^{14}C]glucose (solution used as regular insulin), and [^{3}H]glucose (solution used as NPH). Subjects regularly using a pen device (n = 24) were asked to make measurements using both the pen and the syringes. For patients on an insulin mixture, the solution containing [^{3}H]glucose was sampled to determine the amount of contamination with [^{14}C]glucose. The absolute error in drawing up doses of regular insulin smaller than 5 units was 4.9 ± 1.6% using the pen devices and 12.3 ± 2.6% using the insulin syringes (p < 0.01). However, both devices were comparable for regular insulin doses greater than 5 units (2.2 ± 0.4% vs. 2.9 ± 0.5% for pen and syringe, respectively). The accuracy in drawing up NPH doses was similar for small and large insulin doses (mean percent error of 5.7 ± 0.9 and 5 ± 1.2% for insulin doses ≤5 or >5 units, respectively). Children with diabetes were as accurate as their caregivers in drawing up the insulin in doses less than 5 units (mean percent error of 11.6 ± 4.2 for parents vs. 14.5 ± 5.4% for children). Only 1 patient contaminated the NPH vial with regular insulin. We conclude that pen devices are more accurate than insulin syringes at low insulin doses and that regular insulin, which is drawn up first, is less accurately delivered than NPH when an insulin mixture is used.

Long-Term Follow-Up of Siblings of Type 1 Diabetic Children Initially Evaluated for Islet Cell Antibodies (ICA) and HLA Haplotypes

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During the period 1981–1989, 179 siblings of Caucasian children with type 1 diabetes were screened for ICA by indirect immunofluorescence using type O human pancreas and were HLA typed for HLA A, B, C, DR by the microlymphocytotoxicity technique. Most were followed once or twice yearly for up to 12 years (mean 3.75 years) for ICA status and diabetes concordance (C) and all but 15 were recontacted after 8–16 years for C by history. *Results:* Six siblings were initially ICA-positive (3.3%) and remained ICA-positive with five becoming C after 8 months to 12 years. One ICA-positive sibling remains nonconcordant (NC) after 12 years (ICA-positive 6 times). One ICA-negative sibling became C after 3 years, remaining ICA-negative in 4 specimens pre-C, at C and 6 months post-C. Of 122 ICA-negative siblings followed at least 2 years with serial ICA, 5 converted to ICA after 2–6 years (2–10 prior negative specimens) and have remained positive for 3–13 years, but none is yet C. [3 converters were entered into the ENDIT study (ICA positivity confirmed).] Two other initially ICA-negative siblings were found ICA-positive but NC after long lapses in follow-up. Five of the original 6 ICA-positive siblings were DR3, DR4, as were 4 of the 7 converters (p = 0.01). Five of the original 6 were HLA identical to probands whereas 6 of 7 converters were haploidentical (p = 0.001). *Conclusions:* Long-term follow-up confirms that ICA positivity is associated with a high probability of C but interval to C varies considerably. HLA DR3, DR4 haplotypes confer susceptibility to develop ICA, with siblings HLA identical to probands becoming positive earlier than those not HLA identical.

Prevalence of Atopy in Children with Diabetes mellitus Type 1

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Background: Atopy is characterized by a chronic inflammatory reaction that is predominantly of a Th2-cell type. Diabetes mellitus type I (DM) is Th1-cell-dominated. We hypothesized that the prevalence of atopy may be lower in children with DM, since Th1 and Th2 cells reciprocally counteract each other as is reported for rheumatic arthritis and multiple sclerosis.
Objective: To compare the prevalence of atopic disease between children with DM and age-matched controls.
Methods: All Dutch pediatricians invited the parents of children with DM (younger than 18 years of age) to complete the ISAAC questionnaire on the prevalence of atopy. A cross-sectional survey (ISAAC II study) was used as a control group. Asthma was defined as the presence of symptoms and/or a doctor's diagnosis. Eczema and hay fever were defined as the presence of symptoms and a doctor's diagnosis, to differentiate from swimmer's eczema and common cold, respectively. The differences between the two groups were tested by using the χ^2 test.
Results: We received 555 questionnaires, which is estimated to be 15% of the total number of Dutch children with DM. The control group consisted of 604 children. The questionnaires of 254 DM patients were age-matched with the controls. The prevalence of asthma was 17.8% in DM patients compared with 25% in controls (p < 0.01). Eczema was reported to be present in 7.7% of DM patients compared with 13.4% of controls (p < 0.01). In contrast, hay fever was significantly more reported in DM patients compared with controls: 7.2 and 3.9%, respectively (p < 0.001).
Conclusion: In this study, the lower prevalence of asthma and eczema in DM patients compared with controls is consistent with the Th1/Th2 concept. Neither symptoms nor diagnosis of asthma, rhinitis or eczema were found in 82.2, 76.8 and 76.4% of children with DM compared to 72.4, 64.6 and 71.5% of controls.

Beta-Cell Autoimmunity at Birth and Early Onset Insulin-Dependent Diabetes mellitus

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Recent reports suggest that beta-cell autoimmunity could start early in infancy and sometimes in pregnancy. Antibodies to glutamic acid decarboxylase (GAD) and to protein tyrosine phosphatase (IA-2) are useful markers of prediabetes in family members and in the general population and are present in about 5% of relatives of type 1 diabetic patients. GAD and IA-2 antibodies can be measured by

immunoprecipitation on recombinant protein, using blood samples obtained by capillary drawing adsorbed on filter paper. The aim of the study was to assess autoimmunity to beta cells (GAD and IA-2 antibodies) at neonatal age in patients who developed early-onset insulin-dependent diabetes (<5 years).

Patients: Through the IDDM Registry in Lombardia, Italy, we have identified 17 patients, born between 1991 and 1995 with onset of IDDM from 1992 to 1996. We obtained blood spot collected in the first 3 days of life for metabolic neonatal screening of these IDDM patients and 35 controls subjects born in the same period with negative history for type 1 diabetes up to 5 years of age; 20 spots from infants of IDDM mothers were also obtained.

Methods: GAD and IA-2 antibodies were measured by immunoprecipitation on eluates of blood spots. We have verified that the assay can be performed on such eluates.

Results: 4 newborns of IDDM mothers showed elevated antibody levels. One of these children developed IDDM at 4 years of age. No significant antibody levels were found at birth either in type 1 diabetic patients or in control subjects. The absence of GAD and IA-2 antibodies at birth suggests that autoimmunity associated with type 1 diabetes must usually start after birth.

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Seasonality of IDDM Incidence in Slovak Children

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The aim is to analyze the seasonality of IDDM and its differences in six gender-age groups. The total of 1,369 newly diagnosed cases is from the National Register 1985–1997. There were 276 cases for 0–4 years, 481 for 5–9 years and 612 for 10–14 years. The cumulative IDDM incidence was 7.90 per 100,000 children. The analysis was done by cosinor regression (fig. 1) (95% confidence intervals). There was no significant sea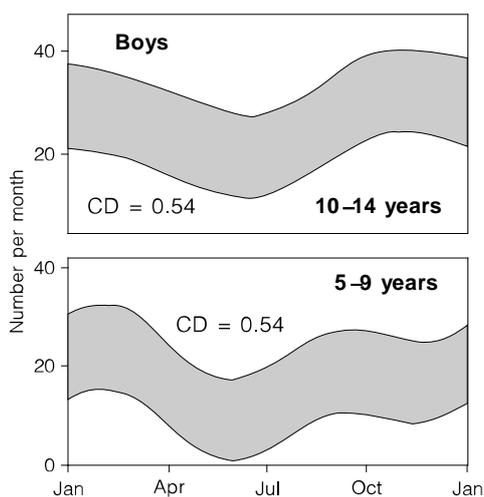sonality in either gender of the youngest groups as well as in girls aged 5–9. Significant autumn-winter peaking was revealed for boys aged 5–9 and for girls and boys aged 10–14 years.

In conclusion, no seasonal variation at diabetes onset – at variance with some reports – was found for the youngest children. Nevertheless, an autumn-winter peaking of the IDDM incidence was unequivocally confirmed for boys aged 5–15 and for girls aged 10–14. Thus, the seasonality was more prenounced in older children and appeared earlier in boys.

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Coxsackie Infection and IDDM Incidence in Slovak Children: A Close Chronobiometric Similarity

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This analysis compares monthly sampled coxsackie and IDDM data 1985–1997 to reveal trens and a priori supposed periodicities of 1, 3.5, 7 and 10 years, as known from geomagnetism studies.

Six hundred and eight randomly taken healthy Slovak children were investigated on anti-Coxsackie IgM antibodies (Cx). IDDM incidence figures are from the Slovak National Register. The Cosinor regression procedure was adopted to test the above-mentioned hypotheses.

The results are in the table (p values) and in the figure.

	Trend	1 year	3.5 years	7.0 years	10.0 years
Coxsackie	>0.05	10^{-19}	0.05	10^{-6}	0.05
IDDM	0	10^{-11}	0.0004	0.0004	0.0012

Fig. 1.

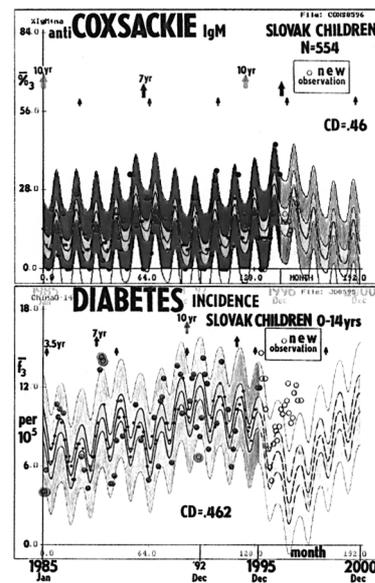**Fig. 1.** Number of new cases vs. calendar months. CD = Determination coefficient.

The figure displays the processed data 1985–1996 (Cx) and 1985–1995 (IDDM), both supposing a zero trend. The prediction was very good for Cx 1996 and sufficient for IDDM 1996 but failed for IDDM 1997 when all newly observed values were shifted over the prediction corridor. The IDDM curve laggs behind that of Cx by 3 months (for 1-year rhythm), and by 1–5 years (3.5- to 10-year rhythm).

In conclusion, the tested periods alone explain the data for Cx while for IDDM the linear increasing trend is necessary since 1997 – the year of a boom increase of IDDM.

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Diabetes Incidence in Children of Different Nations in Germany

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Migration studies have been a classical epidemiological method to analyse the aetiological effect of genetic markers vs. environmental factors.

Baden-Württemberg is a federal state of Germany covering 10.0% of the country. Among 9.75 million inhabitants, 10.7% are foreigners; under the age of 15 years, 14.5% are foreigners.

Our incidence registry is based on 1,160 children who were analyzed retrospectively. In addition, data of 965 children were analyzed prospectively. The total incidence of childhood diabetes was reported to be 11.6/100,000 (95% CI, 10.9–12.2).

Results: (1) The incidence rate (IR) of German children is significantly higher than the IR of foreigners ($\chi^2 = 25.31$, d.f. = 1; $p < 0.0001$). (2) The IR for German children alone is 12.2 (95% CI, 11.4–13.0), and for foreign children it is 7.1 (95% CI, 5.7–8.7). In detail: IR of Turkish children 5.2 (95% CI, 3.4–7.5), of Italian children 9.4 (5.6–14.6), of children from former Yugoslavia 5.5 (3.1–9.1), of children from Greece 5.0 (1.4–12.8). (3) The difference in the IR of children of different nations is highly significant ($\chi^2 = 33.59$, d.f. = 5, $p < 0.0001$). (4) The IR of children from different nations corresponds to the IR reported for the particular home country of these children.

Conclusion: These results may point to a link between the genetic basis and the pathogenesis of diabetes mellitus. Further analysis will be done by evaluation of the prospective data.

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Risk Factors for the Development of Microvascular Complications in Young Patients with Diabetes

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The DCCT showed a close relationship between metabolic control and diabetes-related complications in adolescents and adults with type 1 diabetes. Whether the same relation exists in younger children is, however, less evident. A Danish nationwide cohort of children and adolescents with type 1 diabetes was followed for 9 years on three occasions (1987, 1989, 1995) with assessment of metabolic control and development of complications in kidneys, eyes and nerves. The aim of the 1995 follow-up study was to determine risk factors and prevalence of complications in young Danish patients with diabetes. Furthermore, the significance of the pre- and postpubertal diabetes duration was analyzed in relation to development of microvascular complications. Clinical information, HbA_{1c}, AER, arterial blood pressure, fundus photos (central reading) and vibration perception threshold (VPT) was obtained from 353 patients (50% of the inception cohort), mean age: 20.7 ± 3.3 years and mean diabetes duration: 13.2 ± 3.2 years. HbA_{1c} (normal range 4.3–5.8, mean 5.3%) and AER (upper normal limit (95%): 20 µg/min) in at least two timed overnight urine collections were anlyzed centrally. Average HbA_{1c} was $9.7 \pm 1.7\%$ (mean $\pm$ SD). Elevated AER (>20 µg/min) was diagnosed in 12.8% of the patients. Risk factors for elevated AER (1995) were high AER (1989) ($p < 0.001$) and high HbA_{1c} (1989) ($p < 0.001$). Retinopathy was present in 58% and risk factors were long pre- ($p < 0.01$) and postpubertal ($p < 0.001$) diabetes duration and high HbA_{1c} level (1989) ($p < 0.0001$). Elevated VPT (>6.5 V) was shown in 60% and was related to male sex ($p < 0.05$), older age ($p < 0.001$) and elevated AER (1989) ($p < 0.05$). The present study confirmed the close association between long-term metabolic control and the development of microvascular complications in young diabetic patients. The prepubertal diabetes duration contributes to the development of diabetic retinopathy but to a lesser extent than the postpubertal duration. There is a major need for the development of better management guidelines and quality assessment programmes for young people with diabetes.

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The Oxygen Availability in Children with IDDM

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Introduction: Numerous studies have demonstrated that hypoxia is considered to be one of the main etiopathogenic factors in diabetic neuropathy. It is well known that hyperviscosity of blood, decrease of erythrocyte deformability, reduplication of the capillar basement membrane and increase of $Hb-O_2$ affinity may reduce the supply of O_2 to the nerves. The traditional parameters: oxygen tension, hemoglobin, and oxygen saturation may give misleading information. The computer program – 'Oxygen Status Algorithm' Siggaard-Andersen's and new parameters: px, cx, Qx shed more light on tissue hypoxia. Oxygen extraction tension –px defined as the oxygen tension which is required to extract 2.3 mmol O_2/liter blood, reflects the integrated effects of changes in the arterial O_2, oxygen capacity and $Hb-O_2$ affinity on the O_2 delivery to the tissue.

Aim: The analysis of the oxygen availability and determination of the risk factors of tissue hypoxia in children with IDDM.

Material, Method: 42 (25 girls, 17 boys) patients with IDDM have been examined. Average age 17. 1 SD 2.6; diabetes duration 6.6 SD 3.37; average HbA1c 9.34 SD 2.41. Patients with ketoacidosis and hypoglycemia have been excluded. pO_2, sO_2, PCO_2, pH, totHb, FHbCO, and FHbMet were measured from arterial blood samples by cooximeter and hemoximeter and the next was introduced into

24th Annual Meeting of the International
Society for Pediatric and Adolescent
Diabetes

Horm Res 1998;50:107–140

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