Childhood Diabetes Mellitus with Emphasis on Perinatal Factors

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Background

Diabetes mellitus (DM) is an ancient syndrome described by Aetios in Greece approximately 500 AD and by Chang Chung-Ching in China around 200 AD. From available information it seems that the incidence of diabetes was low for centuries. In the last half-century technological advances have enabled on one hand a better understanding of the underlying causes but, on the other hand, together with changes in lifestyle there has been a dramatic increase in the incidence of DM [1].

Definition

Childhood DM is a group of endocrine and metabolic diseases characterized by hyperglycemia resulting from absolute or relative insulin deficiency. Chronic hyperglycemia induces a series of metabolic abnormalities which with time cause various organ failures due to micro- or macrovascular complications and a shortened life span. Improved therapy postpones but cannot prevent these complications and prolongs life.

Classification

DM can be divided into two great categories: (1) insulin deficiency to absence, and (2) insulin resistance which may lead to β-cell exhaustion and thus both types may need insulin replacement therapy. Table 1 presents an etiologic classification of DM. Some types are very rare in childhood (pancreas

agmosis; mitochondrial DNA mutations), others are rare at any age (association with chromosomal or rare genetic disorders), or develop the clinical symptoms in adult age despite being of genetic origin (MODY types), gestational diabetes, etc. [2] (table 2). The following is a review of present evidence that environmental factors cause the development of type-1 or type-2 diabetes in the perinatal period.

**Table 1.** Etiologic classification of childhood diabetes mellitus (DM)

<table>
<thead>
<tr>
<th>I</th>
<th>Type-1 DM (autoimmune β-cell destruction)</th>
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<tbody>
<tr>
<td>II</td>
<td>Type-2 DM (from insulin resistance to insulin deficiency)</td>
</tr>
<tr>
<td>III</td>
<td>Genetic types</td>
</tr>
<tr>
<td>a</td>
<td>Neonatal DM (transient or permanent)</td>
</tr>
<tr>
<td>b</td>
<td>MODY types (6 different molecular defects)</td>
</tr>
<tr>
<td>c</td>
<td>Mitochondrial DNA</td>
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<tr>
<td>d</td>
<td>Insulin receptor defects (severe insulin resistance)</td>
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<tr>
<td>IV</td>
<td>Exocrine pancreas disease (cystic fibrosis, trauma, etc.)</td>
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<tr>
<td>V</td>
<td>Endocrinopathies</td>
</tr>
<tr>
<td>a</td>
<td>Cushing's syndrome</td>
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<tr>
<td>b</td>
<td>Pheochromocytoma</td>
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<tr>
<td>c</td>
<td>Hyperthyroidism</td>
</tr>
<tr>
<td>VI</td>
<td>Drugs</td>
</tr>
<tr>
<td>a</td>
<td>Glucocorticoids</td>
</tr>
<tr>
<td>b</td>
<td>Growth hormone</td>
</tr>
<tr>
<td>c</td>
<td>Diazoxide</td>
</tr>
<tr>
<td>d</td>
<td>Dilantin</td>
</tr>
<tr>
<td>VII</td>
<td>Associates with syndromes:</td>
</tr>
<tr>
<td></td>
<td>Wolfram, Down, Klinefelter, Turner's, Prader-Willi, Friedreich's ataxia, Roger, Alstrom, Wolcott-Rallison, etc.</td>
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**Table 2.** Diabetes mellitus of genetic origin

| 1 | PDX1 (IPF1) mutation causes pancreas hyperplasia and type-2 DM |
| 2 | HNF-4α (MODY1), chromosome 20 |
| 3 | Glucokinase (MODY2), chromosome 7 |
| 4 | HNF-1α (MODY3), chromosome 12 |
| 5 | Insulin-promoter factor-1 (MODY4), chromosome 12 |
| 6 | HNF-1β (MODY5), chromosome 17 |
| 7 | NeurDI (MODY6), chromosome 2 |
| 8 | Mitochondrial DNA |

Childhood Type-1 Diabetes Mellitus

Childhood type-1 DM (CT1DM) is an autoimmune disease which, if triggered in a genetically susceptible subject, induces a progressive process
which, depending on the frequency and force of subsequent insults, develops into clinical diabetes once 70–80% of the pancreatic $\beta$ cells are destroyed. This process can last months in babies to years in older children (fig. 1). The exact mechanism of the autoimmune process is not completely known, but in its course results in insulin autoantibodies (IAAs), anti-islet cell antibodies (ICAs) and glutamic acid decarboxylase isoform 65 antibodies (GADs), etc. [3]. Type-1 DM is often associated in the same child with celiac disease (CD; see below), with thyroiditis or Graves disease or even autoimmune gastritis [4]. These autoimmune diseases may appear before or after the clinical diagnosis of diabetes.

**Epidemiology**

Validated registers for childhood diabetes (CT1DM) were started in 1965 in 4 countries (USA, Finland, Japan, Israel) by the Diabetes Epidemiology Research International [2]. When other countries and regions followed, it became evident that there were great differences in incidence between countries and ethnic groups, and that the incidence of CT1DM was progressively increasing. Starting in the 1980s the rise accelerated steeply [2] even in children below age 5. As genetic factors did not change, it was concluded that environmental factors were involved, seemingly connected to changes in lifestyle [3]. Toxic substances (nitrate in water, pesticides used in agriculture) could not be blamed for the worldwide rise. Immunological studies have clearly shown that the autoimmune process and onset of CT1DM can begin early in life. The two most possible culprits for the initiation of this process focused on viral infections and nutrition.
Evidence for the Viral Etiology of Type-1 Diabetes

Analyzing the register in Israel, a country with several ethnic groups, we observed that in the Jewish population with a higher incidence of CT1DM the children and adolescents who subsequently developed the disease had a different seasonality in month of birth than the general population [5]. Subsequent studies in several countries and various populations in 4 continents confirmed these observations [6]. The interpretation of these data is that children conceived in the fall or winter during virus epidemics start to develop the anti-β-cell autoimmune process already in utero [7] or perinatally, and subsequently pathogenic agents, causing further damage or enhancing the autoimmune process, lead to the clinical disease [8].

Viruses can cause β-cell damage and HLA alleles which determine the risk for type-1 DM (such as HLA-DR3) modulate the clinical course of many virus infections [9].

The evidence for a link between virus infections and type-1 DM has been obtained from congenital rubella, mumps and enteroviruses, especially coxsackie B outbreaks (table 3). Further examples are the finding of enterovirus RNA in twins who developed CT1DM at age 14 months [10]. Echovirus was also isolated from a child at the onset of diabetes [11] and enterovirus was isolated from the pancreatic islets of some diabetic patients [12].

Mothers with virus infections can transmit the virus to the fetus in utero or by breast milk to the newborn. In case the fetus or baby is genetically susceptible to CT1DM, the pathogenic virus will initiate an autoimmune disease, in this case CT1DM. On the other hand if the mother transmits antiviral antibodies to the susceptible fetus or baby, it will be protected from the pathogenic action of these viruses [13].

Table 3. Environmental factors involved in the etiology of autoimmune type-1 diabetes mellitus

<table>
<thead>
<tr>
<th>Class</th>
<th>Specific agent</th>
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</table>
| Viruses     | Enteroviruses
              | Coxsackie B
              | Rubella (congenital)
              | Mumps
              | Rotoviruses
              | Cytomegalovirus
              | Echo
              | Encephalomyocarditis
              | Epstein-Barr
| Nutritional | Cow’s milk and cow’s milk-based infant formulas
              | Duration of breastfeeding
              | Nitrates (N-nitroso compounds)
              | Bafilomycin A1
| Life-style  | Exposure to β-cell toxins (e.g. Vacor)                              |
Infections and the development of immunization by antibody formation are more common in crowded, non-hygienic conditions, such as more often encountered in lower economic classes. This may possibly explain the lower incidence of CT1DM in underdeveloped countries than in developed ones with a high degree of hygiene [14]. This hypothesis is in line with a recent multi-country study including our group which revealed that a low frequency of enterovirus infections in the background populations would increase the susceptibility of young children to the diabetogenic effect of enteroviruses [15].

**Does Vaccination Affect the Incidence of Type-1 DM?**

On the basis of ecologic evaluations it has been claimed that vaccination as such and its timing are associated with an increased risk of type-1 DM 2–4 years after vaccination [16]. This could not be confirmed [17] but deserves further investigations as vaccinations may be associated with the etiology of autoimmune diseases in general [18, 19].

**Nutritional Risk Factors in the Development of Children with Type-1 DM**

The nutritional risk factors possibly involved with the initiation of type-1 DM has been recently reviewed [20]. A much-discussed issue is that of the role of cow’s milk (CM) proteins. Increased concentrations of IgA-class β-lactoglobulin and IgA CM formula antibodies were related to an increased risk of CT1DM [21, 22]. There was also a direct correlation between milk consumption and CM antibodies [22] and risk for CT1DM [23], however these findings remain controversial. To clarify the issue whether indeed CM proteins are a risk factor for type-1 DM in early infancy and whether breast-feeding confers protection [24], an international prospective study was initiated.

**The TRIGR Study**

The TRIGR (Trial to reduce type-1 DM in the genetically at risk) study started October 2001. Inclusion criteria was a first-degree family member with type-1 DM and DR3/4. DQB1*G362, etc., genotype. The plan is to randomize 2,800 of 6,220 infants screened. Source of candidates are medical centers in 15 countries (12 in Europe; main source Finland, Sweden and Poland) and USA (3 centers). The test formulas are casein hydrolysate (Nutramigen™, Mead Johnson) not containing antigenic CM protein, or a CM protein formula with a 20% addition of Nutramigen. The intervention is at least age 6 months. If breastfed, 2 additional months of test formula are advised. In addition to the genotyping at birth, serum for ICA, IAA, GAD, CM antibodies and glucose as well as the clinical state are being registered at 3, 6, 9, 12, 18 and 24 months and yearly up to 10 years of age. This study is also expected to provide information on effects of autoreactive T cells and cytokine repertoires related to infant feeding.
The fact that the results of the genetic screening are disclosed to the family is prone to induce long-lasting anxiety, and may have negative effects if leaked to insurance companies, future employers, etc.

**Association between CT1DM and CD**

Ziegler et al. [25] from the BABYDIAB study in Germany and Norris et al. [26] from the DAISY (Diabetes Autoimmunity Study of the Young) study in the US present a link between early infant nutrition and the development of autoantibodies against the pancreatic β cells. Both studies suggest that the age at which an infant is fed cereal is important in determining the risk for CT1DM. These studies fail to support the CM hypothesis but associate type-1 DM with CD.

CD is a chronic inflammatory autoimmune disease of the gut induced by gliadin (gluten) or prolamin proteins present in wheat, barley and rye. Upon digestion gliadin is deaminated by transglutaminase [27]. Genetically susceptible subjects develop autoreactive T lymphocytes which cause injury to the small bowel mucosa characterized by crypt hyperplasia and partial or complete atrophy of intestinal villi [28] as well as other organ damage. The frequency of CD in the general population of Europe and North America ranges between 0.4 and 1% [29].

CD and type-1 DM are both autoimmune diseases which share common major histocompatibility antigens (HLA). The association between the two diseases is well established. About 1/20 children with CT1DM have CD and approximately 1/10 express antitransglutaminase autoantibodies and half of these (1/20) have CD proven by biopsy [30]. Of note is that patients with CD who develop T-cell lymphomas express the HLA-DR3/4 genotype [31] so characteristic for CT1DM. The association between CD and CT1DM has both academic and also practical aspects [32]. In most instances the diagnosis of CD is made after the clinical diagnosis of CT1DM [33, 34]. As digestive abnormalities have a negative influence on diabetes control, some clinics propose screening all children with CT1DM for CD (serum for IgA, TG) on a regular basis [35].

Also the inverse procedure has been proposed as in one study 23% of the patients with CD have been found to have GAD and 1A-2 antibodies heralding future type-1 DM [36]. It was also reported that when CD is diagnosed before type-1 DM the clinical onset of the latter is severe with a high prevalence of DKA [37].

In a recent study we found that similar to childhood-onset type-1 DM in homogenous populations [6], subjects with CD have a different seasonality of month of birth than the general population (Lewy et al., submitted) which is again suggestive that the autoimmune onset of disease is during the perinatal period and possibly of viral origin. Considering the high grade associations between the two autoimmune diseases (similarity in genetic background, possible etiologic interrelation, or even a common trigger) led to investigations as
to whether a gluten-free diet in infancy can prevent the development of CT1DM [25] as was found to be possible in NOD mice [38]. So far, the experience in humans is not encouraging [39, 40]. Could better results be obtained by starting a gluten-free diet in mothers with type-1 DM before or during pregnancy?

Possible Role of Vitamin D in the Autoimmune Process

In animal models the active form of vitamin D (1,25-dihydroxyvitamin D) prevents diabetes and other autoimmune diseases [41]. Use of vitamin D supplementation during infancy in a European case-control study (The EURODIAB Study, 1999), and the addition of cod liver oil during the first year of life in Norway, lowered the risk of CT1DM [42], however, augmentation of the vitamin D supplementation to 2,000 IU/day in Finland did not prevent the increase in incidence.

Attempts to Cure, or Late Prevention Trials of CT1DM

At present there is no cure available or in sight. Trials with tertiary prevention (stopping the disease at clinical diagnosis) including nonspecific immunosuppression with cyclosporine or secondary prevention by nicotinamide (ENDIT trial) and insulin (DPT-1 and 2 trials) have failed [43, 44], so has the trial with DiaPep277 (a synthetic peptide of 65 heat shock protein) which gave negative results in children [45]. This peptide when combined with a hydrolyzed casein diet protected BB rats against type-1 DM [46]. Segmental or pancreatic islet cell transplantation, even if successful, has a time-limited effect and bears serious complications [47] including life-long immunosuppressive therapy. All the above interventions target both the autoreactive T cells as well as the ‘good’ T cells, which compromise the immune function of the patient. Also new research on stem cell therapy may not necessarily lead to the most suitable tissue for transplantation [48].

Gene Therapy

Not having found any specific gene linked to type-1 DM, this therapy is at present not feasible. On the other hand, investigations to deliver genes of somatic (non-pancreatic) insulin-secreting cells are being performed [49], but how to control the metabolic responses of transgenic cells is a problem.

Childhood Type-2 Diabetes Mellitus

Type-2 DM is a complex metabolic-endocrine disorder of heterogeneous etiology with different genetic backgrounds (table 1). Some forms, such as that caused by obesity and insulin resistance or parental diabetes and that linked to perinatal environmental factors have been found to have an increasing prevalence in the last half-century [50]. To adapt to the present symposium
only the forms with proven, or suspected in utero, or perinatal etiology will be reviewed.

Numerous studies have reported that the offspring of mothers with type-2 DM are more likely to develop obesity, childhood type-2 DM (CT2DM), or impaired glucose tolerance at an earlier age than the offspring of fathers with diabetes. Studies in Pima Indians suggested that the increase in childhood type-2 DM can be attributed to the diabetic intrauterine environment [51] independent of the genetic predisposition [52]. More subtle is the link between high birth weight and increased risk for future obesity and glucose intolerance [53] in non-diabetic mothers.

The following observations need special attention. In 1992 Hales and Barker [54] proposed the hypothesis that one of the major consequences of poor fetal and early postnatal nutrition is impaired development of the endocrine pancreas and a greatly increased susceptibility to the development of type-2 DM. Series of large studies in the US [55], in Sweden [56] and India [57] show that with a decreasing birth weight, birth length and placental weight there is an increase in future development of type-2 DM.

The mechanisms involved are not completely clear but certainly affect the liver and muscle metabolic disturbances with subsequent slowly progressing development from childhood to adult age of insulin resistance, glucose intolerance, hyperlipidemia and even cardiovascular disease. Of interest also is the observation that children who were born prematurely have an isolated reduction in insulin sensitivity which is a risk factor for type-2 DM [58]. Thus also type-2 DM may be preprogrammed in utero possibly caused by intrauterine malnutrition.

**Prevention of Type-2 DM**

Postnatal nutrition is modifiable by education and so is a change in lifestyle. Both methods could reduce the incidence of obesity, and resulting hyperinsulinism, hyperlipidemia and the development of type-2 DM with its complications. Theoretically this is easy but less so in practice. How to prevent or treat intrauterine growth retardation and/or malnutrition is largely unknown. Improved metabolic control of pregnant mothers with DM may improve, but not abolish the subsequent complications. Better control of in vitro fertilization and a reduction in multiple pregnancies may be a positive measure. But what of the premature infant with appropriate or low weight for gestational age? And what about the malnourished mother due to illness or low economic class? One needs to learn more about the postnatal adaptive mechanisms of intrauterine, metabolic and endocrine restrictions. Is adiponectin the culprit [59]? Only long-term follow-up will demonstrate whether prenatal treatment of intrauterine growth restriction [60] and present neonatal intensive care of premature babies is sufficient to deliver healthy children and healthy adults.
Conclusions

We are at present confronted with a continuous and worldwide increase in incidence of both CT1DM as well as CT2DM, the first possibly linked to improved hygiene [61, 62] and changes in nutrition acting in the perinatal period. Type-2 DM increases due to intrauterine conditions but mostly due to postnatal changes in lifestyle involving nutrition, and lack of physical exercise leading to obesity, insulin resistance and its exhaustion.

As CT1DM secondary intervention trials have proven to be ineffective [43, 44] only primary prevention is the hope [62]. Is immunization of mothers before or during pregnancy the solution [13]? Immunizations against which virus? Exclusive long-term breastfeeding? Prevention of CT2DM can be envisioned by preventing or early treatment of obesity and increasing energy expenditure. Is this feasible in a modern media-dominated society? New strategies are needed [63]. As animal models do not provide the complete and sometimes not the right answer [64], this is a difficult task.

References

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Discussion

Dr. Björkstén: I have a comment and a question. I would caution against delayed introduction of a gluten-free diet in infancy. I think we have a scary example from Sweden where the routine was not to introduce gluten until after 6 months of age and
we observed an extreme incidence of celiac disease. Then by changing the practice and introducing gluten gradually at an earlier age we got back to normal figures. With that experience it is close to unethical to delay the introduction.

**Dr. Laron:** I have no personal experience other than the knowledge of the relationship between celiac disease and type-1 diabetes. We are looking into further relationships and I can tell you that we are writing a paper showing that also patients with multiple sclerosis (MS) present the same epidemiological changes, i.e. a different seasonality of month of birth than the general population [1]. We are looking into what may be a common denominator linking these diseases, probably viruses, but I don't know whether as you said a gluten-free diet is the reply.

**Dr. Björkstén:** That brings me to my question. There are many similarities in the epidemiology of type-1 diabetes and childhood allergies. You can almost superimpose the increases in diabetes and IgE-mediated allergy on a log scale. So what is known regarding the induction of T-regulatory function in diabetes?

**Dr. Laron:** It is known that we have a change from T cells type 1 and there was the Peptor protein trial to switch T1 over to T2 cells. There is no question that a cytokine process is going on. We are just now starting also to study atopic dermatitis to find out the month of birth epidemiology.

**Dr. Björkstén:** The major driving factor for induction of normal immune regulation is actually the colonization of the gut microbiota, whether that has an impact for diabetes is a hypothesis, however. But I would like to draw your attention to a very interesting study that was done in Melbourne. If you raise mice of a strain that will develop autoimmune disease, as adults under germ-free conditions, they die from fulminant diabetes. The story is similar to what I am going to discuss about allergies. I am therefore wondering whether some of the dietary issues that you brought up are related to the normal colonization of the gut microbiota?

**Dr. Laron:** I think we have to look a little bit further in order find out what the cause is and what the effect is. We really do not know what starts it and at what stage things happen. However there is a relationship, there is no question that type-1 diabetes is an strong ongoing autoimmune process. The late change in this immune process has not succeeded so far, so my idea is that only prevention or very early intervention might be helpful. The allergy process or immune process is perhaps like the kidney stone story, you take it out but it will come again, the 'anlage' is there, and the same thing may happen if we are too late to intervene in the immune process that destroys the β cells and probably also other organs like the thyroid.

**Dr. Klish:** I have also heard similar arguments for inflammatory bowel disease, which has some similarities to all this.

**Dr. Hamburger:** Are you familiar with any studies on probiotics related to the onset of type-1 diabetes?

**Dr. Laron:** No.

**Dr. Björkstén:** Yes, there are ongoing studies both in Finland and Sweden.

**Dr. Laron:** I would appreciate the opinion of the audience as to whether early intervention, meaning during pregnancy in the mother, might influence the perinatal immune process.

**Dr. Björkstén:** We don't know that yet. It has been tried but not systematically and pre- and postnatal interventions haven't been separated properly. There are studies going on in germ-free animals but it is very difficult to answer that question in human studies.

**Dr. Sorensen:** I had a lot of trouble following your hypothesis to explain seasonality because it is very unlikely first of all that they all get the viral infections because they would be protected already, most adults are. Then the transmission of antibodies at best will last 15–16 months after delivery. By then all IgG antibodies that the mother will have transferred transplacentally are completely gone, so the child will be
exposed to the development of all those viral infections. So I have trouble understanding how these maternal antibodies could offer a protective effect against virally triggered diabetes.

*Dr. Laron:* First of all one fact has been established, that part of the seasonality of birth of children who develop diabetes, not all, differs from the general population. So it seems to be with celiac disease, also possibly other autoimmune diseases. This is a fact. Now there may be more than one explanation. I think that the antibodies of the mother cross to the fetus during a period where it cannot produce its own antibodies. There is one clear thing which has been demonstrated in animals by Dr. Kolb in Düsseldorf. He took mice which develop spontaneous diabetes, and when they were put in a dirty cage they did not develop diabetes. So there is substantiation that infections may prevent diabetes both in animals as well as in men, not in everybody, depending again on genetic susceptibility or protection by HLA subgroups. It is probably also not one virus. If it were one virus it would be easy to vaccinate. The epidemics in different countries may be caused by different viruses, and this is what we are trying to clarify. In collaboration with Dr. Viskari, we examined several virus antibodies, also polio, and the study showed a correlation between viral antibodies in pregnant mothers and the incidence rate of childhood type-1 diabetes [2].

*Dr. Sørensen:* Is there any seasonality to diabetes itself, because if this is related to a viral infection then you should see seasonality of the onset of diabetes in children.

*Dr. Laron:* We don’t know when the onset occurs because the destruction of the β cell is a very slow process and it probably starts already in utero or perinatally. What is known and was described in the UK in 1972 is the diagnosis of clinical diabetes at a stage when 70 or 80% of the β cells have already been destroyed.

*Dr. Klish:* I can’t help but ask if there is commonality in the causality between atopic disease and type-1 diabetes mellitus. It should be possible to look at the studies of hydrolyzed protein that have shown a decrease in atopic dermatitis to see if there is also a decrease in diabetes. Dr. Van Berg, is your cohort old enough yet to be able to see this?

*Dr. Laron:* We don’t know. There is a hypothesis and more has to be done to prove it. Not only antibodies pass from the mother, viruses pass from the mother, this has been shown with hepatitis virus C.

*Dr. von Berg:* Actually we are just starting to look at type-1 diabetes in our cohort. We haven’t done it yet but it is coming.

*Dr. Seidman:* I enjoyed your lecture very much. There are many parallels between celiac disease and type-1 diabetes, but there are also major differences although they both share HLA haplotypes. In fact that only explains perhaps 25% of celiac disease amongst diabetics, and most studies have suggested that it is the diabetes that occurs first and then celiac disease secondarily at some later point, which raises my question. Why do you think that a virus would cause type-1 diabetes, which occurs basically in the first two decades of life, whereas celiac disease, with the same genetic background where the dietary antigen is known, the occurrence which has also been implicated to virus can occur any time in life?

*Dr. Laron:* I don’t know. I think perhaps the assembly of gastroenterologists here may have better ideas than me.

*Dr. Seidman:* I think that if we really believe that a virus causes type-1 diabetes then we should think about viruses that only effect people in the first two decades of life, and Epstein-Barr virus would become one of the more likely candidates. Is there an association between Epstein-Barr virus infection and the onset of type-1 diabetes?

*Dr. Laron:* How would you explain the fact that we have data from this country, from the Mayo Clinic, in which we found that patients who develop celiac disease have a different seasonality of month of birth than the general population? How would you explain this?
Dr. Seidman: I haven’t seen the data, I can’t really comment.

Dr. Sampson: One of the ways to look at the possible effect of transmitted maternal antibodies is to look at preterm infants. They don't receive much in the way of antibodies from the mothers. Has anyone looked to see if preterm infants lose the seasonality effect you are talking about?

Dr. Laron: Not that I know.

Dr. Björkstén: Can you clarify, I was slightly confused from the immunological point of view. You mentioned a score of viruses. The way I understand it, at least some of the literature, is that people are actually discussing molecular mimicry for certain enteroviruses which of course, as you know, is again a very challenged hypothesis from the immunological point of view. But how would you reconcile this? You are mentioning numerous viruses and under those circumstances molecular mimicry or that sort of attack on the islet cells would certainly not be relevant.

Dr. Laron: The idea of mimicry was put up by Trucco in Pittsburgh, and at the beginning had quite a few adherents, but in the last few years virologists in Calgary do not speak of that. I am not an immunologist to really give you a scientific answer.

References